Advances in Endoscopy in Inflammatory Bowel Disease

Toshifumi Hibi
Tadakazu Hisamatsu
Taku Kobayashi *Editors*

Springer

Advances in Endoscopy in Inflammatory Bowel Disease

Toshifumi Hibi • Tadakazu Hisamatsu
Taku Kobayashi
Editors

Advances in Endoscopy in Inflammatory Bowel Disease

Springer

Editors
Toshifumi Hibi
Center for Advanced IBD Research and Treatment
Kitasato University Kitasato Insitiute Hospital
Minato-ku
Tokyo
Japan

Taku Kobayashi
Center for Advanced IBD Research and Treatment
Kitasato University Kitasato Insitiute Hospital
Minato-ku
Tokyo
Japan

Tadakazu Hisamatsu
The Third Department of Internal Medicine
Kyorin University School of Medicine
Mitaka
Tokyo
Japan

ISBN 978-4-431-56016-6 ISBN 978-4-431-56018-0 (eBook)
DOI 10.1007/978-4-431-56018-0

Library of Congress Control Number: 2017946490

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer Japan KK
The registered company address is: Chiyoda First Bldg. East, 3-8-1 Nishi-Kanda, Chiyoda-ku, Tokyo 101-0065, Japan

Preface

Gastrointestinal endoscopy is indispensable for the treatment of gastrointestinal diseases. Its advances have been impressive; progress of diagnostic techniques and therapeutic procedures for neoplastic diseases in both the upper and lower gastrointestinal tracts has been especially remarkable. On the other hand, endoscopy has had a limited role in inflammatory diseases compared with neoplastic diseases, as it had been regarded solely as a tool for diagnosis. However, medical treatments and therapeutic strategies for patients with inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn's disease have been revolutionized since the introduction of biologics including anti-TNF alpha antibodies. Many novel medical treatments have emerged targeted to control intestinal inflammation and correct abnormal immune response.

Endoscopy gradually has become more indispensable in the field of intestinal inflammation for the appropriate diagnosis and monitoring of the clinical course as medical treatments have become more complex and selection of the appropriate treatment is necessary. It has been my growing concern that there were only a few textbooks for endoscopy addressing this situation; however, now this new guide has been published as a useful textbook for inflammatory bowel disease clinicians. Fields of gastrointestinal endoscopy should be classified differently, into those for neoplasms and those for inflammation. A role of endoscopy for neoplastic diseases is to cover all the aspects from diagnosis to treatment, while less attention is paid to clinical symptoms, their course, or both. This book has been written by renowned specialists not only from Japan but also from other countries, and its main focus is on endoscopy for intestinal inflammation, especially for inflammatory bowel disease.

There are four main roles of endoscopy to treat patients with inflammatory intestinal diseases such as inflammatory bowel disease.

1. The first role of endoscopy is to serve as a diagnostic tool. Successful medical management of inflammatory bowel disease begins with an accurate diagnosis distinguishing it from other diseases by endoscopy in addition to obtaining a complete medical history and conducting thorough physical examinations and stool and blood tests.

2. The second role of endoscopy is to monitor the therapeutic response and clinical course. Making a judgment of whether to change, continue, or discontinue inflammatory bowel disease treatment by monitoring the disease state is crucial in treating inflammatory bowel disease. Moreover, endoscopy plays a vital role in accurately visualizing and assessing the disease state and helping in deciding the appropriate medical treatments for each patient. Recently, endoscopic mucosal healing is being emphasized as an objective factor that predicts favorable long-term prognosis.
3. Moreover, endoscopy is necessary for the appropriate surveillance of colitis-associated cancer.
4. Finally, endoscopic interventions play important roles in endoscopic dilation technique for strictures and hemostasis for bleeding, similar to endoscopy for neoplastic diseases.

This book focuses on the four roles of endoscopy for inflammation, and it contains abundant endoscopic pictures by some of the world's top specialists, particularly in Asia. I hope the book will be useful in daily clinical practice for treating patients with inflammatory intestinal diseases.

Tokyo, Japan — Toshifumi Hibi
Tokyo, Japan — Tadakazu Hisamatsu
Tokyo, Japan — Taku Kobayashi

Contents

Part I
The Role of Endoscopy in IBD

Chapter 1
The Role of Endoscopy in Inflammatory Bowel Disease

Haruhiko Ogata

Abstract Endoscopic assessment of mucosal lesions has emerged as an important concept of disease activity in inflammatory bowel disease (IBD), and recently mucosal healing has generally been regarded as a therapeutic goal not only in ulcerative colitis (UC) but also in Crohn's disease (CD). Several pieces of evidence have now accumulated to show that mucosal healing determined by endoscopy can alter the course of IBD, as it is associated with sustained clinical remission, and reduced rates of hospitalization and surgical resection. Generally, clinical activity indices established in IBD are mainly determined based on subjective/objective signs and the results of laboratory tests. However, those indices sometimes lead to discrepancy compared with endoscopic indices. Although endoscopy has been rarely investigated as a predictor of the clinical course of IBD, there is now growing evidence that morphological examination, including endoscopy, may help to identify among IBD patients those who should be treated with more intensive treatments. Furthermore, as demonstrated in a recent study assessing early intervention with combination of biologics and immunomodulators, endoscopy may help to select patients who will obtain the best results with early intervention. This chapter summarizes the role of endoscopy in IBD by introducing several modalities such as colonoscopy, balloon-assisted enteroscopy, and video capsule endoscopy, as well as CT colonography and MR enterography.

Keywords Inflammatory bowel disease • Ulcerative colitis • Crohn's disease, endoscopy • Mucosal healing • Activity indices • Medical therapy • Surgery

H. Ogata
Center for Diagnostic and Therapeutic Endoscopy, Keio University School of Medicine,
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: hogata@z8.keio.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_1

1.1 Introduction

The management of ulcerative colitis (UC) and Crohn's disease (CD), the two major forms of inflammatory bowel diseases (IBD), has dramatically changed over the last decade. Progress has been supported by the increasing evidence from therapeutic strategies, the introduction of biologics providing more alternative options in patients with severe diseases, and new concepts as to how and when treatments should be used [1, 2]. Immunomodulators and biologics are classically used following a step-up approach in patients with refractory disease, who are unresponsive to conventional therapies or are steroid-dependent. Beyond their high efficacy in induction and maintenance of remission, it has been demonstrated that anti-tumor necrosis factor (TNF) therapies can close fistulae and heal mucosal lesions, and reduce rates of hospitalization and surgery [3]. Several recent studies suggest that early intervention with combination therapy may modify the long-term course of CD [4–6]. Meanwhile studies performed with regard to prediction of the disease activity have mainly focused on clinical and biological parameters, and endoscopy has been rarely investigated as a predictor of the clinical course of IBD. However, there is now growing evidence that morphological examination, including endoscopy, may help to identify among IBD patients those who should be treated with more intensive treatments. Furthermore, as demonstrated in a recent study assessing early intervention with combination of infliximab and azathioprine in CD, endoscopy may help to select patients who will obtain the best results with early intervention [4].

Endoscopic assessment of mucosal healing is usually assessed by colonoscopy in patients with UC. In fact, there are several indices proposed to measure endoscopic severity in UC (see Chap. 16); however, they have not been fully validated, and are subject to inter-observer variation. Recently, the development of a validated ulcerative colitis index of severity (UCEIS) has been established, and the American Gastroenterological Association is going to provide a forum for discussing the possibility of design and interpretation of future clinical trials in UC using UCEIS (see also Chap. 16). Meanwhile, the assessment of mucosal healing of CD has been performed by ileocolonoscopy, and recently balloon-assisted small-bowel enteroscopy and video-capsule endoscopy have also contributed to the evaluation of disease activity of small-bowel CD (see Chap. 17). Furthermore, CT-guided colonoscopy (virtual colonoscopy) and MR enterocolonoscopy also have contributed to diagnosis, monitoring, and therapy against IBD. In this chapter, the overview of important aspects of bowel involvement in IBD is discussed.

1.2 Feasibility of Endoscopy in Active UC

Carbonnel et al. [2] demonstrated that total colonoscopy is feasible in 86% of cases of severe UC (73/85). In this study, endoscopy accurately identified severe endoscopic lesions (extensive deep ulcerations). Eighty-five consecutive patients with

attacks of UC were reviewed. Extensive deep colonic ulcerations were diagnosed in 46 of them. No complication related to colonoscopy occurred except for one colonic dilatation. Forty-three of the 46 patients with severe endoscopic colitis underwent surgery. Extensive ulcerations reaching at least the circular muscle layer were found on pathological examination, and were confirmed in 42/43 of cases [7]. Because of potential risks of complications, some rules have to be applied when performing colonoscopy in patients presenting severe attacks of UC, including pre-radiological examination to exclude megacolon and minimal insufflations; and when severe lesions are detected, the examination can be stopped as further examination has no additional prognostic value.

1.3 Mucosal Healing Evaluated by Endoscopy Contributes to a Better Outcome in UC

To date, there is no consensus on the definition of mucosal healing in UC [1]. The International Organization of IBD proposed the following definition: absence of friability, blood, erosions, and ulcers in all visualized segments of the gut mucosa. According to this definition, disappearance of the normal vascular pattern is compatible with mucosal healing [1, 3]. It has been shown that mucosal healing can be obtained with 5-aminosalicylates (5-ASA), steroids, azathioprine or methotrexate, and infliximab. Mucosal healing has been assessed in recent trials with different formulations of 5-ASA. In the ASCEND studies, evaluating different dosages of a delayed-released oral mesalazine in patients with mild or moderate UC, complete remission (including endoscopic remission) ranged between 18% and 25% at week 6 [4, 10]. Truelove et al. [5] demonstrated in 1954 that mucosal healing can be obtained with a high-dose of oral steroids in 30% of patients at week 6, compared with 10% in patients who received placebo ($P = 0.02$). In a recent review, it was considered that corticosteroids induce mucosal healing in 12–41% of patients with UC, depending on the method of administration and the medication [1]. Some data suggest that mucosal healing may also be obtained with azathioprine or methotrexate [6, 13]. Anti-TNF agents probably induce mucosal healing more rapidly. In ACT 1 and ACT 2, patients with refractory moderate-to-severe UC received placebo or infliximab intravenously [14]. Induction therapy with infliximab resulted in mucosal healing at week 8 in 61% of patients (148/242) compared with 32% (79/244) in the placebo groups ($P < 0.001$) [14]. At week 54 (ACT 1), scheduled maintenance therapy with infliximab resulted in mucosal healing in 45.5% (55/121) of patients compared with 18.2% (22/121) in the placebo group ($P < 0.001$). Data from several studies suggest that mucosal healing may be associated with a better outcome in UC, more specifically a decreased risk of relapse. Reduced relapse rates have been demonstrated in UC patients who achieved mucosal healing with steroids. In a study published in 1966, Wright et al. [7] found that 40% of patients who achieved mucosal healing with oral and rectal steroids did not relapse during 1 year of follow-up, as compared to 18% of those who still had lesions. In the ACT1 and ACT2 studies

on infliximab maintenance in patients with moderately to severely active UC, 48.3% of the patients who achieved mucosal healing at week 8 were in remission at week 30, as compared to only 9.5% of those who did not achieve mucosal healing [13]. Mucosal healing may also be associated with reduced risk of surgery in UC. In the IBSEN population-based study, UC patients who achieved mucosal healing at 1 year (whatever the treatment) had a decreased risk of colectomy at 5 years (2% vs 7%, $P = 0.02$) [16]. A study performed in the Leuven cohort of UC patients treated with infliximab showed that colectomy was more frequent in patients who did not achieve mucosal healing at week 4 or 10 (Mayo endoscopic subscore greater than 1) [17]. In ACT1 and ACT2, it was shown that patients treated with infliximab were less likely to undergo colectomy through 54 weeks than those receiving placebo [18]. However, data on the relationship between mucosal healing and risk of colectomy are not available in these studies. Finally, there is a clear relationship between the grade and chronicity of inflammation in the colon and the risk of colorectal cancer. Better control of inflammation, as demonstrated with mucosal healing, may be associated with decreased risk of colorectal cancer.

1.4 Endoscopic Severity of UC Contributes to an Increased Risk of Colectomy

Among patients hospitalized for a severe attack of UC, the presence of extensive and deep ulcerations at colonoscopy is associated with an increased risk of colectomy on that admission [7]. In their study performed in the prebiologic era, Carbonnel et al. [2] showed that colectomy was performed in 43 of the 46 patients who presented severe endoscopic lesions (93%), as compared to 10/39 (26%) of those without such lesions (OR 41). In another study performed in severe UC patients, severe endoscopic lesions at colonoscopy were significantly more frequent in non-responders to medical treatment (91%) compared with responders (34%) (OR >20) [19]. The colonoscopies performed during severe attacks of UC also have an impact on the long-term outcome, with an increased rate of surgery in the long term in patients who exhibit extensive and deep ulcerations at index colonoscopy [20]. Namely, although intravenous cyclosporine treatment could exert high initial efficacy for severe attacks of UC, 50% of patients who had relapse required a colectomy. Specifically, mucosal healing evaluated by a novel endoscopic activity index [8] at day 14 after cyclosporine injection was associated with the 1-year colectomy rate [21].

1.5 Severe Mucosal Lesions of Colonic CD Evaluated by Endoscopy

Severity of colonic lesions in CD relies on the extent in depth and in surface of the mucosal damage. A previous interobserver variation study targeted on evaluation of ileocolonoscopic lesions in CD [9] has shown that deep ulcerations and estimation of

ulcerated surface were among the most reproducible endoscopic items. Such lesions were also selected by multivariate analysis for the construction of the CDEIS [22]. Nahon et al. [10] demonstrated that colonoscopy accurately predicts the anatomical severity of colonic CD attacks. In this retrospective study of 78 patients operated for colonic CD resistant to medical treatment, criteria of severity in colectomy specimens were defined as either deep ulcerations eroding the muscle layer, or mucosal detachments, or ulcerations limited to the submucosa but extending to more than one third of one defined colonic segment (right, transverse, left colon). Three endoscopic criteria of severity were defined: (a) deep ulcerations eroding the muscle layer, (b) deep ulcerations not eroding the muscle layer but involving more than one third of the mucosal area, and (c) mucosal detachment at the edge of ulcerations. Evaluation of endoscopic severity correlated well with findings on colectomy specimens. At least one of these criteria was found in 95% of patients with severe anatomic lesions on colectomy specimens. The extent of ulcerations at colonoscopy was correlated to the results of colectomy specimen examination ($P < 0.001$). This study further demonstrates that colonoscopy can accurately assess anatomical severity of colonic CD.

Endoscopic severity may have an impact on the long-term course of the disease. Allez et al. [11] showed in a retrospective study that patients with CD exhibiting deep and extensive ulcerations at colonoscopy have a more aggressive clinical course with an increased rate of penetrating complications and surgery. Among the 102 patients included, 53 had severe endoscopic lesions at index colonoscopy, defined as extensive and deep ulcerations covering more than 10% of the mucosal area of at least one segment of the colon. During the follow-up (median 52 months), 37 patients underwent colonic resection. Furthermore, patients with severe endoscopic lesions needed significantly more colonic resections than patients without severe lesions [23]. These data suggest that a subset of CD patients have a more aggressive disease, characterized by severe endoscopic lesions in the ileocolon during symptomatic phases, and a higher risk of surgery [23].

1.6 Mucosal Healing Evaluated by Endoscopy after Medical Treatment against CD

Therapeutic effect in clinical trials against CD is usually assessed by improvement defined by a decrease of the CDAI. Assessment of endoscopic improvement was not usually performed until recently in clinical trials assessing the efficacy of drugs in CD. The main reason for this was that steroid-induced clinical remission is not associated with mucosal healing in two-thirds of CD patients. However, there is growing evidence that mucosal healing during therapy is a sign of a good efficacy of a drug [1, 24]. Data from the IBSEN cohort strongly suggests that mucosal healing predicts a generally favorable outcome of disease based on all types of treatment strategies, and is related to treatment efficacy, reduced frequency of surgery and hospitalizations [16]. Moreover, it is now clearly demonstrated that mucosal healing can be achieved with azathioprine and anti- TNF [25–29]. Rates of mucosal healing under azathioprine vary among studies, probably due to differences in the timing of

endoscopy and the population analyzed. In a randomized controlled trial performed in steroid-dependent CD patients, Mantzaris et al. [12] have recently shown that azathioprine was superior to budesonide in inducing mucosal healing at 1 year; complete or near complete healing was achieved in 83% of azathioprine-treated patients compared with only 24% of budesonide-treated patients ($P < 0.0001$). In a GETAID study, long-lasting remission (≥42 months) maintained with azathioprine was associated with a complete mucosal healing (CDEIS = 0) in only 36% of CD patients [30]. In the SONIC study, which concerned CD patients naïve to immunomodulators and biologics, only 15.6% of patients treated with azathioprine achieved mucosal healing at week 26 [4]. In the endoscopic substudy of the ACCENT I study, patients treated with scheduled maintenance therapy with infliximab had superior rates of mucosal healing, and those who maintained complete mucosal healing over 1 year had a lower rate of hospitalizations and surgeries [13, 31]. A study of mucosal healing in a cohort of CD patients under long-term treatment with infliximab was recently reported [32]. In this study from the Leuven group, 214 patients had a colonoscopy before and a second one within months after starting infliximab. Mucosal healing was observed in 68% of the 183 initial responders. Mucosal healing was associated with a significantly lower need for major abdominal surgery during long-term follow-up (14.1% major surgeries in patients with mucosal healing vs 38.4% in patients without mucosal healing, $P < 0.0001$). Several studies suggest that immunomodulators and anti-TNF therapy may be more effective when given early in the course of the disease. Recently there are two studies of "top-down" therapy performed in CD patients naïve to immunomodulators and biologics, which refers to early introduction of immunosuppressive or biologic therapies. In the SONIC study, infliximab therapy was superior to azathioprine in inducing mucosal healing at week 26 (30.1% vs 15.6%), but inferior to infliximab plus azathioprine combination therapy [4]. D'Haens et al. [14] compared a top-down strategy to a more classical step-up strategy. Top-down strategy, which consisted of early induction with infliximab and maintenance with azathioprine, resulted in mucosal healing in 19/26 of patients (73%) at week 104. In the other arm (step-up strategy), mucosal healing was significantly less frequent (7/23 patients, 30%). Additionally, when mucosal healing was achieved at 2 years (SES-CD score at 0), 70% of the patients (17/24) were in stable clinical remission during the following 2 years as compared to only six of the 22 (27%) who had mucosal lesions (SES-CD score above 0) [6]. Fifteen of the 17 patients with mucosal healing at year 2 maintained in remission without further infliximab infusions during the following 2 years. Furthermore, mucosal healing obtained with immunomodulators or anti-TNF agents was also associated with a decreased risk of surgery in the long term. Altogether, these data would suggest checking endoscopic response in patients treated with immunosuppressants or anti-TNF. In a placebo-controlled study by GETAID, presence of ulcerations at ileocolonoscopy before withdrawal of azathioprine was not predictive of the risk of relapse [30]. A recent study from GETAID assessed the risk of relapse after infliximab discontinuation in patients in remission on combined maintenance therapy, who continued the immunosuppressant (azathioprine or methotrexate). Mucosal healing was among the factors strongly associated with a decreased risk of relapse [33].

1.7 Endoscopic Assessment Contributes in Predicting Relapses of CD after Surgery

It is generally accepted that CD patients who have ileal resection and ileocolonic anastomosis are exposed to a high risk of postoperative recurrence [34]. Rutgeerts et al. [15] demonstrated that ileocolonoscopy performed within 1 year of surgery may predict the risk of clinical recurrence. Eighty-nine patients treated by ileal resection for CD were included in this prospective cohort follow-up to study the natural course of early postoperative lesions. Within 1 year of surgery, ileocolonoscopy detected recurrent lesions in the neo-terminal ileum in 73% of the patients, although only 20% had a clinical relapse. The rate of clinical relapse was 34% at 3 years. A score was devised to assess the severity of recurrent endoscopic lesions. The course of the disease was best predicted by the severity of the early postoperative lesions, as observed at ileocolonoscopy, on the anastomosis and/or on the neoterminal ileum. Indeed, patients with less severe endoscopic lesions according to Rutgeerts' score (less than five aphtoid ulcers at anastomosis site), have a lower risk of clinical recurrence risk at 9% compared with 100% risk at 4 years for patients with more severe endoscopic recurrence (Rutgeerts' score i2 or greater). This score is widely used in clinical practice, and ECCO guidelines state that ileocolonoscopy should be the gold standard for the diagnosis of postoperative recurrence by defining the presence and severity of morphologic recurrence and predicting the clinical course. Ileocolonoscopy is recommended within the first year after surgery where decisions of postoperative treatment may be affected [35]. Furthermore, recently Regueiro et al. [16] showed that administration of infliximab soon after intestinal resection was effective at preventing endoscopic recurrence of CD. They randomly assigned 24 CD patients who had undergone ileocolonic resection to receive intravenous infliximab, administered within 4 weeks of surgery and continued for 1 year, or placebo. The rate of endoscopic recurrence at 1 year was significantly lower in the infliximab group (one of 11 patients; 9.1%) compared with the placebo group (11 of 13 patients; 84.6%) ($P = 0.0006$).

1.8 Conclusion

In patients with active IBD, endoscopy may help to select patients who should receive early and active therapies. One reason is that severe endoscopic lesions may predict a poor outcome with increased risk of colectomy and complications. Next, patients with no lesions gain no benefit in receiving active treatments with potential risks. In treated IBD patients, mucosal healing is associated with a better outcome, with decreased risks of relapse and major surgery. Assessment of mucosal healing may help to characterize the response to treatments and in decisions of optimal strategies. Finally, endoscopy, which allows a direct assessment of severity and extent of mucosal lesions, may thus help in the management of IBD.

References

1. Pineton de Chambrun G, Peyrin-Biroulet L, Lémann M, et al. Clinical implications of mucosal healing for the management of IBD. Nat Rev Gastroenterol Hepatol. 2010;7:15–29.
2. Carbonnel F, Lavergne A, Lémann M, et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. Dig Dis Sci. 1994;39:1550–7.
3. Lichtenstein GR, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2010;16:338–46.
4. Hanauer SB, Sandborn WJ, Dallaire C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: the ASCEND I trial. Can J Gastroenterol. 2007;21:827–34.
5. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; preliminary report on a therapeutic trial. Br Med J. 1954;2:375–8.
6. Paoluzi OA, Pica R, Marcheggiano A, et al. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-ficacy and tolerability in inducing and maintaining remission. Aliment Pharmacol Ther. 2002;16:1751–9.
7. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. Am J Dig Dis. 1966;11:847–57.
8. Daperno M, Sostegni R, Scaglione N, et al. Outcome of a conservative approach in severe ulcerative colitis. Dig Liver Dis. 2004;36:21–8.
9. Modigliani R, Mary JY, Simon JF, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives. Gastroenterology. 1990;98:811–8.
10. Nahon S, Bouhnik Y, Lavergne-Slove A, et al. Colonoscopy accurately predicts the anatomical severity of colonic Crohn's disease attacks: correlation with findings from colectomy specimens. Am J Gastroenterol. 2002;97:3102–7.
11. Allez M, Lemann M, Bonnet J, et al. Long term outcome of patients with active Crohn's disease exhibiting extensive and deep ulcerations at colonoscopy. Am J Gastroenterol. 2002;97:947–53.
12. Mantzaris GJ, Christidou A, Sfakianakis M, et al. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. Inflamm Bowel Dis. 2009;15:375–82.
13. Rutgeerts P, Diamond RH, Bala M, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc. 2006;63:433–42.
14. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008;371:660–7.
15. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99:956–63.
16. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology. 2009;136:441–50.
17. Allez M, Lémann M. Role of endoscopy in predicting the disease course in inflammatory bowel disease. World J Gastroenterol. 2010;16:2626–32.
18. Hanauer SB. Positioning biologic agents in the treatment of Crohn's disease. Inflamm Bowel Dis. 2009;15:1570–82.
19. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362:1383–95.
20. Baert F, Moortgat L, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;138:463–8.
21. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. Am J Gastroenterol. 2005;100:2478–85.

22. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–76.
23. Ferrante M, Vermeire S, Fidder H, et al. Long-term outcome after infliximab for refractory ulcerative colitis. J Crohns Colitis. 2008;2:219–25.
24. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology. 2009;137:1250–60.
25. Carbonnel F, Gargouri D, Lémann M, et al. Predictive factors of outcome of intensive intravenous treatment for attacks of ulcerative colitis. Aliment Pharmacol Ther. 2000;14:273–9.
26. Kobayashi T, Naganuma M, Okamoto S, et al. Rapid endoscopic improvement is important for 1-year avoidance of colectomy but not for the long-term prognosis in cyclosporine A treatment for ulcerative colitis. J Gastroenterol. 2010;45:1129–37.
27. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Thérapeutiques des Affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989;30:983–9.
28. Rutgeerts P, Vermeire S, Van Assche G. What is the role of endoscopy in predicting Crohn's disease relapse or course? Inflamm Bowel Dis. 2008;14(Suppl 2):S183–4.
29. van Assche G, Vermeire S, Rutgeerts P. Mucosal healing and anti TNFs in IBD. Curr Drug Targets. 2010;11:227–33.
30. D'Haens G, Geboes K, Ponette E, et al. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. Gastroenterology. 1997;112:1475–81.
31. Baert FJ, D'Haens GR, Peeters M, et al. Tumor necrosis factor alpha antibody (infliximab) therapy profoundly down-regulates the inflammation in Crohn's ileocolitis. Gastroenterology. 1999;116:22–8.
32. Lémann M, Mary JY, Colombel JF, et al. A randomized, doubleblind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. Gastroenterology. 2005;128:1812–8.
33. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359:1541–9.
34. Schnitzler F, Fidder H, Ferrante M, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis. 2009;15:1295–301.
35. Rutgeerts P, Van Assche G. What is the role of endoscopy in the postoperative management of Crohn’s disease? Inflamm Bowel Dis. 2008;14(Suppl 2):S179–80.

Chapter 2
Current Progress of Endoscopy in Inflammatory Bowel Disease: Colonoscopy

Yutaka Endo and Fumiaki Ueno

Abstract The diagnostic ability of colonoscopy has improved dramatically in the past decade. Recent progress of endoscopy is largely based on the advent and the diffusion of innovative endoscopic technology, such as high-definition endoscopes, image-enhancement modalities, and magnifying endoscopes. Advanced technology has enabled detailed observation of the mucosa and mucosal lesions. Not only at initial evaluation for inflammatory bowel disease, but also during the follow-up period, colonoscopy is widely used in order to assess response to treatment. For detailed endoscopic observation, an excellent quality of bowel cleansing is mandatory. Recent progress of colonoscopy in clinical practice of inflammatory bowel disease is described, with special regards to bowel preparation, advanced endoscopic equipments, detailed endoscopic diagnosis, differential diagnosis, follow-up, and cancer surveillance in IBD in Japan.

Keywords Colonoscopy • High-definition endoscope • Image-enhancement • Bowel preparation • Mucosal healing

2.1 Introduction

Colonoscopy (CS) is essential in the diagnosis of inflammatory bowel disease (IBD). It is useful for establishing initial diagnosis, evaluation of disease extent and activity, monitoring response to treatment, and surveillance of dysplasia and cancer. Current consensus of treatment target in IBD, mucosal healing (MH), can be assessed only by endoscopy. Colonoscopy also has therapeutic potential for intestinal complication, such as stenosis. Recent progress of colonoscopy will be described.

Y. Endo • F. Ueno (✉)
Center for Gastroenterology and Inflammatory Bowel Disease, Ofuna Chuo Hospital, Kamakura, Kanagawa, Japan
e-mail: tiger44@wa2.so-net.ne.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_2

2.2 Bowel Preparation and Additional Cleansing during Colonoscopy

The quality of bowel preparation seems to vary significantly among countries. For detailed observation using modern endoscopic technology, excellent cleansing is always required. In most of the facilities in Japan, polyethylene glycol isotonic electrolyte solution (PEG-ELS) is administered exclusively on the same day of the procedure, not only for patients' convenience but also for higher quality of cleansing, as the time interval between completion of preparation and procedure is critical. Two liters of PEG-ELS are given in the morning on the day of CS, with or without additional solution, depending on the turbidity of the excreted solution as confirmed by trained personnel. Supplemental administration of laxatives the night before is helpful to shorten preparation time, particularly in those with constipation. In our facility, average preparation time is 153 ± 126 min.

As other cleansing agents, isotonic magnesium citrate solution and sodium phosphate tablets are used, mainly for palatability. However, safety and quality of those alternative methods are inferior to PEG-ELS. Recently, hypertonic PEG-ELS with ascorbic acid (MoviPrep) has been widely used, as a similarly good quality of bowel preparation can be attained with reduced volume and shortened time. Approximately a quarter of patients can accomplish bowel preparation within 2 h, and two-thirds within 3 h [1]. Inspection of the stool passage by a trained endoscopy assistant is very helpful in ensuring good preparation.

During endoscopic observation, residual feces and adherent mucus may prevent adequate observation, and can be rinsed and removed from the observation target by injection of water through the accessory channel. Automated injection equipment is available in the market, and has gained popularity in Japan. Meticulous cleansing by water injection is frequently required for detailed observation of the target lesion.

2.3 Recent Advances in Endoscopic Equipment

In the majority of endoscopy units in Japan, high-definition endoscopes are used in daily clinical practice. Furthermore, magnifying endoscopy and image-enhancement endoscopy (IEE), such as chromoendoscopy, narrow-band imaging (NBI) and blue laser imaging (BLI) are available in most institutions in Japan. Chromoendoscopy with spraying 0.08–0.2% indigo carmine can visualize slight convexity and concavity of the target lesion, and has been widely used in most institutions since the 1970s, mainly for the diagnosis of neoplasms. This is frequently used for cancer surveillance in ulcerative colitis (UC) to visualize the lesions detected by regular observation more precisely. Pan-chromoendoscopy with methylene blue is not commonly used in Japan.

NBI uses narrow-band light of 415 and 540 nm for absorbance of hemoglobin, and BLI uses laser light 410 nm as the irradiation light. Both modalities improve the

visibility of blood vessels, and are originally and mainly used for the diagnosis of neoplasia [2]. NBI is often used in accordance with magnifying observation in Japan. It enables observation of tumor blood vessels and surface pattern under magnifying observation of the lesion up to 80-fold, and is utilized for diagnosis of neoplasia (neoplasia vs non-neoplasia, depth of invasion) [3]. Although NBI is also used in cancer surveillance of UC, it does not contribute to the detection of cancer/dysplasia [4].

During the quiescent phase of UC, magnifying observation under a good bowel cleansing delineates the boundary between neoplasia and non-neoplastic mucosa. Sporadic cancer usually shows a distinct boundary, and this finding may assist in differentiating from colitic cancer (Figs. 2.1 and 2.2). There is no evidence for the usefulness of NBI magnifying observation. A multi-center prospective study using second-generation NBI by the Research Group of the Ministry of Health in Japan is in progress, and the results are awaited.

NBI magnifying observation is also useful for the evaluation of MH in UC. Mucus adhesion often mimics erosion on normal observation, but presence or absence of epithelial defects is distinctly visible on NBI magnifying observation (Fig. 2.3).

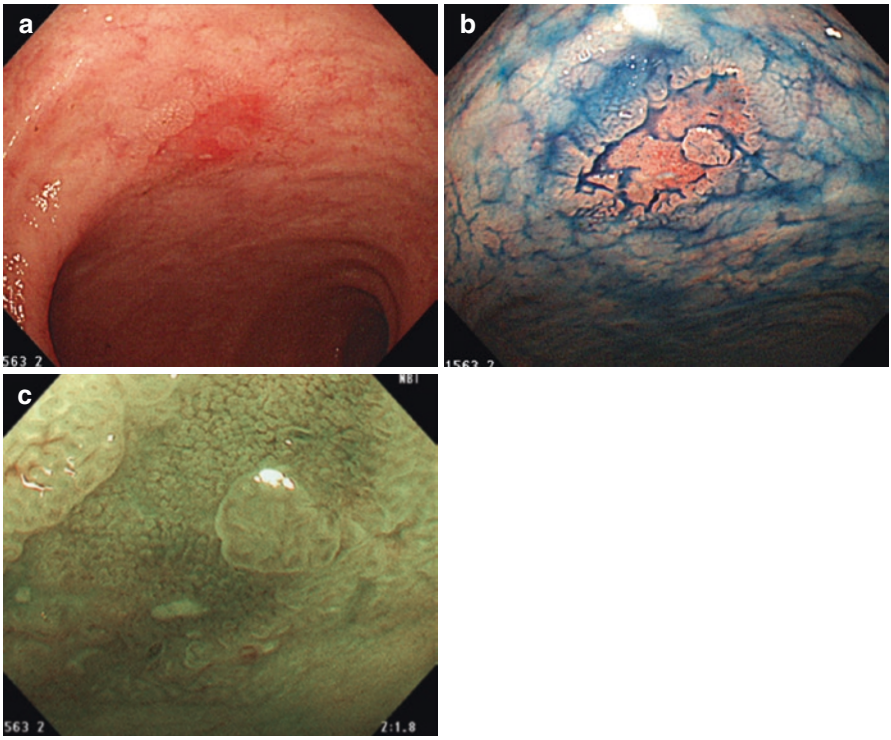


Fig. 2.1 Sporadic cancer of the colon. High-definition white-light endoscopy (**a**), chromoendoscopy with indigo carmine spraying on the target lesion (**b**), and corresponding narrow-band imaging with magnification (**c**). Boundary of the lesion is distinctly visualized

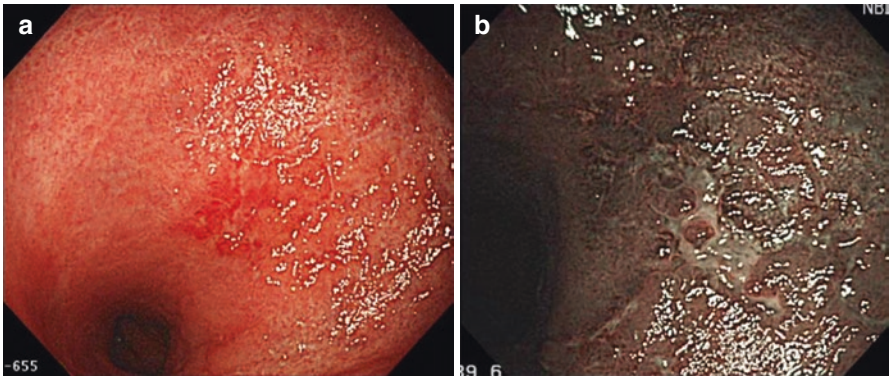


Fig. 2.2 Dysplasia in quiescent ulcerative colitis. High-definition white-light endoscopy (**a**), and corresponding narrow-band imaging (**b**). The margin of the lesion is less distinct, compared to sporadic cancer shown in Fig. 2.1

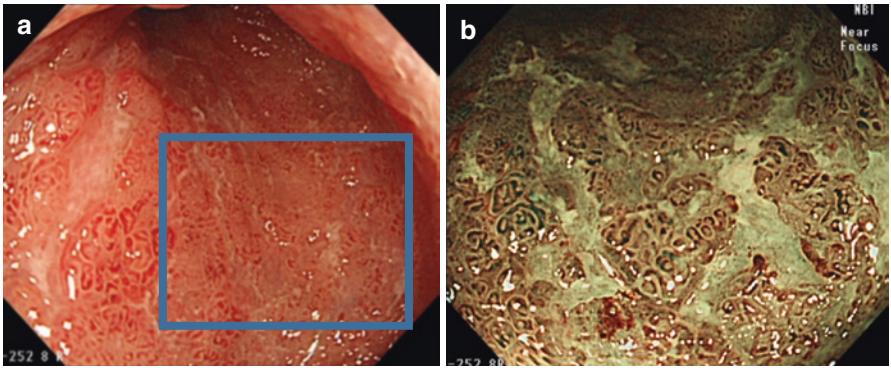


Fig. 2.3 High-definition white-light endoscopy (**a**) in a case of ulcerative colitis. *White area in the square* in (**a**) mimics mucus adhesion over the mucosa. Narrow-band imaging with magnifying observation of the corresponding area (**b**) shows mucosal defect clearly

Both CS and MRI are diagnostic modalities of choice for the evaluation of colonic lesions of Crohn's disease (CD) [5]. Among the problems of CS in CD is the difficulty of inserting a scope in the presence of adhesion or stenosis [6]. Availability of a narrow-caliber colonoscope with passive bending mechanism and balloon-assisted enteroscope has reduced this problem. A recently developed colonoscope, Olympus PCF-PQ260L (Fig. 2.4), has outside diameter of 9.2 mm and effective length of 1680 mm, and provides passive bending mechanisms in addition to the usual manipulative bending of the scope tip. It produces less discomfort, and patients' acceptability for future examination is higher [7].

The balloon-assisted enteroscope can shorten the intestinal tract by fixing the intestine with a balloon, and it can be easily inserted, particularly in otherwise difficult cases. In our experience with cases with failure of cecal insertion by regular

Fig. 2.4 Narrow-caliber colonoscope with passive bending mechanism (Olympus PCF-PQ260L)

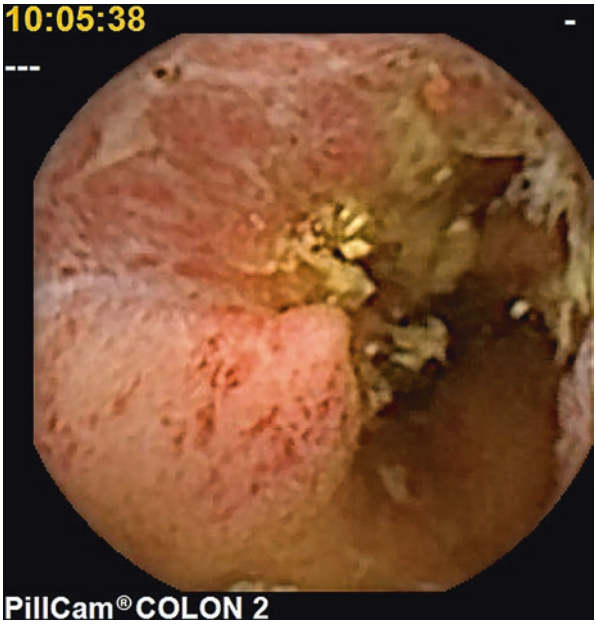


Fig. 2.5 An image of colon capsule endoscopy in the ascending colon of a patient with ulcerative colitis

colonoscopes, 94.8% were successful by PCF-PQ260L (36/38), and 100% by double balloon-assisted enteroscopes (EN-450T5, EC-450BI5).

In severely active UC, risk of perforation or exacerbation associated with endoscopic insertion is known. As a less invasive modality, in addition to ultrasound, CT-, and MR-colonography, the use of the colon capsule endoscope (CCE) has been attempted [8]. CCE can inspect the entire colon without producing discomfort (Fig. 2.5). A multi-center study to evaluate its efficacy and safety is undergoing as a research project of the Research Group of the Ministry of Health, Labor and Welfare of Japan.

2.4 Diagnosis of IBD and Differential Diagnosis

2.4.1 Ulcerative Colitis

Diagnosis of IBD should not entirely depend on endoscopy. Comprehensive diagnostic approach, including history, physical examination, stool bacteriology, and histopathological finding, is necessary.

Although there is some controversy about worsening of UC by bowel preparation for colonoscopy, poor preparation precludes observation of diffuse inflammation and submucosal capillary network, discrimination of hyperemia from erosion, and estimation of the depth of ulcers. At least for initial diagnosis, evaluation of mucosal healing, and cancer surveillance, excellent bowel preparation by whole gut lavage is desirable.

The typical endoscopic image of UC is continuous and diffuse mucosal roughness or fine granularity extending from the rectum toward proximal portion, with hyperemia, edema, exudation, friability, erosions, ulcers, and inflammatory polyps. For hyperemia, edema and friability, inter-observer difference is higher, while it is low for vascular network, erosions, and ulcer. Not infrequently, skipped lesion is observed in the orifice of the appendix.

Moreover, in the early phase after the onset or a longstanding case particularly on treatment, rectal sparing and discontinuity of inflammation are occasionally encountered. Even without endoscopic inflammation, histological inflammation is frequently observed. Therefore, biopsy from endoscopically inactive mucosa including the rectum occasionally contributes to the confirmation of continuity of inflammation. According to the distribution of inflammation, each case of UC can be classified to proctitis, (distal colitis), left-sided colitis, extensive colitis, and right-sided or segmental colitis. This is important for selection of topical therapy. Although there are several different endoscopic severity indices available, most Japanese endoscopists apply the endoscopic severity classification of the Ministry of Health, Labor and Welfare in Japan, as well as Mayo endoscopic sub-scores.

In the differential diagnosis of UC, radiation enteritis, drug-induced enteritis, ischemic colitis, infectious enterocolitis (salmonellosis, *Campylobacter* infection, *E. coli* infection, tuberculosis, amebic dysentery, cytomegalovirus infection, etc.), Crohn's colitis, and Behcet's disease should be considered. Among them, the most important is infectious colitis, in which inflammation is not entirely diffuse or continuous, but often skipped. Bacterial cultures of stool, suctioned fluid in the colonic lumen, and biopsied tissue specimen during colonoscopy all contribute to accurate diagnosis. *Campylobacter* enterocolitis sometimes exhibits continuous inflammation and mimics UC, but in 80% of cases of the former, ulcer is noted on the ileocecal valve, and this finding is helpful for differential diagnosis. Diffuseness and continuity of inflammation is also important to differentiate Crohn's colitis.

Amebic dysentery is rather important disease in Japan, and even more in tropical countries. There were 1582 cases of *Entamoeba histolytica* infection (0.79/100,000) in 2012–2013, 84.3% of which were intestinal amebiasis (National Institute of Infectious Diseases website). Endoscopic findings include erosions and ulcers with

adhered white coating mixed with blood, showing dirty appearance. The cecum and the rectum are predominantly involved. Diagnosis is established by identifying amoeba trophozoites in stool or biopsy specimens, as well as serum antibody.

Since many UC patients receive immunosuppressive therapy, concomitant cytomegalovirus (CMV) infection should be in mind. The typical endoscopic finding is a discrete deep ulcer. Diagnosis is established by blood CMV antigen and biopsy (nuclear inclusions, immunostaining, PCR)

2.4.2 Crohn's Disease

CD results in a full-thickness inflammation in all of the digestive tract. Predominant sites are the terminal ileum and the cecum. Ideally, the entire digestive tract should be investigated at the time of initial evaluation. The esophagus, the stomach, and the duodenum are inspected by upper gastrointestinal endoscopy, and the terminal ileum and the anus should be inspected during colonoscopy. Field of observation for the ileal lesions by colonoscopy is limited. Concomitant use of small intestinal radiography, CT/MR enterography, balloon-assisted enteroscopy, and video capsule endoscopy are often required. Small intestinal radiography, CT/MR enterography, and video capsule endoscopy are capable of observing the entire small intestine. CT and MR can evaluate inflammation of the intestinal wall and the adjacent area. Endoscopy has advantage of direct visualization, and is superior for the observation of fine lesions such as erosions and aphthous ulcers [9]. Balloon-assisted enteroscopy in more popular in facilities in Japan, compared to those in Europe and North America.

Longitudinal or serpiginous ulcers and cobblestone appearance are typical endoscopic findings of CD (Fig. 2.6a). Presence of non-caseating granuloma in

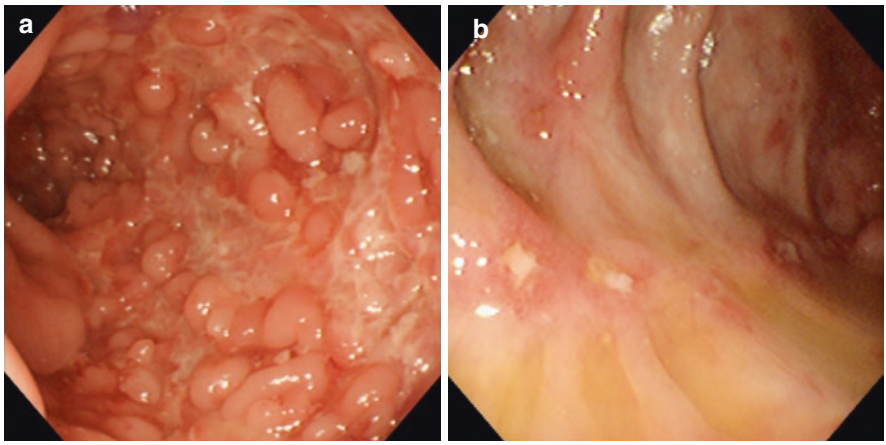


Fig. 2.6 Endoscopic finding of CD. Irregular, serpiginous ulcers and cobblestone appearance are noted (**a**). Aphthous ulcers are typically distributed longitudinally (**b**)

the biopsy specimen may assure the diagnosis of CD. Irregular small ulcers, aphthous ulcers, erosions are also observed. Aphthous ulcers characteristically present in longitudinal distribution (Fig. 2.6b). In upper gastrointestinal endoscopy, bamboo-like notches are sometimes observed, interposing a normal mucosa (skip lesion).

As an important differential diagnosis in Japan, intestinal tuberculosis, intestinal Behcet's disease, and UC are to be included. The prevalence of tuberculosis is 18.2 per 100,000 population in Japan, and 23,231 patients with Behcet's disease are enrolled in 2012, and this is much higher than in Western countries. The ileocecal region is frequently involved in both tuberculosis and Behcet's disease.

Ulcers in tuberculosis are usually distributed circularly, often distributed on the opposite side of the mesenteric attachment in the ileum, whereas ulcers in CD are longitudinal and distributed to the side of the mesenteric attachment. The typical lesion of intestinal Behcet's disease is a discrete deep ulcer with clear margin. Various forms of ulcer may be observed throughout the digestive tract in atypical cases. Diagnosis of tuberculosis is established with histological proof, culture, skin test, and blood tests. Diagnosis of Behcet's disease is usually established by the involvement of other organs, such as the eyes, the skin, and the central nervous system, but it is known that intestinal Behcet's disease often lacks ocular involvement.

Differentiation of colonic CD and UC are often difficult, particularly when longitudinal ulcer is present. In detailed observation, however, longitudinal UC ulcer accompanies inflammation in the surrounding mucosa, while the CD ulcer is more distinct (Fig. 2.7). If discrimination is difficult, diagnosis is left as unclassified IBD (IBD-unclassified). Follow-up observation may show progress of the lesion to the continuity in UC, while the lesion remains skipped or developing stenosis in CD.

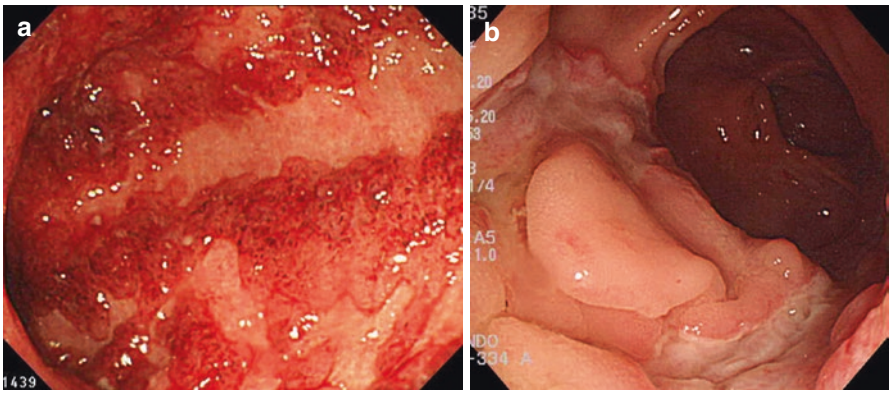


Fig. 2.7 Longitudinal ulcers in IBD. The mucosa surrounding longitudinal ulcer shows active inflammation in UC (**a**), while the adjacent mucosa is relatively intact in CD (**b**)

2.5 Colonoscopic Follow Up

2.5.1 Monitoring of Ulcerative Colitis

Endoscopic evaluation of therapeutic effect is carried out in many facilities, with a usual interval of 1–3 years. Interval of examination is not deliberately scheduled, but is individualized depending on severity, tendency to relapse, therapeutic implication, and preference of the patient.

Endoscopic observation may detect inflammation before clinical relapse, and prompt modification of the treatment may prevent clinical relapse. Patients who achieve mucosal healing (MH) require less hospitalization and surgery, and can maintain higher quality of life. MH has been deliberately defined as Mayo endoscopic sub-score 0 or 1 [10]. Since the relapse rate between the Mayo 0 and 1 is significantly different [11], many adopt Mayo 0 as MH in Japan. To differentiate Mayo 0 and 1, excellent bowel preparation is required to observe mucosal hyperemia, friability, and vascular network, and magnifying observation with NBI is occasionally useful (Fig. 2.8).

Currently in Japan, fecal calprotectin and immunological fecal occult blood test (FIT) are not approved by health insurance for clinical use in IBD. Although indication of CS in the follow-up of IBD may be less required by wide application of biomarkers, confirmation of MH by CS remains valuable for modification of treatment and for estimation of long-term prognosis after clinical remission.

2.5.2 Monitoring of Crohn's Disease

MH of CD is defined as a state where there is no ulcer. The aim of endoscopic follow-up in CD is to determine adequate timing to modify treatment. Although top-down approach is advocated by some investigators [12], it is not approved

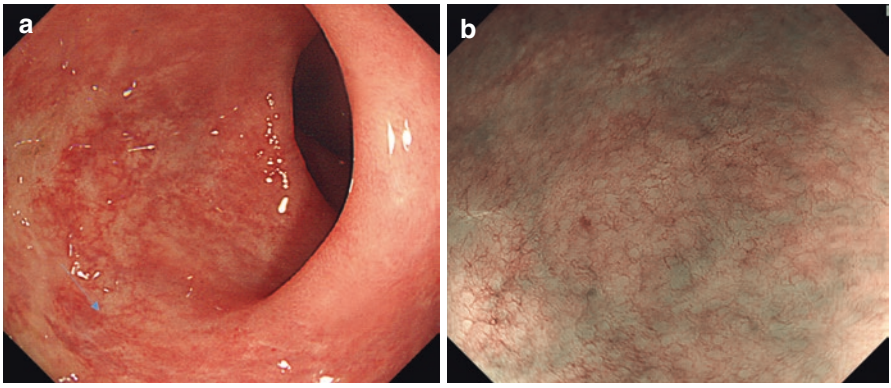


Fig. 2.8 Endoscopic observation of mucosal healing. High-definition white-light endoscopy (**a**). Corresponding narrow-band imaging with magnification (**b**) reveals normal surface pattern with regeneration of capillaries

by health insurance in Japan. Accelerated step-up approach is adopted by many centers for IBD in Japan. Endoscopic evaluation is essential for the judgment of appropriate use of biologic agents in clinically quiescent cases. Also, endoscopic evaluation may predict long-term outcome of patients with quiescent CD [13].

In Japan, however, not many facilities have a scheduled endoscopic follow-up program, and endoscopic indices, such as CDEAI [14] and SES-CD [15], are not regularly utilized in clinical practice. In many facilities, the most significant lesion at the time of initial evaluation will be followed endoscopically for confirmation of MH or for modification of treatment. If stenotic lesion is identified, endoscopic balloon dilatation is applied.

2.6 Cancer Surveillance

A report from Japan indicates incidence of cancer complicated with UC is 5% in 10 years, and more than 10% in 20 years. Annual colonoscopic surveillance is suggested 7 years after the onset of extensive and left-sided UC. High-definition endoscopes are used in most facilities, and magnifying endoscopes are also used by many. Dysplasia- and cancer-related UC is a flat lesion with minor discoloration, hyperemia, or fading (Figs. 2.1 and 2.2). Detailed observation is difficult in the presence of active disease, and surveillance colonoscopy should be performed during remission. If the lesion is suspected, chromoendoscopy with indigo carmine spraying to highlight uneven surface is helpful (Fig. 2.1) [16]. Indigo carmine has been widely used in Japan since the 1970s for the diagnosis of neoplasia of the stomach and the colon. Pan-chromoendoscopy with methylene blue is not popular in Japan.

Method of surveillance colonoscopy has become controversial between traditional step (or random) biopsy (four biopsy specimens for every 10 cm, or a total of 33 or more biopsy specimens) and target biopsy using newer equipment. A recent report of multicenter prospective study in Japan revealed no significant difference between step and target biopsy for the detection of dysplasia, and therefore, target biopsy is preferred at many facilities in Japan. Biopsy of the mucosa surrounding the target lesion in addition to biopsy of the lesion may facilitate histopathological diagnosis between sporadic and UC-associated lesions [17].

Image-enhancement endoscopes, such as NBI, AFI, and FICE have also been used in cancer surveillance. Endoscopic diagnosis with NBI observation does not contribute to detection at normal magnification, but the margin is distinctively visualized with a combination of NBI and magnifying endoscopy, and this may contribute to the discrimination of UC-related dysplasia/cancer and sporadic adenoma/cancer. The lesion is clearly demarcated in sporadic lesions, while demarcation is somewhat obscure in UC-related lesions.

2.7 Summary

Despite the advances in other diagnostic imaging modalities, colonoscopy is essential in diagnosis and treatment of IBD. Since the current therapeutic goal of IBD is mucosal healing, the scopes and image-enhancement method should be selected in accordance with the purpose of endoscopic procedure. Furthermore, appropriate bowel preparation is mandatory to have full benefit of newer equipment for accurate endoscopic diagnosis.

References

1. Ueno F, Kudo S, Igarashi M, Endo Y, Inoue N. A new, rapid, effective, tolerable, and safe preparation suitable at any time of the day: a multicenter study. Am J Gastroenterol. 2012;107(suppl1):S764.
2. Hayashi N, Tanaka S, Hewett DG, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. Gastrointest Endosc. 2013;78:625–32. doi:10.1016/j.gie.2013.04.185.
3. Sano Y, Tanaka S, Kudo SE, et al. Narrow-band imaging (NBI) magnifying endoscopic classification of colorectal tumors proposed by the Japan NBI Expert Team. Dig Endosc. 2016;28:526–33.
4. Laine L, Kaltenbach T, Barkun A, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology. 2015;148:639–51.
5. Pariente B, Mary J-Y, Danese S, et al. Development of the Lémann Index to assess digestive tract damage in patients with Crohn's disease. Gastroenterology. 2015;148:52–63.
6. Morimoto K, Watanabe K, Noguchi A, et al. Clinical impact of ultrathin colonoscopy for Crohn's disease patients with strictures. J Gastroenterol Hepatol. 2015;30(Suppl 1):66–70.
7. Ogawa T, Ohda Y, Nagase K, et al. Evaluation of discomfort during colonoscopy with conventional and ultrathin colonoscopes in ulcerative colitis patients. Dig Endosc. 2015;27:99–105.
8. Usui S, Hosoe N, Matsuoka K, et al. Modified bowel preparation regimen for use in second-generation colon capsule endoscopy in patients with ulcerative colitis. Dig Endosc. 2014;26:665–72.
9. Yamagami H, Watanabe K, et al. Small bowel endoscopy in inflammatory bowel disease. Clin Endosc. 2013;46:321–6.
10. Mazzuoli S, Guglielmi FW, Antonelli E, et al. Definition and evaluation of mucosal healing in clinical practice. Dig Liver Dis. 2013;45:969–77.
11. Barreiro-de Acosta M, Vallejo N, de la Iglesia D, et al. Evaluation of the risk of relapse in ulcerative colitis according to the degree of mucosal healing (Mayo 0 vs 1): a longitudinal cohort study. J Crohns Colitis. 2016;10:13–9.
12. Ghazi LJ, Patil SA. Step up versus early biologic therapy for Crohn's disease in clinical practice. Inflamm Bowel Dis. 2013;19:1397–403.
13. Nagamuna M, Hisamatsu T, Matsuoka K, et al. Endoscopic severity predicts long-term prognosis in Crohn's disease patients with clinical remission. Digestion. 2016;93:66–71.
14. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Gut. 1989;30:983–9.
15. Daperno M, D'Haens G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60:505–12.

16. Matsumoto T, Nakamura S, Jo Y, et al. Chromoscopy might improve diagnostic accuracy in cancer surveillance for ulcerative colitis. Am J Gastroenterol. 2003;98:1827–33.
17. Watanabe T, Ajioka Y, Mitsuyama K, et al. Comparison of targeted vs random biopsies for surveillance of ulcerative colitis associated colorectal cancer. Gastroenterology. 2016;151: 1122–30. doi:10.1053/j.gastro.2016.08.002.

Chapter 3
Current Progress of Endoscopy in Inflammatory Bowel Disease: Balloon-Assisted Enteroscopy

Tomonori Yano and Hironori Yamamoto

Abstract Balloon-assisted endoscopy, an endoscopic method that, through use of an overtube with a balloon, prevents bowel deflection during endoscope insertion, has allowed endoscopic evaluation and treatment of IBD lesions deep inside the small bowel. The technique is useful in each phase of diagnosis and follow-up of IBD, for balloon dilation of strictures, preoperative evaluation, and postoperative follow-up, but is limited by its inability to be used for evaluating the inner part of deep ulcers or strictures.

Keywords Balloon-assisted endoscopy • Double-balloon enteroscopy • Single-balloon enteroscopy • Spiral enteroscopy

3.1 Small Bowel Endoscopy in the Twentieth Century

The small bowel consists of three parts: the duodenum, jejunum, and ileum. While the duodenum is fixed to the retroperitoneum, the jejunum and ileum are connected to the mesenterium; these are scarcely fixed, and bend intricately within the peritoneal cavity. To reach the small bowel from outside the body via the gastrointestinal tract, an endoscope must pass through the esophagus and the stomach from the mouth or through the large bowel from the anus. These anatomical characteristics make endoscopy of the small bowel technically difficult.

To insert a conventional endoscope into the bending and unfixed intestine, manipulative force is consumed by the extension of bending parts and is hardly transmitted to the tip of the endoscope. Therefore, push enteroscopy with a long,

T. Yano • H. Yamamoto (✉)
Division of Gastroenterology, Department of Internal Medicine, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan
e-mail: ireef@jichi.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_3

thin endoscope has limited insertion capability, reaching only 60–80 cm anal side from the ligament of Treitz. Insertion deep inside the small bowel is impossible.

Successful observation of the entire small bowel by endoscopy in the past was recorded using the ropeway method and sonde method. In the ropeway method, an intestinal string is inserted orally (or nasally) and discharged from the anus after 2 days, is passed into the forceps channel of the endoscope, and the endoscope is inserted by pulling the string. Because the forceps channel is blocked by the intestinal string, intervention is impossible. The sonde method involves trans-nasal insertion of a soft, thin endoscope [1] without a forceps channel or angle mechanism, which is advanced over a long period by peristalsis of the intestine to the large bowel. Observation is done while the endoscope is being pulled out, but as it provides no forceps channel, intervention is impossible and operation of tip of the scope is also impossible.

Consequently, the ropeway method and sonde method have not been widely used. In cases that require endoscopic observation and intervention deep inside the small bowel, which are difficult to reach with an endoscope using the push method, intraoperative methods using laparotomy have been selected.

3.2 New Generation of Small-Bowel Endoscopy

In the twenty-first century, with the invention of new generations of small-bowel endoscopy, capsule endoscopy, and double-balloon endoscopy [2], diagnosis and treatment of small-bowel disease has greatly advanced.

3.2.1 Double-Balloon Endoscopy (DBE)

The real cause of the difficulty of inserting an endoscope deep inside the small bowel is that operation of a pushing scope is absorbed by deflection of the bending intestine, preventing manipulative force from being transmitted to the tip of the scope. DBE makes the transmission of hand operations to the tip of the endoscope possible, maintaining operability deep inside the small bowel, by preventing bowel deflection using an overtube with a balloon (Fig. 3.1). During DBE, the overtube is advanced after advancing the scope as far as possible; a balloon is also fitted to the tip of the scope to prevent it from pulling out when the overtube is advanced (Fig. 3.2). The endoscope is inserted deep into the small bowel by advancing the scope and the overtube alternately. By advancing the overtube, which, by balloon dilation, holds the intestine in place at the tip of overtube, and by retracting the overtube together with the scope, it can prepare the shape of the distal bowel for insertion and also pleat the proximal bowel over the overtube, retracting it. With this effect, a length of small bowel longer than the working length of the endoscope can be examined.

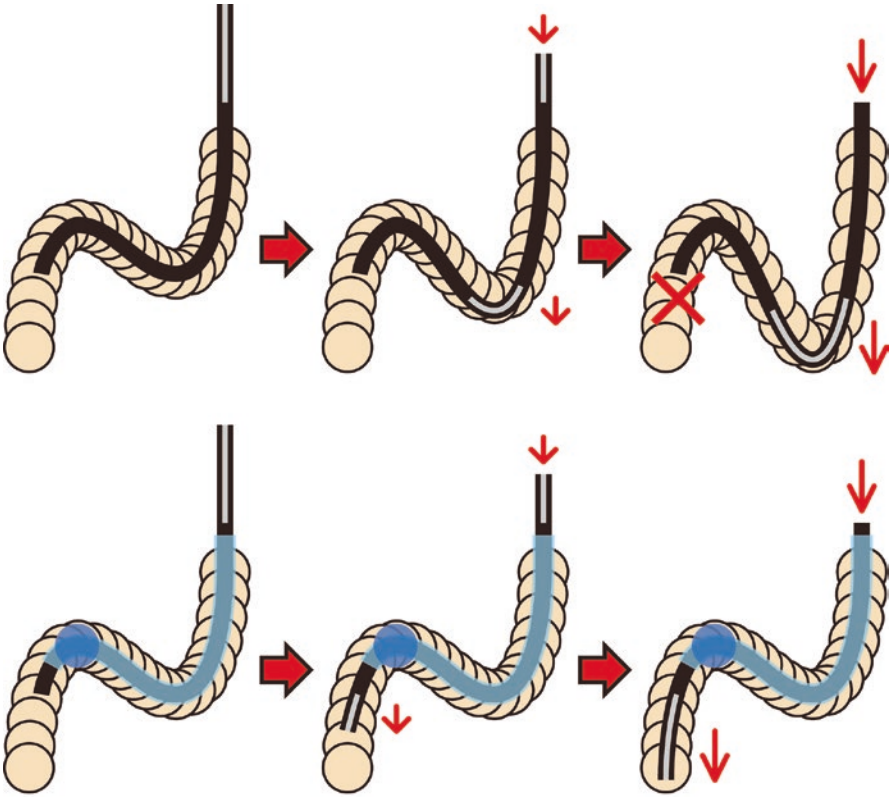


Fig. 3.1 Basic principle of balloon-assisted enteroscopy

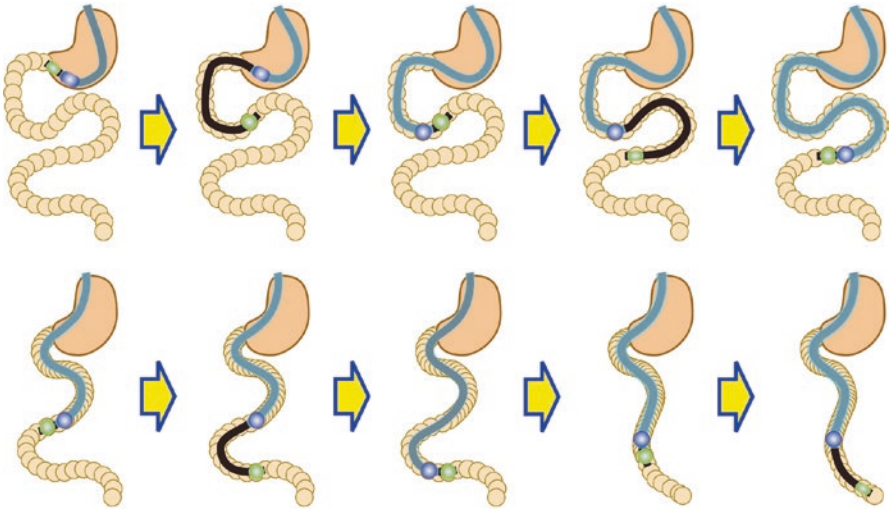


Fig. 3.2 Sequential maneuvers of anterograde insertion of double-balloon endoscopy

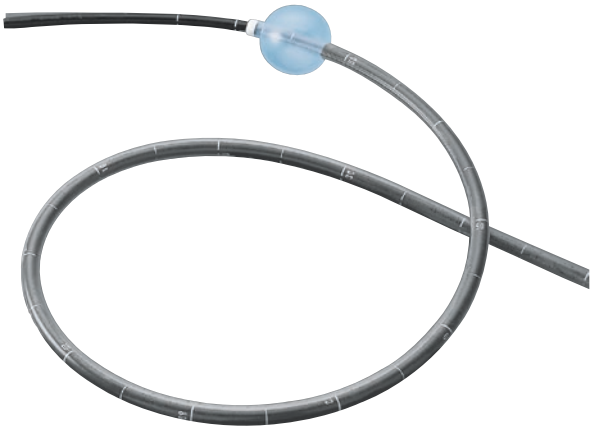


Fig. 3.3 Single-balloon enteroscopy

3.2.2 Single-Balloon Endoscopy (SBE)

SBE [3] (Fig. 3.3) is a simplified DBE system that omits the balloon at the tip of the scope. As it utilizes a similar overtube with a balloon to that in DBE, it can reach deep inside the small bowel while maintaining operability. As attachment of a tip balloon to the scope is unnecessary, SBE has the advantage of simpler and shorter preparation. However, as the scope tends to be pulled out while advancing the overtube and the holding force during retraction is weaker, SBE is reported to be inferior in terms of success rate of observation of the entire small bowel compared to DBE [4, 5]. Additionally, in selective contrast study as described below, the reflux of contrast agent cannot be prevented in SBE because of the lack of the balloon at the tip of the endoscope. Balloon-assisted endoscopy (BAE; balloon-assisted endoscopy) is a unifying terminology referring to both DBE and SBE.

3.2.3 Spiral Endoscopy (SE)

In addition to BAE, SE [6] has been invented as another endoscope that can reach deep inside the small bowel. SE is a small-bowel endoscopy system (Fig. 3.4) comprising an overtube with a screw-like spiral projection at the distal end (Discovery Small Bowel: Spirus Medical, Inc.) and an endoscope fitted to the size of the overtube (inner diameter 9.8 mm, total length 118 cm). The spiral projection on the tip of the overtube is hooked into the folds of the small bowel and, by simple rotation of the overtube, the bowel is pleated over it. Once the tip of the overtube passes the Treitz ligament and is advanced into the jejunum, an assistant can advance the endoscope simply by rotating the overtube, without having to operate the body of the endoscope back and forth.

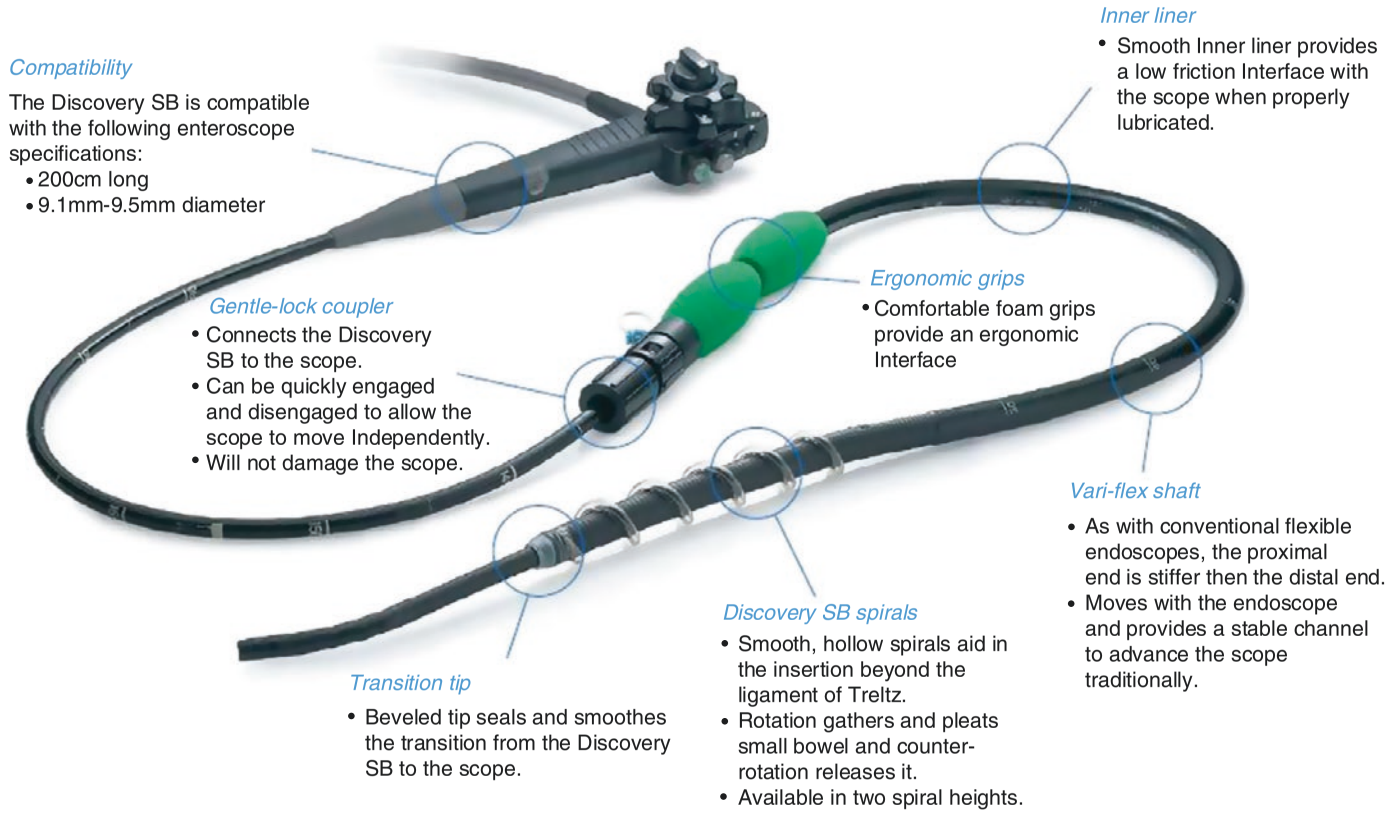


Fig. 3.4 Spiral enteroscopy

There are a few studies that directly compare BAE and SE [7–9]. While DBE is capable of inserting the endoscope deeper, the procedural time is shorter for SE; there is no significant difference in diagnosis rate and treatment rate for both systems. However, in a randomized comparative study (Messer/2012) that compared the success rate of observation of the entire small bowel, the reported observation rate among 13 subjects without previous surgery of the large or small bowel was 8% for the SE group and 92% for DBE group, demonstrating a significant difference. Additionally, for transanal insertion, SE's capability of being inserted deep inside the small bowel is poor and its usefulness is limited for diagnosis and treatment of IBD, for which most lesions are in the ileum.

3.2.4 Usefulness of Insufflation of Carbon Dioxide Gas

When a BAE pleats the intestine over the overtube with a balloon and shortens it, gas remaining inside the intestine may interrupt the retraction operation, much like an air spring. Recently, the usefulness of insufflation of carbon dioxide instead of air during endoscopy has been reported and become widely used, mainly in colonoscopy. Carbon dioxide gas tends to be absorbed by water and into the body at 100 times or more the speed of air; it is also excreted in exhaled air. This profile is useful particularly for BAE, as the tendency for carbon dioxide to leave the intestine more quickly means that it tends not to interrupt the retraction operation. Insufflation of carbon dioxide gas is now an essential part of BAE operation.

3.2.5 Usefulness of Selective Contrast Study

Selective contrast study, in which water-soluble contrast is injected from the forceps channel of the endoscope, is an effective procedure for examining areas that are unreachable by endoscope. However, particularly in IBD cases, deformation and stricture of the intestine can prevent the injected contrast from flowing ahead, frequently rendering evaluation impossible with a standard endoscope. Because dilation of the balloon at the tip of the scope can suppress the reflux of contrast agent, DBE can make contrast examination of the deep small bowel possible, even when there is deformation or stricture of the intestine. Information obtained from examination with water-soluble contrast is limited compared with contrast enteroclysis with barium, but if carbon dioxide gas is used for insufflation and the contrast agent is injected slowly after aspiration of remaining gas and then the contrast imaging is taken, sufficient information can be obtained to evaluate the presence and absence of stricture.

3.3 Advantages of BAE in Diagnosis and Treatment of IBD

3.3.1 Diagnostic Phase

BAE can reach deep inside the small bowel relatively less invasively than conventional methods and also enables detailed observation of morphology, including the color hue of small bowel mucosa, in real time. Flushing of the mucosal surface is available if necessary with BAE, and detailed observation of villi using dye spray or underwater observation is also possible. Additionally, BAE permits histopathological and bacteriological examination via biopsy through the forceps channel.

For the diagnosis of IBD, it is essential to obtain information about the presence/absence of small-bowel lesions, morphology, the distribution of lesions, and the extent of disease. In particular, information on whether the small bowel lesions are on the mesenteric side (characteristic of Crohn's disease) or antimesenteric side is essential for differential diagnosis of IBD; this information is obtainable from the insertion form of endoscopy and location on the screen in BAE [10].

BAE enables direct observation of fine lesions that are difficult to detect by other modalities, and can detect abnormalities even in early phases of disease development when typical morphological changes are incomplete. Even if no definitive diagnosis is made due to insufficient findings in the first examination, the relatively low invasiveness of the examination allows for easy re-examination at a later date. Early diagnosis is expected to enable improvement of long-term prognosis through early intervention.

3.3.2 Follow-Up Phase

Medical treatment of IBD can be divided into remission-induction therapy and remission-maintenance therapy. Even if clinical remission is achieved with improvement of clinical symptoms from remission-induction therapy, direct observation with endoscopy is needed to evaluate whether mucosal healing has been attained. Examination is performed after completion of oral steroids and early therapy phase of biological drugs, and 1–2 months after the transition from remission-induction therapy to remission-maintenance therapy. From the results, a decision is made about whether to continue or intensify the current therapy. In the short term after remission-induction, particular attention should be paid to the fact that Crohn's disease causes transmural inflammation and deep ulcers, and that the strength of intestinal wall may have not fully improved even if superficial mucosa at the site of ulcer have healed. Additionally, these sites are often complicated by deformation of the intestine and partial retraction of the mesenterium, which, as a result of concentrated pressure, can be perforated if the endoscope is pushed too forcefully.

In the phase of remission-maintenance therapy, it is important in the follow-up of IBD to evaluate whether the current therapy is sufficient. In many cases, an ulcer can remain even as clinical symptoms and the inflammatory reaction are relieved, and examination is necessary to confirm mucosal healing within 1 year after remission-induction. Thereafter, it is recommended that disease condition be assessed by regular examination and therapy adjustment, according to the disease condition for each case.

3.3.3 Endoscopic Balloon Dilation

With deep ulcer healing, the intestine becomes deformed in the process of healing with scar formation, causing a narrow lumen. Mild narrowing is not problematic, but since the inner diameter of the small bowel is originally small, narrowing tends to cause stricture. Before BAE, only surgical therapy was indicated for cases of stricture deep inside the small bowel that were difficult to reach with a conventional endoscope. BAE, on the other hand, has made it possible to perform endoscopic balloon dilation (EBD).

Resection of stricture by surgical therapy does not bring complete cure of the IBD itself. If an ulcer develops without maintenance of mucosal healing, stricture may recur after repeated remission and relapse. Repeated partial resection of the small bowel shortens the residual small bowel and, in the worst cases, causes short-bowel syndrome. Therapy by EBD does not bring about short small bowel, and repeated therapy for re-stricture does not cause short-bowel syndrome.

In cases of multiple strictures across a wide length of the small bowel, surgical resection can result in long portions of intestine being resected. For such multiple strictures, the scope is passed through the stricture after EBD and EBD is repeated for the next stricture at a deeper site. It is not uncommon that, even if EBD is executed to a diameter larger than the outer diameter of the scope, the scope is still difficult to pass through the stricture. If a hood with a smaller diameter tip (Fig. 3.5) [11] is attached to the distal end of the scope, the scope can pass the stricture more easily after EBD, making EBD for all strictures easier even in cases of multiple strictures.

Maintaining deep remission status without re-stricture by medical treatment is ideal, but in the case of recurrence, EBD is recommended as a maintenance therapy. At the regular assessment of disease condition by BAE, EBD is recommended for strictures that the scope cannot pass, even if symptoms of stricture have not been developed.

3.3.4 Preoperative Close Examination Phase

Even if EBD for small-bowel stricture is technically successful, surgical treatment may be needed in cases where the symptoms of stricture do not improve, stricture quickly recurs, or internal fistula occur as a result of problems related to stricture length or intestinal deformation. BAE as a preoperative examination enables specific

Fig. 3.5 Calibrated, small-caliber tip, transparent hood

identification of the site of ulcers, scars, fistulas, and strictures, marking by tattooing, and mapping. This map provides preoperative information about the resection site (X cm anal side from pylorus, and Y cm oral side from the ileocecal valve), making it possible to predict the residual length of postoperative small bowel.

3.3.5 Postoperative Follow-Up (Kono-S Anastomosis is Recommended instead of Functional End-to-End Anastomosis)

If medical treatment is insufficient after surgery, IBD may relapse. It tends to relapse particularly around the intestinal anastomosis site, and often causes stricture. BAE enables direct observation of the anastomosis site and early detection of relapse, assisting any decisions about the necessity of therapy intensification.

However, functional end-to-end anastomosis, which is used widely for ileocecal resection or partial resection of the small bowel, not only causes re-stricture but makes it difficult to pass the scope of BAE through the anastomosis site, as the lumen is folded like a hairpin turn. Kono-S anastomosis, which has recently been reported as an anastomosis method with less re-stricture [12], and for which insertion of a BAE does not become difficult, is expected to be used more widely in the future.

3.3.6 Limitations of BAE

BAE is inserted orally, from the anus, or from a stoma and can reach deep inside the small bowel. However, its reach is limited in cases of deep ulcers with risk of perforation, cases of stricture that the scope cannot pass, and cases where insertion is

difficult due to deformation or adhesion of the intestine. For the unreachable range of the scope, evaluation by the aforementioned selective contrast study should be performed, but if this is insufficient, BAE by the opposite insertion route should also be examined.

References

1. Tada M, Shimizu S, Kawai K. A new transnasal sonde type fiberscope (SSIF type VII) as a pan-enteroscope. Endoscopy. 1986;18:121–4.
2. Yamamoto H, Sekine Y, Sato Y, et al. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc. 2001;53:216–20.
3. Tsujikawa T, Saitoh Y, Andoh A, et al. Novel single-balloon enteroscopy for diagnosis and treatment of the small intestine: preliminary experiences. Endoscopy. 2008;40:11–5.
4. Takano N, Yamada A, Watabe H, et al. Single-balloon versus double-balloon endoscopy for achieving total enteroscopy: a randomized, controlled trial. Gastrointest Endosc. 2011;73:734–9.
5. May A, Farber M, Aschmoneit I, et al. Prospective multicenter trial comparing push-and-pull enteroscopy with the single- and double-balloon techniques in patients with small-bowel disorders. Am J Gastroenterol. 2010;105:575–81.
6. Akerman PA, Agrawal D, Chen W, et al. Spiral enteroscopy: a novel method of enteroscopy by using the Endo-Ease Discovery SB overtube and a pediatric colonoscope. Gastrointest Endosc. 2009;69:327–32.
7. Frieling T, Heise J, Sassenrath W, et al. Prospective comparison between double-balloon enteroscopy and spiral enteroscopy. Endoscopy. 2010;42:885–8.
8. May A, Manner H, Aschmoneit I, et al. Prospective, cross-over, single-center trial comparing oral double-balloon enteroscopy and oral spiral enteroscopy in patients with suspected small-bowel vascular malformations. Endoscopy. 2011;43:477–83.
9. Messer I, May A, Manner H, et al. Prospective, randomized, single-center trial comparing double-balloon enteroscopy and spiral enteroscopy in patients with suspected small-bowel disorders. Gastrointest Endosc. 2013;77:241–9.
10. Sunada K, Yamamoto H, Hayashi Y, et al. Clinical importance of the location of lesions with regard to mesenteric or antimesenteric side of the small intestine. Gastrointest Endosc. 2007;66:S34–8.
11. Hayashi Y, Yamamoto H, Yano T, et al. A calibrated, small-caliber tip, transparent hood to aid endoscopic balloon dilation of intestinal strictures in Crohn's disease: successful use of prototype. Endoscopy. 2013;45(Suppl 2):E373–4.
12. Kono T, Ashida T, Ebisawa Y, et al. A new antimesenteric functional end-to-end handsewn anastomosis: surgical prevention of anastomotic recurrence in Crohn's disease. Dis Colon Rectum. 2011;54:586–92.

Chapter 4
Current Progress of Endoscopy in Inflammatory Bowel Disease: Capsule Endoscopy

Naoki Hosoe

Abstract More than a decade has passed since small-bowel capsule endoscopy (CE) was developed. One of the indication for small-bowel CE is suspected/diagnosed Crohn's disease (CD). Patients who are suspected CD with negative ileocolonoscopy are good candidate for small-bowel CE. In patients with suspected CD, the risk of small-bowel capsule retention is comparable to that when the small-bowel CE is applied for obscure gastrointestinal bleeding. On the other hand, in patients with an established diagnosis of CD, the risk of small-bowel capsule retention is increased, particularly in those with known intestinal stenosis. In the presence of obstructive symptoms or known stenosis, small-bowel cross-sectional imaging or patency capsule, which is a self-dissolving dummy capsule, should generally precede small-bowel CE. Colon CE (CCE) was first reported in 2006. CCE may be appropriate for inflammatory bowel disease; however, the efficacy of CCE on IBD has not been still unconfirmed. A possible application for CCE for IBD is ulcerative colitis.

Keywords Video capsule endoscopy • Ulcerative colitis • Crohn's disease • Patency capsule

4.1 Introduction

More than a decade has passed since small-bowel capsule endoscopy (CE) was developed and reported by Iddan [1]. CE allows visualization of the small intestinal mucosa non-invasively, and facilitates detection of small intestinal abnormalities.

N. Hosoe
Center for Diagnostic and Therapeutic Endoscopy, School of Medicine, Keio University,
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: nhosoe@keio.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_4

European guideline recommends small-bowel video capsule endoscopy (VCE) as the first-line device for investigation in patients with obscure gastrointestinal bleeding (OGIB) [2]. With respect to the IBD, Several studies have shown the high value of CE for IBD.

In the present chapter, I have focused on the current progress of capsule endoscopy for IBD.

4.2 Small-Bowel VCE for IBD

One of the indications of small-bowel CE is suspected/diagnosed Crohn's disease (CD). Several studies have shown that small-bowel CE is useful in the evaluation of small bowel in patients with suspected/diagnosed CD [3, 4]. However, ileocolonoscopy should be the first endoscopic examination in diagnosing and evaluating CD. Because more than 60% of CD patients have small-bowel involvement at diagnosis [5], and approximately 90% of patients with small-bowel CD, the disease involves the terminal ileum [6]. Patients who are suspected CD with negative ileocolonoscopy are good candidates for small-bowel CE. In the case of suspected CD, careful patient selection (using the clinical history and serological/faecal inflammatory markers) prior to small-bowel CE should be conducted to improve the diagnostic accuracy of CE. Drugs which may induce mucosal damage such as nonsteroidal anti-inflammatory drugs (NSAIDs) should be stopped 1 month before CE [2]. The main adverse event of CE is capsule retention, observed in 1.8–5.8% of investigations for obscure gastrointestinal bleeding (OGIB) [7]. In patients with suspected CD, the risk of small-bowel capsule retention is comparable to that when the small-bowel CE is applied for OGIB. On the other hand, in patients with an established diagnosis of CD, the risk of small-bowel capsule retention is increased, particularly in those with known intestinal stenosis. In the presence of obstructive symptoms or known stenosis, small-bowel cross-sectional imaging such as MR enterography, CT enterography, and small-bowel follow-through (SBFT) should generally precede small-bowel CE [7]. The PillCam patency capsule, which is a self-dissolving dummy capsule, is an additional option to avoid capsule retention [8]. A careful clinical history may be the most useful way to avoid capsule retention [9].

Small-bowel capsule endoscopic images of CD are shown in Fig. 4.1. Mild inflammation which could not be detected by SBFT was clearly visualized (Fig. 4.1a). An ileal stricture with ulcer and a cicatricial circumferential stricture in the ileum are shown in Fig. 4.1b, c. This case received anti-tumor necrosis factor-α therapy, and is clinically in remission. Small intestinal patency was confirmed by the patency capsule in advance. The capsule was egested safely within 2 days.

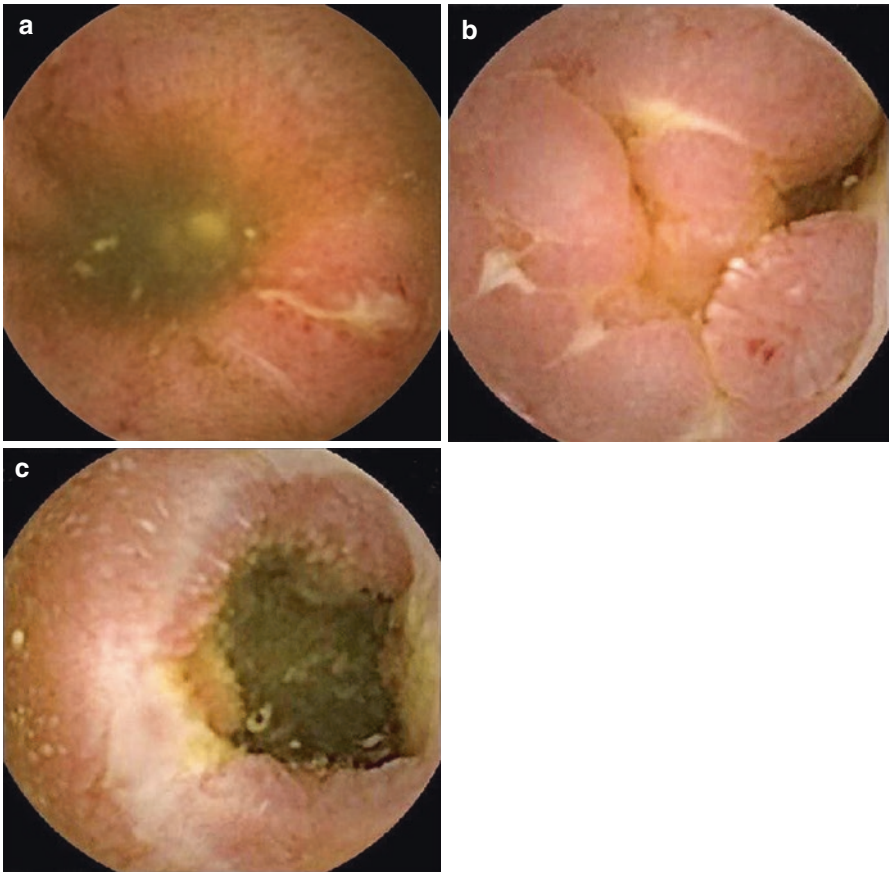


Fig. 4.1 Small-bowel capsule endoscopic image of Crohn's disease. **a** Longitudinal erosion in the jejunum. **b** Inflammatory ileal stricture with ulcer in the ileum. **c** Cicatricial circumferential stricture in the ileum

4.3 Colon CE for IBD

Colon CE (CCE) was first reported in 2006 [10]. The first generation CCE (CCE-1) has some technical differences from the small-bowel capsule: it is approximately 6 mm longer; it has dual cameras that enable the device to acquire video images from both ends, and a frame rate of four frames per second. Currently, CCE has been mainly used for colorectal cancer screening. CCE-1 had moderate sensitivity for surveillance of colorectal neoplasia [11]. To obtain higher sensitivity, second-generation CCE (CCE-2) (PillCam COLON 2®, Covidien Co. Ltd., Yokneam,

Fig. 4.2 Colon capsule (second generation) and data recorder (picture from Covidien co. Ltd., Yokneam, Israel)

Israel) was developed [12]. CCE-2 is equipped with a high frame rate camera which can take 4–35 pictures per second when the capsule is accelerated by peristalsis. The colon CE system (CCE-2 and data recorder) is shown in Fig. 4.2. CCE-2 and data recorder can communicate bi-directionally. The data recorder can receive the information of the transit speed of the capsule, and control the image capture rate. CCE-2 has demonstrated a high sensitivity for the detection of clinically relevant polypoid lesions [13]. A CCE procedure requires a large amount of and multi-step preparation for colon cleansing and the capsule booster [14]. This large amount of preparation might reduce patient acceptance and preference.

Efficacy of CCE on IBD has not been still unconfirmed. With regard to Crohn's disease, only one case series using CCE was reported [15]. The main target disease among IBD for CCE is considered to be ulcerative colitis (UC). Hong Kong's group reported that CCE-1 was a safe procedure to monitor mucosal healing in UC; however, CCE could not be recommended to replace conventional colonoscopy [16]. On the other hand, we have reported that CCE-2 was able to assess the severity of mucosal inflammation in patients with UC [17]. We also created a new reduced bowel preparation regimen for UC in order to obtain high patient acceptance [18]. The current modified bowel preparation regimen for UC is shown in Table 4.1. Patients took a maximum 2.8 l of lavage solution (PEG and magnesium citrate) in two or three divided doses. Even using conventional colonoscopy, UC-associated colorectal cancer is not readily detectable. UC-associated colorectal cancer could not be evaluated by CCE-2 from our experience. The indications for CCE-2 for UC are thus limited to assessments of the severity of inflammation in UC.

Table 4.1 Low-volume PEG with prokinetics regimen

Day	Timing	Procedure
Previous day	Lunch, snack, dinner	Low fiber diet
Examination day	9:00 AM	700 ml PEG
	11:00 AM	Swallowing CCE-2 with mosapride citrate 20 mg and dimethicone 40 mg
	12:00 AM	Confirm CCE-2 in the small intestine Add metoclopramide 10 mg if CCE-2 still remains in the stomach Magnesium citrate 34 g (900 ml) within 30 min and mosapride citrate 20 mg after confirmation of CCE-2 in the small intestine
	2:00 PM	Magnesium citrate 23 g (600 ml) in case CCE-2 has not been egested yet
	5:00 PM	Magnesium citrate 23 g (600 ml) in case CCE-2 has not been egested yet
	6:00 PM	Dinner
		CCE-2 recording continues until battery run down or CCE-2 is egested
		PEG, Polyethylene glycol solution
		CCE-2, Second-generation colon capsule endoscopy

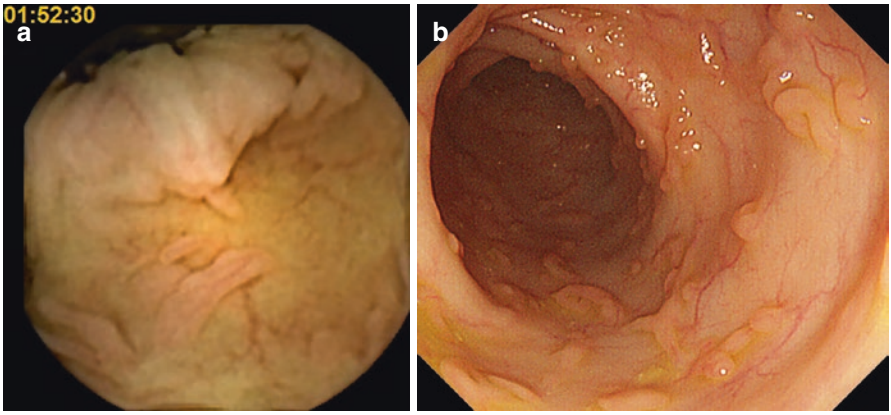


Fig. 4.3 Colon capsule endoscopic image (**a**) and conventional colonoscopic image (**b**) of ulcerative colitis in remission

Colon capsule endoscopic images of UC are shown in Figs. 4.3 and 4.4. Figure 4.3a shows colon capsule endoscopic image of inflammatory benign polyps in the ascending colon. Mucosal healing can be judged from the colon capsule image. Figure 4.3b shows same lesion observed by conventional colonoscopy. Figure 4.3a seems to be identical with Fig. 4.3b. A geographical ulcer with white exudate and inflammatory edematous mucosa was clearly observed by CCE-2 in active UC (Fig. 4.4a). Figure 4.4b shows the same lesion observed by conventional colonoscopy, identical with Fig. 4.4a.

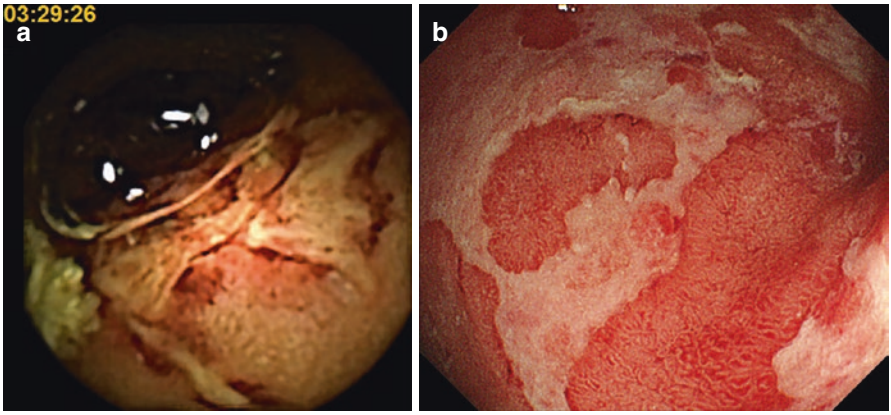


Fig. 4.4 Colon capsule endoscopic image (**a**) and conventional colonoscopic image (**b**) of in active ulcerative colitis

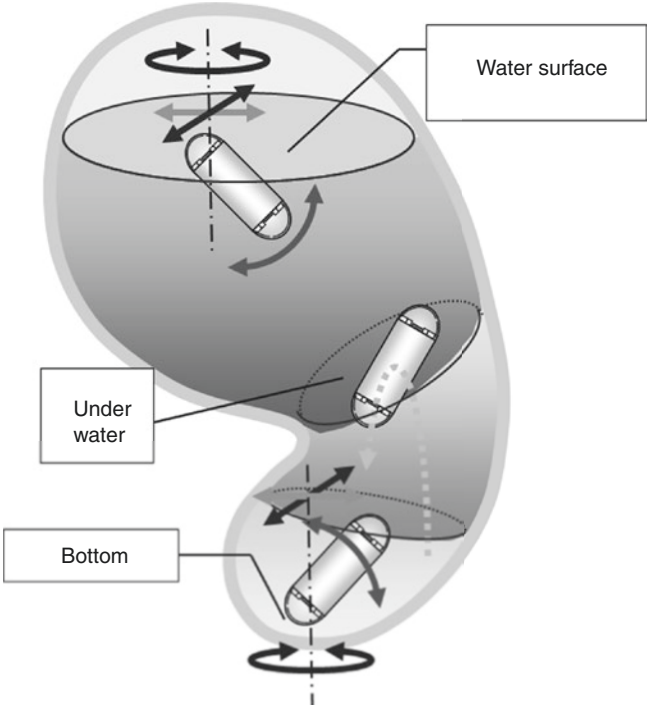


Fig. 4.5 Observation schema of MGCE

4.4 Recent Advances in CE

CE for large luminal organs such as the stomach has recently been developed. Passive CE cannot examine the entire gastric wall by peristalsis. Recently, controllable guided CE have been developed for gastric examination [19, 20]. The magnetically guided capsule endoscope (MGCE) was developed to provide endoscopic visualization of the stomach. The observation schema for MGCE is shown in Fig. 4.5. In a stomach expanded and filled with water, MGCE can observe from the water surface, and underwater like a submarine, with magnetic guidance. The clinical effectiveness of these devices is not still confirmed. Modification and improvement of devices would be necessary.

4.5 Summary

Suspected/diagnosed CD is the one of the indications for small-bowel CE. The main adverse event of CE is capsule retention. In patients with an established diagnosis of CD, the risk of small-bowel capsule retention is increased, particularly in those with known intestinal stenosis. In the presence of obstructive symptoms or known stenosis, small-bowel cross-sectional imaging or patency capsule should generally precede small-bowel CE. CCE may be appropriate for inflammatory bowel disease; however, the efficacy of CCE on IBD has not been still unconfirmed. A possible application for CCE for IBD is ulcerative colitis.

Acknowledgement Naoki Hosoe received a research grant from Covidien Co. Ltd.

References

1. Iddan G, Meron G, Glukhovsky A, et al. Wireless capsule endoscopy. Nature. 2000;405(6785):417.
2. Pennazio M, Spada C, Eliakim R, Keuchel M, et al. Small-bowel capsule endoscopy and device-assisted enteroscopy for diagnosis and treatment of small-bowel disorders: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2015;47(4):352–86.
3. Mehdizadeh S, Chen GC, Barkodar L, et al. Capsule endoscopy in patients with Crohn's disease: diagnostic yield and safety. Gastrointest Endosc. 2010;71(1):121–7.
4. Papadakis KA, Lo SK, Fireman Z, et al. Wireless capsule endoscopy in the evaluation of patients with suspected or known Crohn's disease. Endoscopy. 2005;37(10):1018–22.
5. Van Assche G, Dignass A, Panes J, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. J Crohns Colitis. 2010;4(1):7–27.
6. Jensen MD, Nathan T, Rafaelsen SR, et al. Ileoscopy reduces the need for small-bowel imaging in suspected Crohn's disease. Dan Med J. 2012;59(9):A4491.

7. Bourreille A, Ignjatovic A, Aabakken L, et al. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED–ECCO consensus. Endoscopy. 2009;41(7):618–37.
8. Yadav A, Heigh RI, Hara AK, et al. Performance of the patency capsule compared with non-enteroclysis radiologic examinations in patients with known or suspected intestinal strictures. Gastrointest Endosc. 2011;74(4):834–9.
9. Cheifetz AS, Kornbluth AA, Legnani P, et al. The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. Am J Gastroenterol. 2006;101(10):2218–22.
10. Eliakim R, Fireman Z, Gralnek IM, et al. Evaluation of the PillCam Colon capsule in the detection of colonic pathology: results of the first multicenter, prospective, comparative study. Endoscopy. 2006;38(10):963–70.
11. Van Gossum A, Munoz-Navas M, Fernandez-Urien I, et al. Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. N Engl J Med. 2009;361(3):264–70.
12. Eliakim R, Yassin K, Niv Y, et al. Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. Endoscopy. 2009;41(12):1026–31.
13. Spada C, Hassan C, Munoz-Navas M, et al. Second-generation colon capsule endoscopy compared with colonoscopy. Gastrointest Endosc. 2011;74(3):581–9.
14. Spada C, Hassan C, Galmiche JP, et al. Colon capsule endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2012;44(5):527–36.
15. Negreanu L, Babiuc R, Bengus A, et al. PillCam Colon 2 capsule in patients unable or unwilling to undergo colonoscopy. World J Gastrointest Endosc. 2013;5(11):559–67.
16. Sung J, Ho KY, Chiu HM, et al. The use of Pillcam Colon in assessing mucosal inflammation in ulcerative colitis: a multicenter study. Endoscopy. 2012;44(8):754–8.
17. Hosoe N, Matsuoka K, Naganuma M, et al. Applicability of second-generation colon capsule endoscope to ulcerative colitis: a clinical feasibility study. J Gastroenterol Hepatol. 2013;28(7):1174–9.
18. Usui S, Hosoe N, Matsuoka K, et al. Modified bowel preparation regimen for use in second-generation colon capsule endoscopy in patients with ulcerative colitis. Dig Endosc. 2014;26(5):665–72.
19. Morita E, Ohtsuka N, Shindo Y, et al. In vivo trial of a driving system for a self-propelling capsule endoscope using a magnetic field (with video). Gastrointest Endosc. 2010;72(4):836–40.
20. Rey JF, Ogata H, Hosoe N, et al. Feasibility of stomach exploration with a guided capsule endoscope. Endoscopy. 2010;42(7):541–5.

Chapter 5
Current Progress of Endoscopy in Inflammatory Bowel Disease: CT Enterography and CT Colonography in Inflammatory Bowel Disease

Ken Takeuchi, Miyuki Miyamura, Tsunetaka Arai, Rumiko Ishikawa, Akihiro Yamada, and Yasuo Suzuki

Abstract Since the concept of "mucosal healing" was introduced into clinical practice, endoscopy has been more important in the diagnosis and monitoring in patients with inflammatory bowel disease (IBD). However, the fact remains that there is an IBD population who is not able to have a complete endoscopic examination due to age, severe medical conditions or intestinal complications such as strictures or adhesions. Furthermore, the inflammation of IBD may often progress to extra-enteral organs, particularly in Crohn's disease (CD). Cross-sectional imaging modalities such as computed tomography (CT) are considered to be complementary to endoscopy and more important in those cases. Both CT enterography (CTE) and CT colonography (CTC) have not only a better ability in terms of spatial and temporal resolution for assessing intestinal and extra-intestinal lesions in IBD, but also higher accessibility and better patient tolerance compared with other diagnostic modalities. Although the most significant limitation of CT is radiation exposure, various new technologies combining low-dose CT and an iterative reconstruction algorithm are being developed, so that diagnostically acceptable CT examinations may be performed within the sub-mSv effective dose range in the near future.

Keywords Cross-sectional imaging • CT enterography • CT colonography • Low-dose CT

K. Takeuchi (✉) • M. Miyamura • T. Arai • A. Yamada • Y. Suzuki
Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Sakura Medical Centre, Faculty of Medicine, Toho University, 564-1, Shimoshizu, Sakura, 285-8741 Chiba, Japan
e-mail: ken.takeuchi@med.toho-u.ac.jp

R. Ishikawa
Department of Radiology, Toho University Sakura Medical Centre, Faculty of Medicine, Toho University, 564-1, Shimoshizu, Sakura, 285-8741 Chiba, Japan

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_5

5.1 Introduction

Inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD), are chronic relapsing and progressive disorders of the gastrointestinal tract that are characterized pathologically by intestinal inflammation and injury of the bowel wall [1, 2]. IBD patients can suffer from various clinical manifestations, including abdominal pain, chronic diarrhea, rectal bleeding, fever, weight loss, malabsorption, anaemia, and so on over time. As the inflammation of IBD is not limited to the gastrointestinal tract, patients can often develop extraintestinal complications such as fistula, stenosis, and abscess, which finally lead to surgery. Furthermore, it was revealed recently that prolonged intestinal inflammation and extraintestinal complications are a possible cause of colitis-associated neoplasias in IBD, particularly in patients with ulcerative pancolitis and colonic CD [3, 4], including anal cancers developed in long-standing anal fistulas. However, the most important point is that these pathophysiological conditions of IBD are not always consistant with the clinical activity of the patients. Therefore, endoscopic and imaging examinations are indispensible for the diagnosis and monitoring in patients with IBD.

The treatment goal of IBD in the past has been mainly improvement of the clinical manifestations. However, after various potent treatments such as anti-TNF agents have been introduced into clinical practice, "mucosal healing" has been recognized as the new treatment goal of IBD [5]. The major reason why the target of IBD treatment has changed is based on various reports that the achievement of mucosal healing is associated with more frequent steroid-free remission of disease, lower rates of hospitalization and surgery, and improved quality of life [6]. Nevertheless, there is still no general consensus on the definition of the term "mucosal healing", although mucosal healing in endoscopy has hitherto usually referred to resolution of the ulcers in CD and the erosions and ulcers in UC [7, 8]. Moreover, endoscopy is not always available to observe lesions of IBD, especially in patients with severe colitis, intestinal stenosis, or adhesions. Therefore, the examination to complement endoscopy is required for diagnosis and monitoring in patients with IBD.

In this section, we introduce new techniques of computed tomography (CT), including CT enterography and CT colonography and present the findings of IBD at each cross-sectional imaging technique with their advantages and disadvantages.

5.2 CT Enterography

Diagnosis of small-bowel pathology has been a challenging issue for both gastroenterologists and radiologists, due to the relative inaccessibility of the small bowel to conventional endoscopy (Figs. 5.1 and 5.2). Therefore, barium tests including small-bowel follow-through (SBFT) have been the primary examinations in the

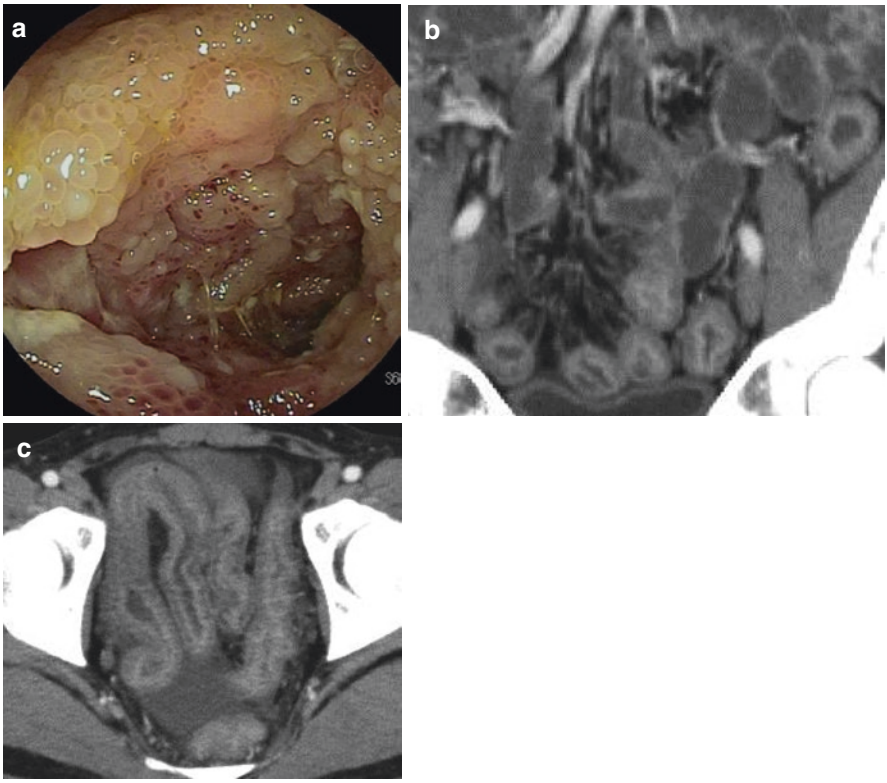


Fig. 5.1 Images of CT enterography in acute Crohn's disease. **a** Appearance of double-balloon enteroscopy shows a longitudinal ulcer in the terminal ileum. **b** The coronal view of CT enterography shows "target sign" in the ileum. **c** The axial view of CT enterography shows mural stratification in the ileum

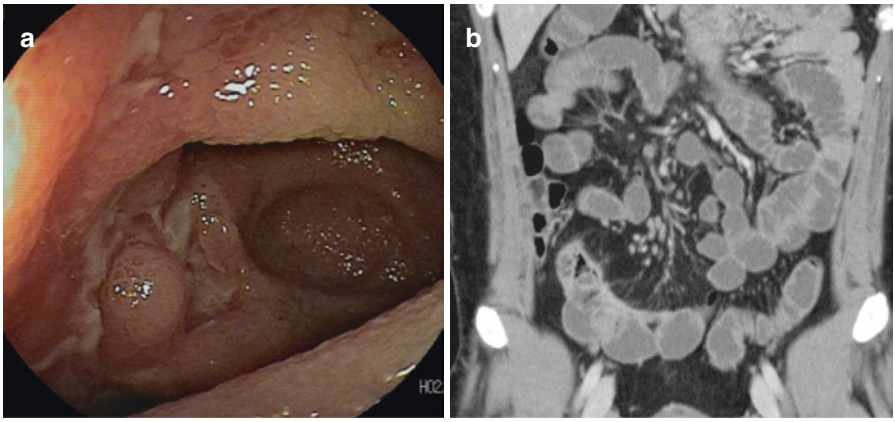


Fig. 5.2 Images of CT enterography in chronic Crohn's disease. **a** Appearance of double-balloon enteroscopy shows a longitudinal ulcer in the terminal ileum with a stricture. **b** The coronal view of CT enterography shows a mural linealization with a contralateral sacculation in the ileum

diagnostic modality for small-bowel CD, although those techniques can only assess the intraluminal pathology and are often limited to showing lesions in the pelvic cavity due to superimposition of bowel loops.

New endoscopic modalities including capsule endoscopy and balloon-assisted endoscopy allow more detailed assessment of the intraluminal pathology of small-bowel CD; however, intestinal adhesions or strictures often hamper the performance of these endoscopic examinations in patients with CD.

In recent years, cross-sectional imaging modalities such as CT and MRI are strongly recommended to be used in the diagnosis and monitoring of the disease activity of CD in the US and Europe [9]. These imaging devices can visualize not only the intestinal wall of the small bowel, but also extra-enteric complications such as fistulae and abscesses in a minimally invasive manner.

In those cross-sectional imaging modalities, CTE was first introduced by Raptopoulos et al. in 1997 [10], and has been the most widely used imaging technique for CD in the US and Europe because of its short scan time, high spatial resolution, usefulness, and tolerability [11].

5.3 Technique

CTE is an imaging method that enables good visualization of the intestinal wall and lumen of the small intestine. CTE is performed by multi-detector row CT (MDCT) with intravascular contrast, after the small intestine is dilated with large volumes (1.3–1.8 l) of neutral or low-density oral enteric contrast material.

For the success of the procedure, it is necessary for patients to ingest at least 1.3 l of oral contrast agent over 60 min. In the US and Europe, a low-density barium sulfate contrast especially designed for CTE, 0.1% VoLumen® (Bracco, Milan, Italy) is commercially available. However, any materials with isotonic and CT attenuation properties similar to that of water can be used for CTE [12]. In our facility, patients drink total 1.8 l of isotonic magnesium citrate solution (Magcorol P®, HORII Pharm., Osaka, Japan) at a steady rate (approximately 450 ml every 15 min) over 1 h before CT scanning, prior to performance of the per rectal balloon-assisted endoscopy in the afternoon of the same day. Anti-peristaltic agents such as glucagon and butylscopolamine are usually administered immediately prior to CT in order to avoid image degradation from peristalses. One hundred and fifty ml of Omnipaque 300 (Daiichi-Sankyo Pharm. Inc., Tokyo) are administered intravenously at 4 ml/s. Supine single-phase images by a more than 64-slice CT scanner are acquired 50–60 s after intravenous contrast administration at 2 mm of slice thickness, with a reconstruction interval of 0.75 mm.

5.4 Findings of IBD

For improvement in accuracy of both luminal navigation and interpretation, it is recommended that reading of CT findings should start with a multiplanar review [11]. Although differential contrast enhancement is important to distinguish abnormal from normal segments, it should be noted that the jejunum enhances more than the ileum, and also that collapsed bowel loops appear to enhance more than the distended loops.

The colon is frequently well distended, and it is possible to assess the associated pathology in the absence of an intraluminal contrast medium; it is, however, important to be aware that the evaluation of colonic pathology using CTE is limited.

Macari et al. [13] described several criteria to help to characterize abnormal small-bowel segments, including pattern of contrast enhancement, length of involvement, degree and symmetry of wall thickening, location in proximal/distal jejunum/ileum, location of pathology within the small-bowel wall (mucosal/submucosal/serosal) and associated abnormality in the adjacent mesentery or vessels.

Active small-bowel CD shows bowel-wall thickening, mural hyper-enhancement, "target" appearance with mural stratification, engorged vasa recta (the "comb sign") and increased density in perienteric mesenteric fat. Chronic changes in CD include fibrotic strictures and submucosal fatty deposition in the bowel wall [14].

Small-bowel mural thickness greater than 3 mm should be considered abnormal. In the pathology of CD, the small-bowel wall is affected asymmetrically, predominantly the mesenteric border, frequently leading to asymmetric inflammation and fibrosis, with pseudosacculation of the antimesenteric border. Small-bowel wall enhancement is closely correlated with disease activity [15]. Mural stratification describes the visible layers of the inflamed small bowel wall shown following administration of intravenous contrast in the enteric phase. However, when mural stratification is assessed, it should be considered that between the strongly enhanced mucosa and serosa, the intervening layer of the intestinal wall enhances to a varying degree, due either to intramural edema (isodense with water), indicating active disease, or to intramural fat, indicating chronic inflammation. The comb sign is created by engorged vasa recta, which consists of the vessels penetrating the bowel wall perpendicular to the bowel lumen, and also indicates active inflammation [16]. Fibrofatty proliferation refers to fatty deposition along the mesenteric border of bowel segments affected by CD, and often remains in clinically quiescent disease. However, the presence of increased fat density surrounding thickened or abnormally enhanced bowel is not like fibrofatty proliferation, highly specific in active disease, because it results from inflammatory cell infiltrations.

It is not rare that luminal narrowing is seen in the bowel segment affected by CD. In the assessment of luminal narrowing, the presence of pre-stenotic dilatation

may be helpful in defining, locating, and assessing the functional significance of a stricture [16], and also, as mentioned, assessing the signs of acute inflammation can be helpful. Recently, Arai et al. [17] reported that a CTE scoring system for disease severity, which is scored based on bowel-wall thickness, mural hyper-enhancement, and engorged versa recta, is significantly correlated to an endoscopic index. Furthermore, faecal biomarker calprotectin also correlated with the CTE score. Hence, a combination of calprotectin and CTE appears to be effective for monitoring CD activity in patients with small intestinal CD, including patients with strictures that cannot be passed by conventional endoscopy.

Furthermore, extra-intestinal complications of CD should be kept in mind, including abscesses, or formation of fistulae between bowel segments and other organs (commonly the anterior abdominal wall, vagina or renal tract), and also the formation of gallstones and urinary calculi resulting from metabolic changes.

5.5 CT Colonography

Computed tomography colonoscopy (CTC) is defined as using helical-CT scanning and computers to produce high-resolution 2-dimensional (2D) and 3-dimensional (3D) imaging [18].

Since Vining et al. launched the first report of CT colonography (CTC) in 1994 [19], CTC has been recognized as a reliable and accurate imaging test for the detection of colorectal cancer as effective as conventional colonoscopy. Although it is well recognized that large polyps ($\geq$10 mm) are accurately identified by CTC, the accuracy of CTC in the identification and characterization of smaller, flat, or depressed lesions is still controversial. Furthermore, histological examination is not available using CTC. Therefore, current CTC indications include the evaluation of patients who had undergone a previous incomplete colonoscopy or those who are unfit for colonoscopy, including elderly and frail individuals, patients with severe underlying clinical conditions, or with contraindication to sedation [20].

Hitherto, there have been very few reports on the ability of CT colonography to diagnose inflammatory bowel diseases [21–23]. Therefore, CTC is not approved as an alternative to standard colonoscopy in patients with UC in the ECCO (European Crohn's and Colitis Organization) statement published in 2012 [24], although CTE together with MRE has been recognized to be an standard imaging technique with the highest diagnostic accuracy for the detection of intestinal involvement and extra-intestinal lesions in CD [9]. In fact, because colonoscopy can provide direct visualization of the colonic mucosa and the ability to collect a biopsy specimen for the histological diagnosis of IBD, colonoscopy is still the first-line procedure in the initial evaluation of patients with unexplained diarrhea and suspected IBD, especially UC [20]. However, CTC can be useful in patients with IBD, who have had incomplete or inconclusive colonoscopy, or who are unsuitable for colonoscopic examination, as mentioned above. The point to which we must pay attention is that CTC should be avoided in IBD patients presenting acute sever symptoms because

of the risk of complications [25]. In these conditions, contrast-enhanced MDCT without CO_2 gas insufflation is necessary and sufficient.

5.6 Technique

In patients with IBD, the technique of CTC is the same as in patients with suspected colon cancers.

Briefly, in our institution, patients have a low residue diet on the day before the examination, and take 0.75% sodium picosulfate (Laxisoberon®, Teijin Pharma Ltd., Tokyo, Japan) in the evening. On the morning of the examination, patients ingest a bowel lavage such as polyethylene glycol solution or isotonic magnesium citrate solution as bowel preps prior to CT scan. In CTC aimed to detect polyps, fecal tagging and electronic cleansing are usually performed to reduce the dose of bowel lavage by ingesting oral positive contrast such as a 40% w/v barium suspension with meals or alone. However, fecal tagging is normally omitted for CTC in patients with IBD, because contrast-enhanced MDCT is usually performed to evaluate the condition of the bowel-wall enhancement for assessing the disease activity of IBD, and tagged residues in the colon may make the enhanced bowel wall vague and unclear.

The colon is distended with carbon dioxide via a rectal tube. Carbon dioxide is given at low-pressure less than 25 mmHg by an automated low-pressure delivery system. The total volume of carbon dioxide gas is 1.5–2.5 l for adequate distension. As mentioned above, in IBD patients with acute symptoms, contrast-enhanced MDCT without CO_2 gas insufflation is sufficient to obtain the necessary information.

Patients should be scanned in both the prone and supine position; that is not only to keep the visualization of the colonic lumen from the residual material, but also due to the difference of colonic distension per segment by the position of scanning [26].

Intravenous contrast medium is usually used for the assessment of the colonic wall enhancement. The acquisition at supine single phase is performed at 50–60 s after intravenous contrast administration. In cases of evaluating the extra-colonic organs, the scan is also performed in the portal phase.

5.7 Findings of IBD

Colonoscopy has become the major modality for assessing the colonic disease activity in patients with IBD, because it is the only modality to be able to evaluate "mucosal healing", which recently became the therapeutic goal in both UC and CD. Colonoscopy can provide only the detailed pathology of the colonic mucosa. CTC is able to provide the information of colonic pathology by identifying endoluminal, intramural and extra-colonic findings [27] with its four different views; the virtual endoscopy view, the air image view, the multi-planar reconstruction

(MPR) view, and the virtual dissection view (Fig. 5.3). In those images, the virtual dissection view, which is the 3D model of the colon stretched out and sliced open being displayed like the "gross pathology", and the virtual endoscopy are usually used for screening mucosal lesions such as polyps. When CTC is being applied for the evaluation of IBD, the colonic pathology may be assessed not only endoluminally but also extraluminally by both the MPR and the air image. On the MPR view of CTC, the active UC lesions shows bowel-wall thickening, mural hyper-enhancement, "target" appearance with mural stratification, engorged vasa recta, and increased density in the perienteric mesenteric fat like the appearance of IBD in CT

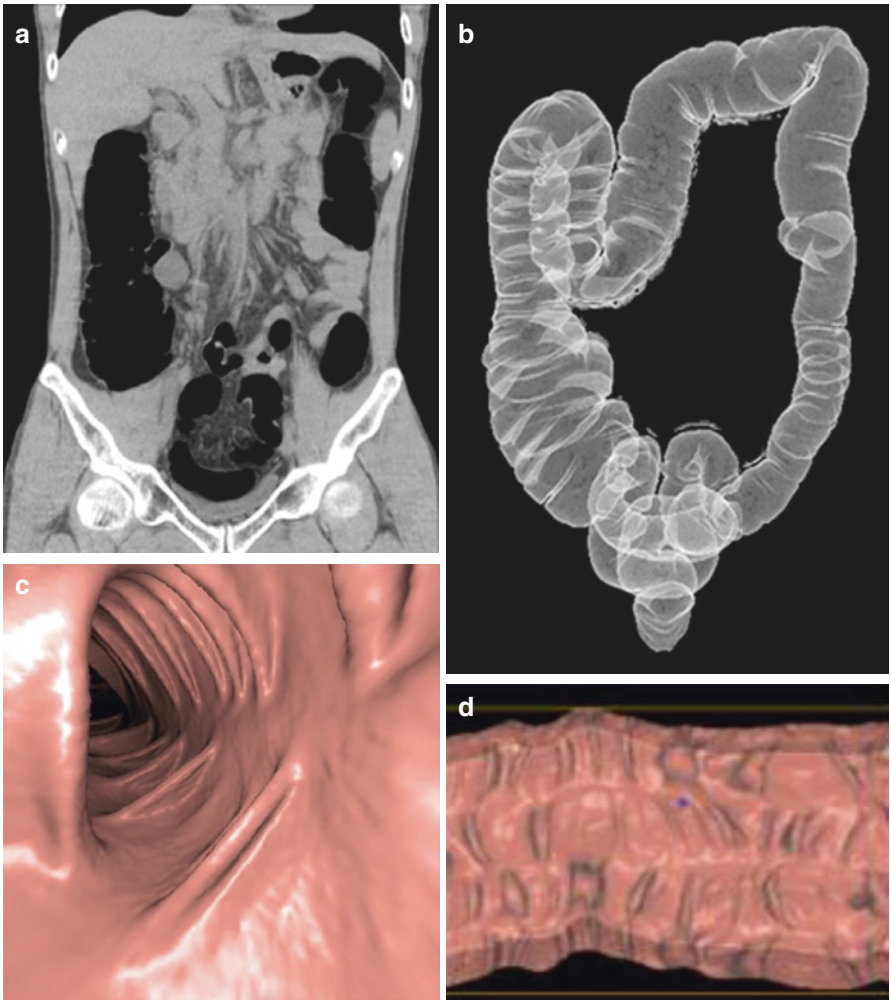


Fig. 5.3 Characteristic views of CT colonography. **a** Multi-planar reconstruction view. **b** Air image view. **c** Virtual endoscopy view. **d** Virtual dissection view

enterography, as well as chronic changes including fibrotic strictures and submucosal fatty deposition in the bowel wall. Further, in the patients with UC, the air image view of CTC can show granular appearance of the colon mucosa, deep ulcerations, pseudopolyps, and loss of haustral folds [28] (Fig. 5.4). These appearances in UC may begin from the rectum and progress proximally in a continuous and circumferential fashion; however, the lesions of CD are distributed discontinuously or in a "patchy" fashion.

There have been a few reports of CTC being applied for the evaluation of IBD. Andersen, et al. reported the high accuracy of CTC in the detection of chronic

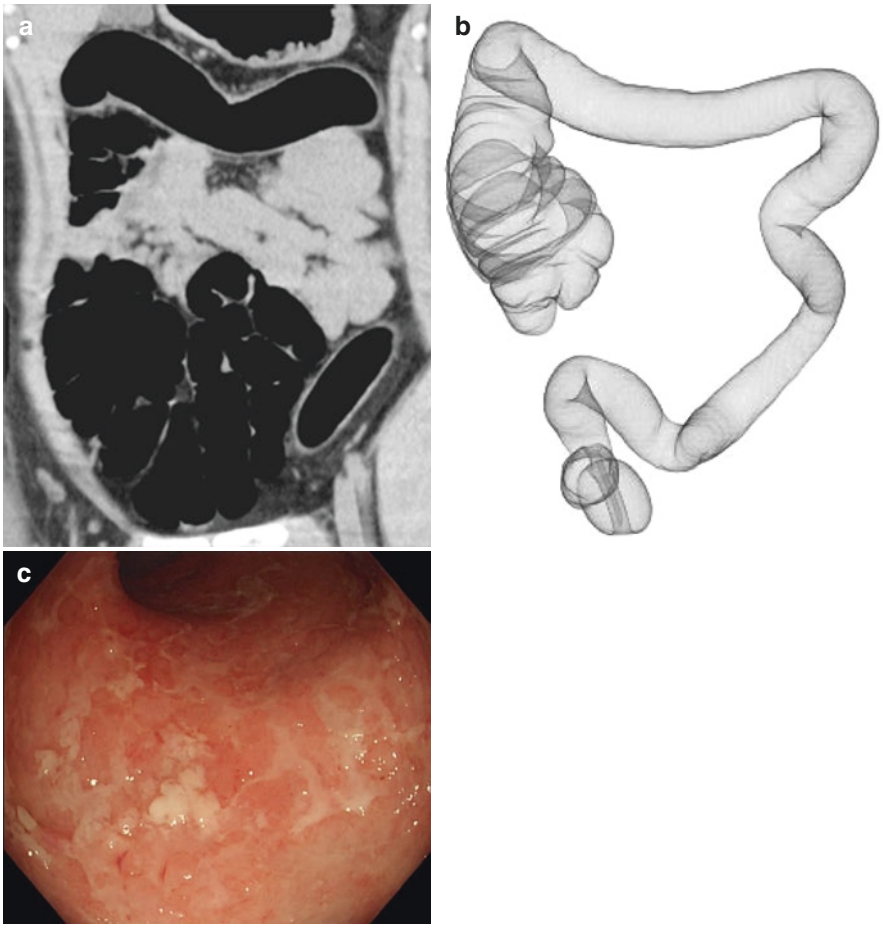


Fig. 5.4 Images of CT colonography in active ulcerative colitis. **a** The MPR view of CT colonography shows mural thickening and hyper-enhancement in the transverse colon and the sigmoid colon. In this view, the increased density in the perienteric mesenteric fat can be seen in the same lesion. **b** The air image view of CT colonography shows luminal narrowing and loss of haustae continuously from the rectum to the transverse colon. This air image view was gained by ultra-low dose technique

findings of IBD with an overall sensitivity and specificity of 100% respectively, although for acute findings, the sensitivity in direct comparison with conventional colonoscopy was low (63.6%) and the specificity was moderate (75%) [23].

Recently, it has become a very important issue that colitis-associated cancer (CRC) in patients with long-standing IBD is detected at an early stage. However, there are very few reports related to the detection of malignant lesions in IBD at CTC. Gore et al. reported that asymmetric mural thickening, focal loss of mural stratification, and mural thickening greater than 1.5 cm might be suspected malignancy without preparation or colonic distension [29]. Mang et al. reported some suspicious findings for the development of colorectal cancer in patients with UC, such as focal wall thickening, shoulder formation, or large polypoid lesions when using CTC [30]. In patients with chronic CD, it is known that the incidence of adenocarcinoma and lymphoma of the small bowel and colon, particularly in the bypassed or excluded segments of the gut, is increased [31]. CTC is also helpful in detecting a tumor mass and providing accurate tumor staging [32].

5.8 Limitations

At present, subtle changes of the surface such as aphthous ulcers or small flat lesions cannot be detected by CTE and CTC. Therefore, CTC cannot be an alternative to colonoscopy as a screening method for CRC in patients with long-standing UC or CD.

The most significant limitation of CTE and CTC is radiation exposure. This issue is particularly relevant to the IBD population, because patients with IBD are often diagnosed at a young age and are likely to require frequent imaging over the course of their lifetimes.

Epidemiological studies suggest a nonzero radiation-induced cancer risk at exposure levels as low as 50–100 mSv, which are likely to be exceeded in patients diagnosed with CD at an early age [33, 34]. Higher levels of cumulative radiation exposure are more likely in patients with IBD, particularly with CD [35]. Magnetic resonance enterography (MRE) has the same ability as CTE in the assessment of intestinal inflammation and fibrosis, as well as the identification of transmural and extraintestinal complications, but is currently compromised by a longer examination time, patient tolerance, and cost [36]. Hence, CT is still the primary modality for the assessment of CD in the acute setting, particularly when extra-luminal complications are suspected.

5.9 CTE and CTC with Low-Dose CT Technique

On reducing radiation exposure during CT scanning, aggressive dose-lowering often resulted in lower image quality and diagnostic performance. Recently, the various low-dose CT systems combined with an iterative reconstruction algorithm have been developed, and these CT systems enables CTE to preserve image quality in the context of radiation dose reductions, typically >30% in patients with CD [37, 38].

CTC identifies colonic polyps and cancers using differences in the X-ray attenuation between these soft-tissue lesions and intraluminal air. The attenuation difference is much greater than that in routine CT examination or in CT enterography, so that the radiation dose in CTC can be reduced to much lower levels than in these CT examinations. In fact, a recent report estimates the effective dose between 1 and 2 mSv in CT colonography [39].

Furthermore, we had confirmed that the air image of the low-dose CTC could evaluate the disease extension and activity significantly correlated with endoscopic severity score in patients with UC, even with an ultra-low dose at 5mAs levels, which is almost equivalent to the dose in abdominal X-ray (Fig. 5.4).

5.10 Summary

Endoscopic examinations including balloon enteroscopy and colonoscopy are the major and essential modality for the evaluation of disease activity and extension in IBD, and become much more important than before because the therapeutic goal has been established as “mucosal healing” or “histologic healing” in both UC and CD. However, the fact remains that there is an IBD population who are not able to have complete endoscopic examination due to severe medical conditions or intestinal complications such as strictures or adhesions. Furthermore, the inflammation of IBD may often progress to the extra-enteral organs, particularly in CD. Cross-sectional imaging procedures such as CT or MRI are considered to be complementary to endoscopic examinations. CT has better ability in special and temporal resolution than other cross-sectional imaging modalities. Furthermore, CTE and CTC can assess intestinal inflammation and fibrosis as well as transmural and extra-intestinal complications in a fast and well-tolerated fashion. The most significant limitation of CT is radiation exposure. However, in the future, the continued development of the technique such as iterative reconstruction algorithms may allow diagnostically acceptable CT examinations to be performed within the sub-mSv effective dose range.

References

1. Danese S, Fiocchi C. Ulcerative colitis. N Engl J Med. 2013;365:1713–25.
2. Baumgart DC, Sandborn WJ. Crohn’s disease. Lancet. 2012;380:1590–605.
3. Bernstein CN, Blanchard JF, Kliewer E, Wajda A. Cancer risk in patients with inflammatory bowel disease: a population-based study. Cancer. 2001;91:854–62.
4. Foersch S, Waldner MJ, Neurath MF. Colitis and colorectal cancer. Dig Dis. 2012;30:469–76.
5. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61:1619–35.
6. Pineton de Chambrun G, Peyrin-Biroulet L, Lemann M, Colombel JF. Clinical implications of mucosal healing for the management of IBD. Nat Rev Gastroenterol Hepatol. 2010;7:15–29.

7. Colombel JF, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141:1194–201.
8. Froslie KF, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133:412–22.
9. Van Assche G, Dignass A, Panes J, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. J Crohn's Colitis. 2010;4:7–27.
10. Raptopoulos V, Schwartz RK, McNicholas MMJ, et al. Multiplanar helical CT enterography patients with Crohn's disease. AJR Am J Roentgenol. 1997;169(6):1545–50.
11. Paulsen SR, Huprich JE, Fletcher JG, et al. CT enterography as a diagnostic tool in evaluating small bowel disorders: review of clinical experience with over 700 cases. Radiographics. 2006;26(3):641–57.
12. Megibow AJ, et al. Evaluation of bowel distention and bowel wall appearance by using neutral oral contrast agent for multi-detector row CT. Radiology. 2006;238(1):87–95.
13. Macari M, Megibow A, Balthazar E. A pattern approach to the abnormal small bowel: observations at MDCT and CT enterography. AJR Am J Roentgenol. 2007;188:1344–55.
14. Hara AK, Swartz PG. CT enterography of Crohn's disease. Abdom Imaging, 2009; 34(3): 289–2295.
15. Bodily KD, et al. Crohn's disease: mural attenuation and thickness at contrast-enhanced CT enterography—correlation with endoscopic and histologic findings of inflammation. Radiology. 2006;238(2):505–16.
16. Ilangovan R, Burling D, George A, et al. CT enterography: review of technique and practical tips. Br J Radiol. 2012;85:876–86.
17. Arai T, Takeuchi K, Miyamura M, Ishikawa R, Yamada A, Katsumata M, Igarashi Y, Suzuki Y. Level of fecal calprotectin correlates with severity of small-bowel Crohn's disease, measured by balloon-assisted enteroscopy and computed tomography enterography. Clin Gastroenterol Hepatol. 2017;15:56. doi:10.1016/j.cgh.2016.08.015.
18. Royster AP, Gupta AK, Fenlon HM, et al. Virtual colonoscopy: current status and future implications. Acad Radiol. 1998;5:282–8.
19. Vining DJ, Gelfand DW. Non-invasive colonoscopy using helical CT scanning. 3D reconstruction and virtual reality. In: Syllabus of the 23rd Annual Meeting, Society of Gastrointestinal Radiologists. 1994.
20. Laghia A, Rengoa M, Graserc A, et al. Current status on performance of CT colonography and clinical indications. Eur J Radiol. 2013;82:1192–200.
21. Tarjan Z, Zagoni T, Gyorke T, Mester A, Karlinger K, Mako EK. Spiral CT colonography in inflammatory bowel disease. Eur J Radiol. 2000;35:193–8.
22. Rao SK, Schilling TF, Sequist TD. Challenges in the management of positive fecal occult blood tests. J Gen Intern Med. 2009;24:356–60.
23. Andersen K, Vogt C, Blondin D, et al. Multi-detector CT colonography in inflammatory bowel disease: prospective analysis of CT findings to high-resolution video colonoscopy. Eur J Radiol. 2006;58:140–6.
24. Dignass A, Eliakim R, Magro F, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis. Part 1: definitions and diagnosis. J Crohn's Colitis. 2012;6:965–90.
25. Berrington de Gonzalez A, Kim KP, Yee J. CT colonography: perforation rates and potential radiation risks. Gastrointest Endosc Clin N Am. 2010;20:279–91.
26. Boellaard NT, de Haan MC, Venema HW, et al. Colon distension and scan protocol for CT colonography: an overview. Eur J Radiol. 2013;82:1144–58.
27. Regge D, Neri E, Turini F, et al. Role of CT colonography in inflammatory bowel disease. Eur J Radiol. 2009;69:404–8.
28. Carroscosa P, Castiglioni R, Capunay C, et al. CT colonoscopy in inflammatory bowel disease. Abdom Imaging. 2007;32:596–601.
29. Gore RM, Balthazar EJ, Ghahremarni GG, Miller FH. CT features of ulcerative colitis and Crohor's disease. AJR Am J Roentgenol. 1997;167:3–15.

30. Mang T, Pokieser P, Maier A, Schima W. Virtual colonoscopy: beyond polyp detection. In: Lefere P, Gryspeerdt S, editors. Virtual colonoscopy: a practical guide. 2nd ed. Berlin: Springer-Verlag; 2010. p. 153–63.
31. Bansal P, Sonnenberg A. Risk factors for colorectal cancer in inflammatory bowel disease. Am J Gastroenterol. 1996;91:44–8.
32. Gore RM, Balthazar EJ, Ghahremani GG, et al. CT features of ulcerative colitis and Crohn's disease. Am J Roentgenol. 1996;167:3.
33. Pierce DA, Preston DL. Radiation-related cancer risks at low doses among atomic bomb survivors. Radiat Res. 2000;154:178–86.
34. Brenner DJ. Should computed tomography be the modality of choice for imaging Crohn's disease in children? The radiation risk perspective. Gut. 2008;57:1489–90.
35. Desmond AN, Mcwilliams S, Maher MM, et al. Radiation exposure from diagnostic imaging among patients with gastrointestinal disorders. Clin Gastroenterol Hepatol. 2012;10:259–65.
36. Ho IK, Cah BD, Cohen H, et al. Radiation exposure in gastroenterology: improving patient and staff protection. Am J Gastroenterol. 2014;109(8):1180–94.
37. Hara AK, et al. Iterative reconstruction technique for reducing body radiation dose at CT: feasibility study. AJR Am J Roentgenol. 2009;193(3):764–71.
38. Kambadakone AR, Chaudhary NA, Desai GS, et al. Low-dose CT examinations in Crohn's disease: impact on image quality, diagnostic performance, and radiation dose. Am J Roentgenol. 2011;195(1):78–88.
39. Neri E, Vagli P, Turini F, et al. Post-surgical follow-up of colorectal cancer: role of contrast-enhanced CT colonography. Abdom Imaging. 2009;35:669–75.

Chapter 6
Current Progress of Endoscopy in Inflammatory Bowel Disease: MR Enterography

Toshimitsu Fujii

Abstract Crohn's disease (CD) is a lifelong, chronic, progressive inflammatory disease of the gastrointestinal tract associated with diarrhea, abdominal pain, bloody stool, and often perianal fistulae. Inflammation throughout the small and large bowels causes irreversible bowel damage, such as strictures, fistulae, and abscesses, despite achieving clinical remission. To optimize therapy for CD, it is necessary to monitor disease activity and evaluate therapeutic interventions. Evaluations based on clinical activity alone are not sufficient, and frequent imaging examinations, particularly of the small bowel, are important. In recent years, many new imaging modalities have been developed, such as video capsule endoscopy (VCE), balloon-assisted enteroscopy (BAE), ultrasonography (US), computed tomography enterography (CTE), and magnetic resonance enterography/enterocolonography (MRE/MREC). A suitable imaging modality should be reproducible, well-tolerated, safe, and free of ionizing radiation because CD is a lifelong disease. MRE and MREC are cross-sectional imaging techniques used to investigate not only extraluminal abnormalities but also intraluminal changes. Recent advances have enabled the use of MRI to assess bowel disorders with high levels of sensitivity, specificity, and accuracy. MRI can evaluate not only intrabowel lesions but also extrabowel lesions, including abdominal abscesses and perianal lesions while eliminating the problem of overlapping bowel loops. Therefore, MRI could potentially be used to evaluate overall CD activity without causing radiation exposure. MRE and MREC are, therefore, suitable first-line imaging modalities for the assessment of CD.

Keywords MRI • MR enterography • MR enterocolonography • Crohn's disease • Activity assessment

T. Fujii
Division of Gastroenterology and Hepatology, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
e-mail: tfujii.gast@tmd.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_6

6.1 Introduction

Crohn's disease (CD) is an idiopathic, chronic, and progressive inflammatory disease [1] that can affect the entire gastrointestinal tract. The onset of CD peaks between 20 and 30 years of age. Inflammation usually involves not only all layers of the bowel wall but also extravisceral structures. CD can progress to fibrosis complicated by strictures and obstruction, with consequent fistulae and abscesses during the course of disease [2]. Even during clinical remission, the bowel is not free from endoscopic and histological inflammation, which often necessitates intestinal resection. Indeed, half of CD patients require surgery and bowel resection within 10 years after diagnosis because of strictures, fistulae, and abscesses. This cycle results in the loss of intestinal function and ability [3].

Recent therapeutic advances in inflammatory bowel disease have led to new treatment targets such as mucosal healing and deep remission [4]. Accurate assessment of disease activity is indispensable when ensuring that appropriate therapies are used. Tools such as patients' symptoms, physical examinations, and laboratory data are often used to assess disease activity and complications; however, these have a low specificity and sensitivity and imaging studies are often needed. These studies, therefore, provide accurate assessments of the disease extent and activity. Recently, the Lémann index was developed for damaged lesion scoring [1] (Table 6.1). Cross-sectional imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) have been recommended for assessing small-bowel wall inflammation as well as extramural complications, together with ileocolonoscopy and biological markers. A multi-center study from 24 centers in 15 countries validated this index [5]. The presence or absence of findings affects subsequent management decisions regarding CD.

Table 6.1 Examinations required for Lémann scoring according to Crohn's disease (CD) location

CD location	Upper endoscopy	Colonoscopy	Abdominal MRI enterography	Pelvic MRI	Abdominopelvic CT enterography[a]
Upper digestive tract	○		○		○
Small bowel			○		○
Colon and/or rectum		○	○		○
Perianal and anal			○	○	○

[a]Computed tomography (CT) enterography will be performed only in some patients

6.1.1 New Modalities and Radiation Exposure in CD Patients

Seventy percent of patients with CD have small-bowel lesions [6]; therefore, small intestinal disease detection is important. Historically, barium studies such as small barium follow-through (SBFT) and conventional enteroclysis have been standard CD evaluation techniques. However, these barium studies are limited with regard to observing the bowel wall, extraluminal extension, and overlapping bowel loops.

Recently, non-invasive imaging has played an increasingly important role in the assessment of CD [7]. Video capsule endoscopy (VCE) performs well, compared to other small bowel imaging modalities, in patients with CD. In a meta-analysis, the yields of VCE and MR enterography did not significantly differ in either suspected or established CD patients [8]. However, VCE has important limitations, including a high risk of retention due to stenosis, poor localization of bowel abnormalities, and a lack of tissue diagnosis [9]. Ultrasonography (US) is an inexpensive modality with widespread availability, although operator dependence and difficulty with gastrointestinal tract viewing are significant disadvantages [10]. Computed tomography (CT) enterography has been the cross-sectional imaging modality of choice when evaluating CD patients. However, recent recognition of the potential long-term effects of repeated ionizing radiation exposure from CT scans has led to increased interest in the application of non-ionizing-radiation-based cross-sectional imaging modalities for patients with chronic diseases [1, 11].

CD is typically diagnosed at a young age. These patients often experience chronic relapses during their lifetimes, necessitating multiple imaging examinations involving radiation. The most recent Australian population-based cohort study assessed the risks in children and adolescents following exposure to low-dose ionizing radiation from a diagnostic CT. All exposures to the funded CT in people aged 0–19 years were identified from a cohort of 10.9 million people from Australian Medicare records. The overall cancer incidence was 24% greater for those exposed to radiation than for those unexposed. A dose–response relationship was also observed, with a 0.16 increase in the IRR for each additional CT scan [12]. In children, limiting radiation exposure is particularly important. CD, a long-term disease, often affects young patients and usually requires the collection of periodic control images; thus, radiation limitation is a serious consideration [13]. CT should thus, be used with caution in young patients with CD.

6.1.2 Magnetic Resonance Imaging in CD

As mentioned above, patients with CD must undergo repeated multiple imaging examinations to monitor disease activity and guide appropriate treatment. For those reasons, the desirable imaging modality would be reproducible, well tolerated, and free of ionizing radiation. Recent studies and reviews have focused on the roles of

new MR techniques optimized for bowel imaging in the evaluation of bowel disorders [14–16]. Relative to MR, CT has advantages such as better spatial resolution, superior image quality, and lower acquisition time, whereas the advantages of MR over CT include a lack of ionizing radiation, high-contrast soft-tissue resolution, and a superior intravenous contrast safety profile. The disadvantages of MRI include higher costs and reduced availability. Recent advances in MRI have allowed the rapid acquisition of high-resolution images, leading to ultrafast sequences and the assessment of bowel disorders. MR can simultaneously assess the bowel surface, bowel wall, and perianal lesions such as perianal fistulae and perianal abscesses without the issue of overlapping bowel loops. A previous study demonstrated that MR and CT provided equally accurate assessments of CD activity and bowel damage [17]. Furthermore, a meta-analysis of 44 studies found no significant differences in sensitivity and specificity among MRI, US, and CT [18]. Therefore, in the second European evidence-based consensus of the European Crohn's and Colitis Organization (ECCO) it was stated that MR had the highest diagnostic accuracy and was the current standard for assessing the small intestine in CD [19].

6.1.3 MR Enteroclysis/MR Enterography/MR Colonography/ MR Enterocolonography

Four methods are available for MRI-based intestinal evaluation: MR enteroclysis, MR enterography, MR colonography, and MR enterocolonography (Table 6.2).

MR enteroclysis requires nasojejunal intubation, sometimes with conscious sedation, and the administration of 1500–2000 ml of contrast agent solution via manual injection. This technique provides superior distension of both the jejunum and ileum. A previous study showed that MR enteroclysis better described mucosal changes relative to MR enterography, and had a high level of accuracy equivalent to that of conventional enteroclysis. On the other hand, some studies reported

Table 6.2 MRI-based intestinal evaluation methods

Methods	Evaluation site	Preparation	Intubation	Sensitivity/specificity
MR enteroclysis	Small intestine	1500–2000 ml (nasojejunal)	Nasojejunal	75–90%/84–100%
MR enterography	Small intestine	1350–2000 ml (oral)	–	88–98%/78–100%
MR colonography	colon	1000–3000 ml (oral) 1000–2000 mL (rectal)	Rectal	87–89%/85–100%
MR enterocolonography	Small intestine and colon	200 ml (oral: day before) 1000 ml (oral)	–	Small intestine 82%/88% Colon 83% / 93%

equivalent sensitivities of MR enterography and MR enteroclysis for moderate to severe CD lesions.

However, MR enteroclysis not only requires a more intensive time commitment and is less tolerable, but also requires exposure to additional ionizing radiation with nasojejunal intubation. For these reasons, MR enteroclysis is recommended only as an initial examination in patients with suspected CD [20].

MR enterography (MRE) requires the oral administration of a large amount of solution. Although several different ingestion algorithms have been used, a volume of 1350–2000 ml is adequate in the majority of cases. Typically, the total volume of PEG is administered via division into multiple smaller volumes within 60 min prior to scanning. The sensitivity and specificity for the detection of active inflammation range was from 88% to 98% and from 78% to 100%, respectively [14–16]. MRE can be used to follow up and monitor disease activity and the effects of medical therapies such as immune-modulating agents, because it is free from the radiation exposure and discomfort associated with nasojejunal intubation.

For MR colonography, patients are required to ingest 1000–3000 ml of PEG orally 4 h before MR for bowel cleansing [21, 22], and 1000–2000 ml of solution is retrogradely instilled into the colon through a rectal balloon catheter. MR and endoscopy results were found to exhibit an acceptable concordance, with a sensitivity of 87–89%, specificity of 85–100%, and significant correlation between CDAI and the MR index [21]. In a recent study, diffusion-weighted imaging (DWI-MRI) colonography without an oral and rectal preparation detected endoscopic inflammation with a sensitivity and specificity of 58% and 85% respectively [23].

MR enterocolonography (MREC) was developed for the simultaneous evaluation of both small- and large-bowel lesions [24]. Magnesium citrate (34 g/200 ml) is ingested the day before the procedure, and 1000 ml of PEG is taken orally 60 min before MR scanning without a nasojejunal intubation or rectal preparation. Compared to the gold-standard balloon-assisted enteroscopy, the respective sensitivities and specificities of MREC for active lesions were 82.4% and 87.6% in the small intestine and 82.8% and 93.2% in the colon [25].

6.1.4 MRE/MREC Assessment

To assess bowel lesions, most centers use a torso coil and a 1.5-T imager to enhance access and image quality reproducibility. Imaging at 3 T yields a higher signal-to-noise ratio and higher spatial resolution but is limited by dielectric effects, banding, and other pulse sequence-related artifacts. MRI scanning protocols comprise various combinations of sequences that highlight different aspects of tissues. The specific sequences, which are defined in Table 6.2, are as follows [16, 26] (Table 6.3): (1) FASE or SSFSE, HASTE, (2) True SSFP or FIESTA, true FISP, bFFE, (3) FSE or TSE with fat-saturation, (4) Diffusion-weighted EPI, (5) SPGR-LAVA or VIBE, eTHRIVE with fat-saturation, and (6) Delayed post contrast 2D T1-weighted SPGR with fat-saturation.

Table 6.3 Sequences for magnetic resonance enterography (MRE)/magnetic resonance enterocolonography (MREC)

Sequences	
Single-shot fast spin echo	(T2 weighted) FASE: fast advanced spin echo (Toshiba) SSFSE: single-shot fast spin echo (GE) HASTE: half-Fourier axial single-shot fast spin-echo (Siemens) SSTSE: single-shot turbo spin echo (Philips)
Steady-state gradient echo	(Axial & coronal) trueSSFP: true steady-state free precession (Toshiba) FIESTA: fast imaging employing steady-state acquisition (GE) trueFISP: true fast imaging with steady-state precession (Siemens) trueRARE: true rapid acquisition with relaxation enhancement bFFE: balanced fast field echo (Philips)
Fast spin echo	(T2 weighted with fat-saturation) FSE: fast spin-echo (Toshiba, GE) TSE: turbo spin-echo (Siemens, Philips)
Echo planar	Diffusion-weighted EPI: echo planar imaging
3D ultra-fast gradient echo	(Pre- and post-gadolinium contrast 3D with fat-saturation) Quick 3Ds: quick dimensional dynamic diagnostic scan (Toshiba) SPGR-LAVA: spoiled gradient recalled acquisition in the steady state–liver acquisition with volume acceleration (GE) VIBE: volumetric interpolated breath-hold examination (Siemens) eTHRIVE: enhanced T1 high-resolution isotropic volume excitation (Philips)

MR can describe active CD-related changes such as wall thickening, ulcerations, increased enhancement, and obstructions. Wall thickness is defined as a thickness >3 mm, but is often affected by the degree of distension. With techniques such as cine-MRI and the ability to obtain multiple sequences, MRI can demonstrate one segment at different degrees of bowel distention. Fibro-stenotic lesions exhibit a lower signal intensity on T2-weighted sequences, compared to thickened lesions with active inflammation. When triaging patients into either medical or surgical management, it is important to distinguish active from the fibro-stenotic disease.

6.1.5 Evaluation of Therapeutic Effectiveness and Prediction of Recurrence

The MR index of activity (MaRIA) is the most validated MRE score:

MaRIA = 1.5 × wall thickness (mm) + 0.02 × relative contrast enhancement (RCE) + 5 × edema (0 or 1) + 10 × ulcers (0 or 1) [21].

{RCE = [(wall signal intensity (WSI) postgadolinium – WSI pregadolinium)/(WSI pregadolinium)] × 100 × [SD noise pregadolinium/SD noise postgadolinium]}.

MaRIA was calculated by adding the values of rectum, sigmoid, descending, transverse and ascending colon and ileum. MaRIA was shown to correlate significantly with the Crohn's Disease Endoscopic Index of Severity (CDEIS) via ileocolonoscopy ($r = 0.83$, $P < 0.001$) [27]. MRE was found to accurately assess responses to anti-TNF antibody therapy. In addition, MRE of mucosal healing with a MaRIA <7 exhibited a sensitivity of 85% and specificity of 78% [28]. When applied to the deep small intestine, MaRIA correlated closely with applied SES-CD, and MRE mucosal healing exhibited a high sensitivity of 87% and a specificity of 86% relative to endoscopic mucosal healing defined by enteroscopy [29].

Recently, MRE was found to accurately detect the presence of severe fibrosis in CD lesions based on enhancement patterns, using the pathological analysis of surgically resected intestinal lesions as a reference standard [30].

Endoscopically confirmed mucosal healing is the gold standard for evaluating CD recurrence. In addition, MRI-based scores for the detection of postoperative recurrence have been developed and validated. With MR enteroclysis, mild bowel-wall thickening and enhancement without stricture are considered signs of low-grade recurrence, although increased thickness and marked strictures have been found to be associated with severe recurrence after ileocolic resection [31, 32]. Furthermore, Fujii et al. reported that patients with active lesions on MREC had significantly higher rates of recurrence, hospitalization, and operation than did patients without active lesions, even among those who had achieved clinical remission and had negative C-reactive protein results, and ileocolonoscopy-confirmed mucosal healing [33]. These data suggest that MREC is useful for predicting CD recurrence, and might also be able to identify patients who require treatment intensification beyond mucosal healing.

6.2 Case Presentation

6.2.1 Normal Case

According to the MREC protocol, contrast agent solution is administered to provide superior distension from the jejunum to rectum in contrast-enhanced gradient echo sequences (e.g., true SSFP) (Fig. 6.1a, b); increased enhancement is not observed on coronal contrast-enhanced T1-weighted fat-saturated 3D images (Fig. 6.1c).

6.2.2 Case of Ulceration 1

Active lesions with inflammation, such as ulcerations, are described as mural irregularities on true SSFP and T2-weighted images. Severe, deep lesions such as longitudinal ulcers in the ileum, shown with balloon-assisted enteroscopy (Fig. 6.2a) and

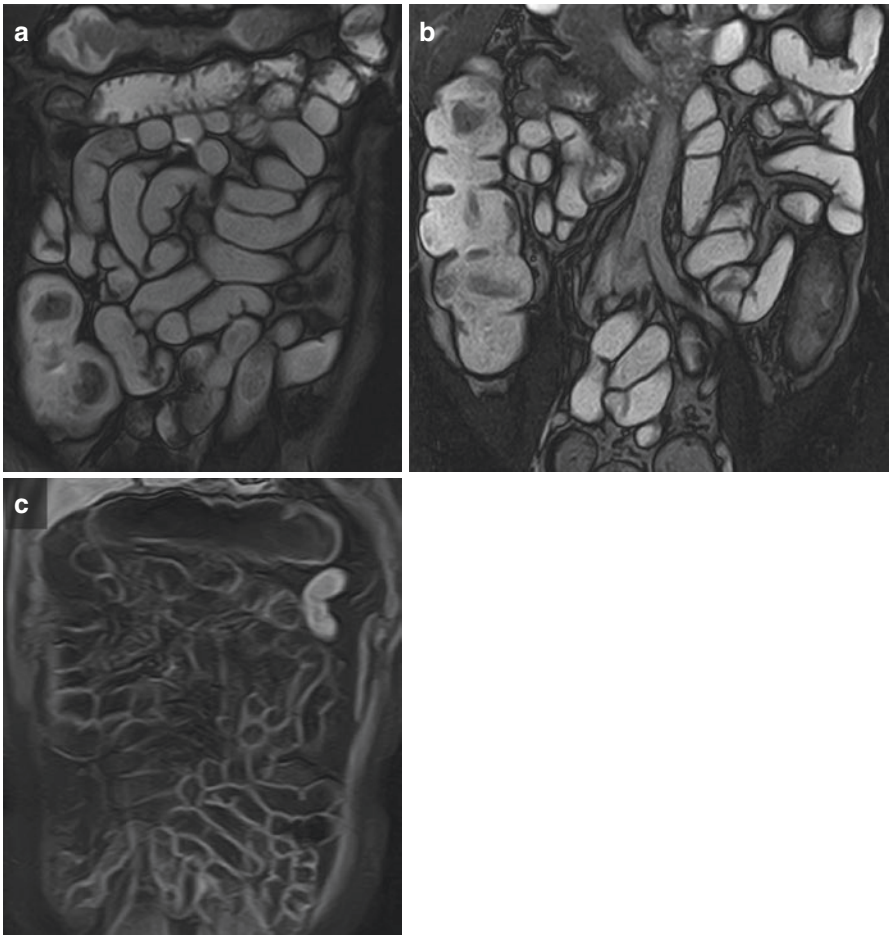


Fig. 6.1 Normal case

SBFT (Fig. 6.2b, arrow) are described as bowel-wall thickening in the ileum on coronal true SSFP images (Fig. 6.2c, arrow).

6.2.3 Case of Ulceration 2

Figure 6.3a shows representative longitudinal ulcers in the ileum. These ulcers appear as bowel-wall thickening (Fig. 6.3b, arrow), and a coronal contrast-enhanced T1-weighted image of the ileum shows uniform wall enhancement with thickening (Fig. 6.3c, arrow). These findings indicate severe inflammatory changes. Severe,

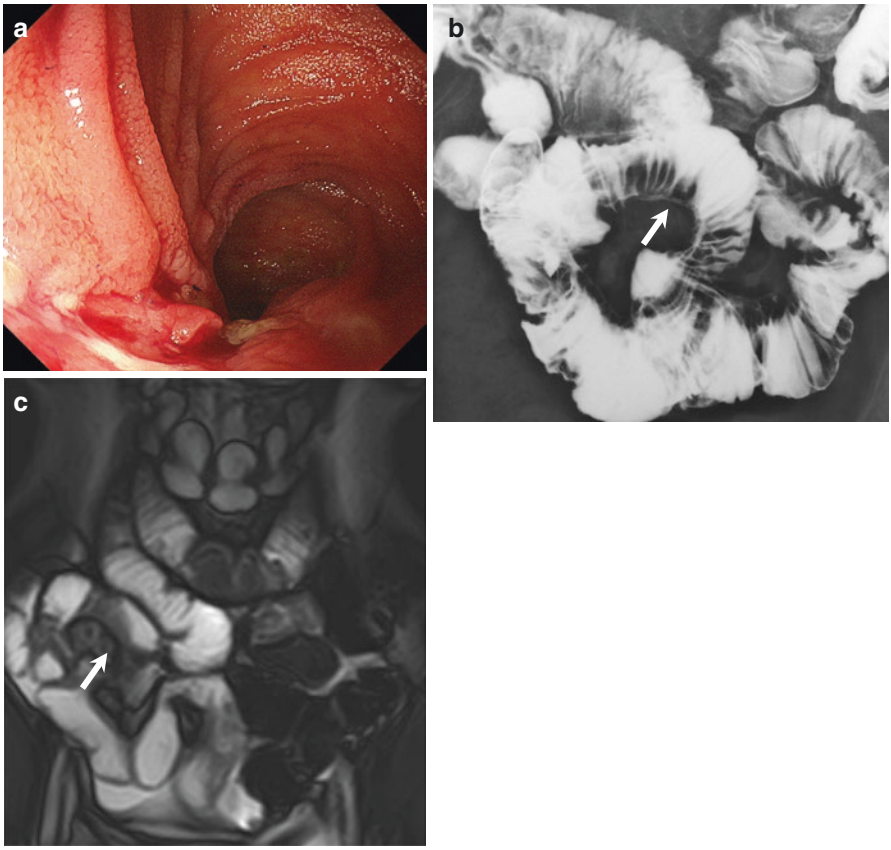


Fig. 6.2 Case of ulceration 1

deep lesions and submucosal edema are indicated by hyperenhancement and often with the "comb sign"; however, mild mucosal lesions appear only as mucosal hyperenhancement.

6.2.4 Case of Fibro-Stenosis

Ileocecal fibro-stenosis shown using balloon-assisted enteroscopy (BAE) (Fig. 6.4a) appears as a lower signal intensity stenosis on a true SSFP image (Fig. 6.4b, arrow) and is not enhanced on a coronal contrast-enhanced T1 image (Fig. 6.4d, arrow) with distention of the proximal ileum. Such fibro-stenosis indicates endoscopic balloon dilation (Fig. 6.4b).

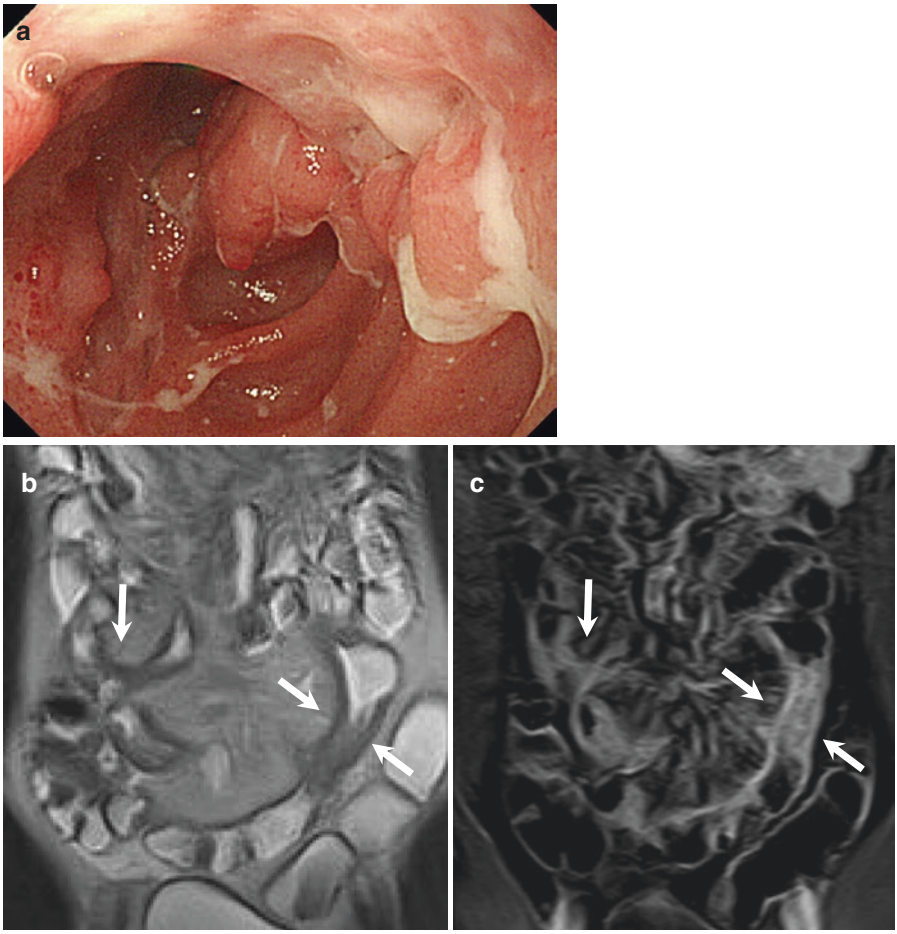


Fig. 6.3 Case of ulceration 2

6.2.5 Case of Stenosis with Ulcer

Multiple stenoses with active inflammation in the ileum are shown as intestinal narrowing with wall thickness, and edema with distention of the proximal ileum in true SSFP images (Fig. 6.5a, b, c, arrows) and as hyperenhancement on contrast-enhanced T1 images (Fig. 6.5d, e, arrows).

6.2.6 Case of Internal Fistula

Cross-sectional imaging, including MR, is superior to barium studies for detecting penetrating lesions. Moreover, cases of abscesses and perianal lesions have shown MR to be an adequate modality. An ileum–ileum fistula, shown in BAE (Fig. 6.6a),

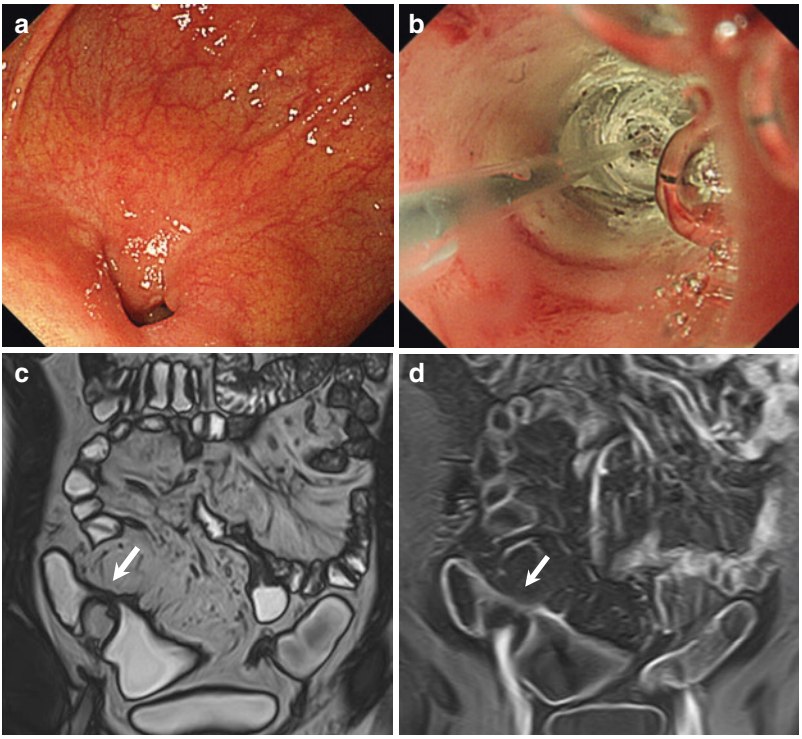


Fig. 6.4 Case of fibro-stenosis

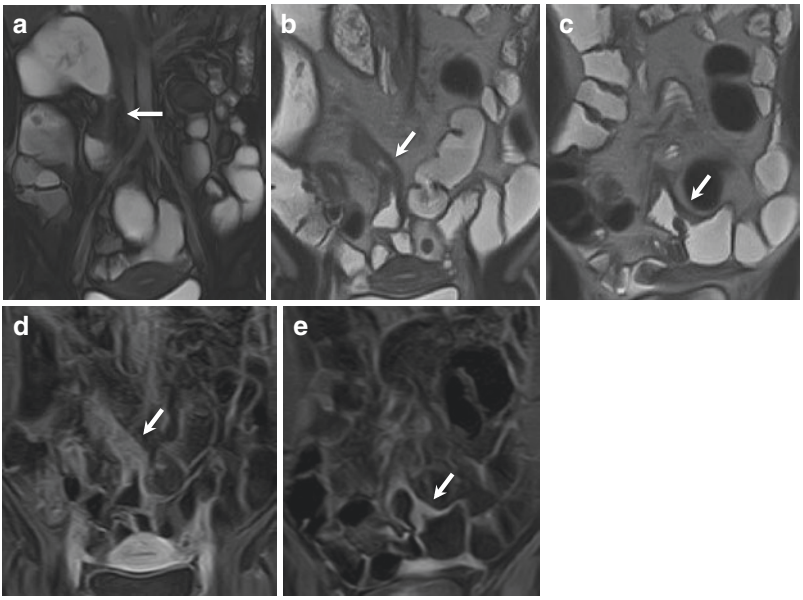


Fig. 6.5 Case of stenosis with ulcer

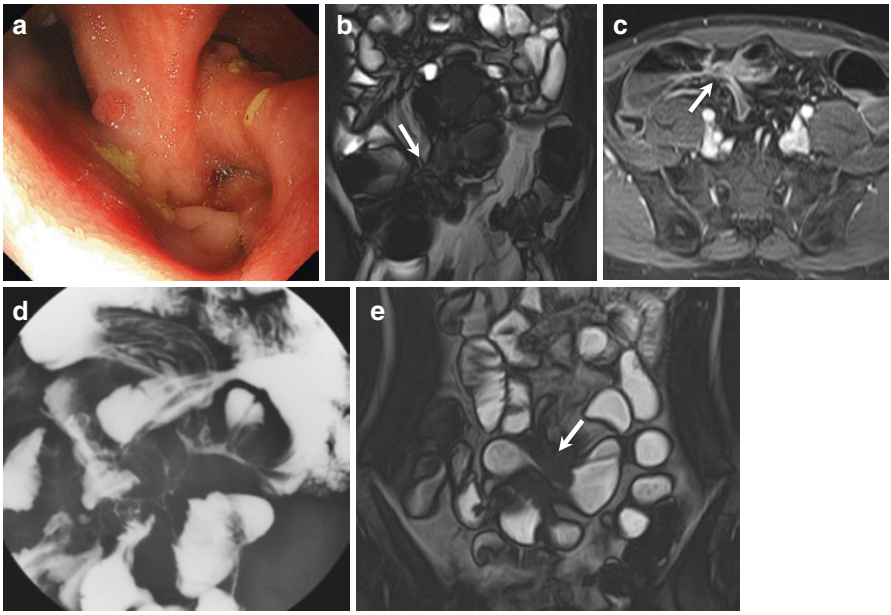


Fig. 6.6 Case of internal fistula

appears as a stellate-appearing complex internal fistula on coronal and axial images (Fig. 6.6b, c, arrows) obtained from contrast-enhanced T1-weighted fat-saturated 3D imaging. Similarly, the complex fistula shown in SBFT (Fig. 6.6d) is clearly recognized on a true SSFP image (Fig. 6.6e, arrows).

6.3 Summary

Recent advances in MRI have led to its reputation as the first-line modality for CD assessment. MRI with colonoscopy should be recommended as the initial mode of investigation in patients with suspected CD. VCE or conventional enteroclysis may be performed as a second-line modality if MRI shows negative findings in patients with suspected CD. If available, balloon endoscopy of the small intestine should also be performed for pathological purposes.

MRI is highly sensitive with regard to disease diagnosis and plays an important role in the assessment of disease activity without requiring ionizing radiation exposure. MRI allows a comprehensive evaluation of overall disease activity, including intra- and extraluminal lesions, and disease monitoring over time, which could be useful for tailoring therapeutic strategies. Moreover, the ability to predict recurrence indicates that MRI could be useful for avoiding repeated colonoscopies in the future.

Further studies of larger populations of patients are required, and remaining issues such as cost, availability, and the experience of radiologists should be addressed.

References

1. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis. 2011;17:1415–22.
2. Cosnes J, et al. Long-term evolution of disease behavior of Crohn's disease. Inflamm Bowel Dis. 2002;8:244–50.
3. Peyrin-Biroulet L, Loftus Jr EV, Colombel JF, et al. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol. 2010;105:289–97.
4. Rutgeerts P, Vermeire S, Van Assche G. Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target? Gut. 2007;56:453–5.
5. Pariente B, Mary JY, Danese S, Chowers Y, et al. Development of the Lémann index to assess digestive tract damage in patients with Crohn's disease. Gastroenterology. 2015;148:52–63.e3.
6. Travis SP, Stange EF, Le'mann M, et al. European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. Gut. 2006;55(Suppl 1):i16–35.
7. Allen PB, De Cruz P, Lee WK, et al. Noninvasive imaging of the small bowel in Crohn's disease: the final frontier. Inflamm Bowel Dis. 2011;17:1987–99.
8. Dionisio PM, Gurudu SR, Leighton JA, et al. Capsule endoscopy has a significantly higher diagnostic yield in patients with suspected and established small-bowel Crohn's disease: a meta-analysis. Am J Gastroenterol. 2010;105:1240–8.
9. Cheifetz AS, Kornbluth AA, Legnani P, et al. The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. Am J Gastroenterol. 2006;101:2218–22.
10. Fraquelli M, Colli A, Casazza G, et al. Role of US in detection of Crohn disease: meta-analysis. Radiology. 2005;236:85–101.
11. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation exposure. N Engl J Med. 2007;357:2277–84.
12. Mathews JD, Forsythe AV, Brady Z, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ. 2013;21:346.
13. Peloquin JM, Pardi DS, Sandborn WJ, et al. Diagnostic ionizing radiation exposure in a population-based cohort of patients with inflammatory bowel disease. Am J Gastroenterol. 2008;103:2015–22.
14. Fiorino G, Bonifacio C, Malesci A, et al. MRI in Crohn's disease–current and future clinical applications. Nat Rev Gastroenterol Hepatol. 2012;9:23–31.
15. Amitai MM, Ben-Horin S, Eliakim R, et al. Magnetic resonance enterography in Crohn's disease: a guide to common imaging manifestations for the IBD physician. J Crohns Colitis. 2012;7:603–15.
16. Zimmermann EM, Al-Hawary MM. MRI of the small bowel in patients with Crohn's disease. Curr Opin Gastroenterol. 2011;27:132–8.
17. Fiorino G, Bonifacio C, Peyrin-Biroulet L, et al. Prospective comparison of computed tomography enterography and magnetic resonance enterography for assessment of disease activity and complications in ileocolonic Crohn's disease. Inflamm Bowel Dis. 2011;17:1073–80.
18. Horsthuis K, Bipat S, Bennink RJ, et al. Inflammatory bowel disease diagnosed with US, MR, scintigraphy, and CT: meta-analysis of prospective studies. Radiology. 2008;247:64–79.
19. Van Assche G, Dignass A, Panes J, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. J Crohns Colitis. 2010;4:7–27.
20. Masseli G, Gualdi G. MR imaging of the small bowel. Radiology. 2012;264:333–48.
21. Rimola J, Rodriguez S, García-Bosch O, et al. Magnetic resonance for assessment of disease activity and severity in ileocolonic Crohn's disease. Gut. 2009;58:1113–20.
22. Schreyer AG, Rath HC, Kikinis R, et al. Comparison of magnetic resonance imaging colonography with conventional colonoscopy for the assessment of intestinal inflammation in patients with inflammatory bowel disease: a feasibility study. Gut. 2005;54:250–6.

23. Oussalah A, Laurent V, Bruot O, et al. Diffusion-weighted magnetic resonance without bowel preparation for detecting colonic inflammation in inflammatory bowel disease. Gut. 2010;59:1056–65.
24. Hyun SB, Kitazume Y, Nagahori M, et al. Magnetic resonance enterocolonography is useful for simultaneous evaluation of small and large intestinal lesions in Crohn's disease. Inflamm Bowel Dis. 2011;17:1063–72.
25. Takenaka K, Ohtsuka K, Fujii T, et al. Comparison of magnetic resonance and balloon enteroscopic examination of the small intestine in patients with Crohn's disease. Gastroenterology. 2014;147:334–42.
26. Fujii T, Naganuma M, Kitazume Y, et al. Advancing MR imaging in Crohn's disease. Digestion. 2014;89:24–30.
27. Rimola J, Ordás I, Rodriguez S, et al. Magnetic resonance imaging for evaluation of Crohn's disease: validation of parameters of severity and quantitative index of activity. Inflamm Bowel Dis. 2011;17:1759–68.
28. Rimola J, Ordás I, Rodriguez S, et al. Accuracy of magnetic resonance enterography in assessing response to therapy and mucosal healing in patients with Crohn's disease. Gastroenterology. 2014;146:374.e1–82.e1.
29. Takenaka K, Ohtsuka K, Kitazume Y, et al. Correlation of the endoscopic and magnetic resonance scoring systems in the deep small intestine in Crohn's disease. Inflamm Bowel Dis. 2015;21:1832–8.
30. Rimola J, Planell N, Rodríguez S, et al. Characterization of inflammation and fibrosis in Crohn's disease lesions by magnetic resonance imaging. Am J Gastroenterol. 2015;110:432–40.
31. Sailer J, Peloschek P, Reinisch W, et al. Anastomotic recurrence of Crohn's disease after ileocolic resection: comparison of MR enteroclysis with endoscopy. Eur Radiol. 2008;18:2512–21.
32. Koilakou S, Sailer J, Peloschek P, et al. Endoscopy and MR enteroclysis: equivalent tools in predicting clinical recurrence in patients with Crohn's disease after ileocolic resection. Inflamm Bowel Dis. 2010;16:198–203.
33. Fujii T, Naganuma M, Kitazume Y, et al. 556 MR enterocolonography is useful to predict clinical recurrence of Crohn's disease and identify patients who need more aggressive treatment. Gastroenterology. 2013;144:S-102.

Part II
Endoscopic Diagnosis of IBD

Chapter 7
Diagnosis of Ulcerative Colitis: Typical Findings and Diagnostic Criteria

Masakazu Nagahori

Abstract Diagnosis of ulcerative colitis (UC) is made by the typical colonoscopic and pathological findings in patients who present with chronic diarrhea. Colonoscopic findings in active disease include erythema, hyperemia, loss of vascularity, granularity, mucopurulent exudates, fragility, and ulcers in a continuous manner. Although colonoscopic and pathological findings are useful for diagnosis, they are not specific and can be observed in patients with other etiology such as infectious colitis. Furthermore, atypical findings such as rectal sparing and skip lesions can be observed in the initial diagnosis. Because appropriate differential diagnosis between UC and Crohn's disease is quite important, especially in the surgical settings, repeated colonoscopy should be considered when appropriate.

Keywords Rectal Sparing • Appendiceal orifice inflammation (AOI) • Backwash ileitis • Endoscytoscopy

7.1 Introduction

Although the evaluation of disease extent by total colonoscopy is important when topical therapy is considered, flexible sigmoidoscopy has been considered to be sufficient for diagnosing UC because of continuous distribution from the rectum. However, with increased recognition of atypical distribution of UC and development of the "easy to manipulate" colonoscope, total colonoscopy is safe and feasible for most active UC patients. Under these circumstances, the knowledge of endoscopic findings of both UC and Crohn's disease as well as appendiceal skip inflammation and backwash ileitis in UC is more important that ever in differential diagnosis between them.

M. Nagahori
Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, Japan
e-mail: nagahori.gast@tmd.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_7

7.2 Endoscopic Manifestation of UC

7.2.1 Pathognomonic Colonoscopic Manifestation

Several pathognomonic manifestations in colonoscopy are useful when to diagnose ulcerative colitis (UC). Inflammation of mucosa initiates from the rectum and is distributed in a continuous manner. The extent of lesions may vary from those limited in the rectum to those extended through the entire colon. However, biopsy should be taken in macroscopically normal-appearing mucosa in the proximal part, as well as in the inflamed distal lesion. It is also known that extension on diagnosis can progress during the follow-up [1].

In colonoscopy, erythema and hyperemia of the colonic mucosa are observed. This is commonly accompanied by the loss of vascularity, granularity, or mucopurulent exudates of the mucosa. When erythematous colonic mucosae are fragile, they bleed easily in minor contact with the colonoscope. However, when the fragility is significant, it may show spontaneous bleeding. Granularity indicates that the surface of mucosa shows unevenness and irregularity, and the degree varies in terms of fineness or roughness.

Ulcers are generally tiny in size and distributed in a limited fashion across the surface, but can grow in size and form linear or circular ulcers. Because mucosal inflammation is pathognomonic in ulcerative colitis, the mucosa surrounding ulcers is also accompanied by erythema or fragility. As ulcers worsen, a wide range of mucosal exfoliation leaves only a portion of the mucosa (Fig. 7.1a–c). When ulcers heal and are replaced with scar tissue; the remaining mucosa protrudes to form polypoid lesions known as pseudo-polyps. If the haustral folds thicken and the hypertrophy or contracture of the muscle layer due to prolonged inflammatory change, the lumen narrows and the haustral folds can be lost. As a result, lumen may appear tube-shaped or show partial stenosis. Colonic strictures are considered to be very uncommon in UC, unlike in CD, especially on diagnosis. However, when it is observed, they should be considered malignant until proven otherwise. In fact, Gumaste et al. reported 29% of strictures turned out to be malignant [2].

7.2.2 Atypical Distribution and Appendiceal Skip Inflammation

Inflammation or ulceration of mucosa initiates from the superjacent area of the anal canal, and is distributed in a continuous and symmetrical manner. Skip lesions are not commonly found. The extent of lesions may vary from those limited in the rectum to those extended to the entire colon. The boundary between the lesion area and the normal mucosa is clearly delineated.

According to a recent study, among the prospective cohort of patients with ulcerative colitis who showed no signs of Crohn's disease, approximately 44% developed skip lesions and about 13% showed lesions that did not involve the rectum [3]. In addition, there were other cases in which patients with ulcerative proctitis or left colitis

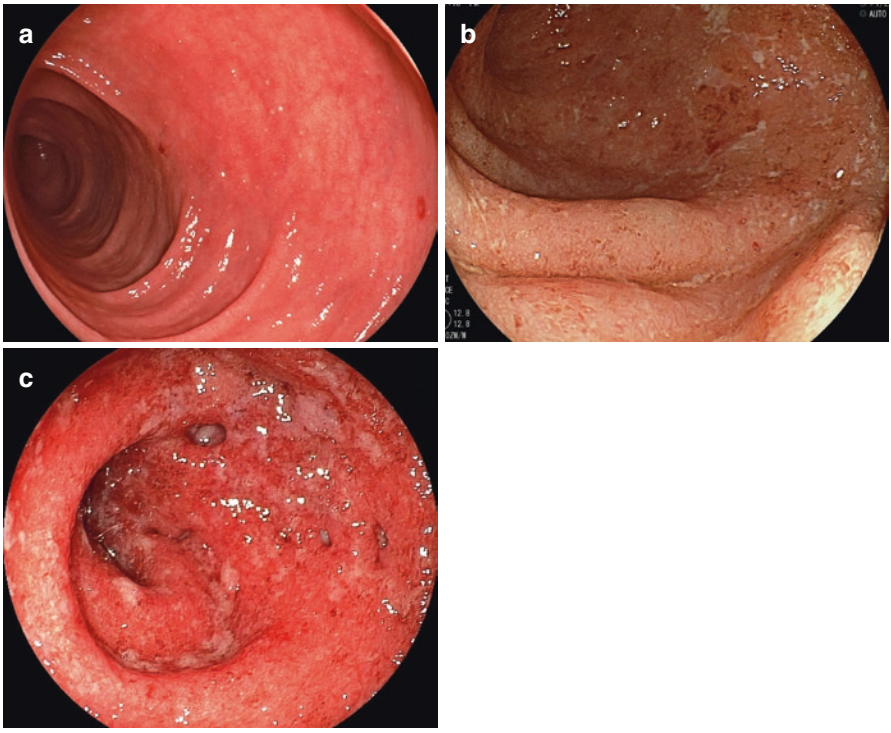


Fig. 7.1 **a** Endoscopic image of a mild UC patient, which show erythema, loss of vascularity, and granularity. **b** Endoscopic image of a moderate UC patient, which show tiny ulcers and mucopurulent exudates. **c** Endoscopic image of a severe UC patient, which show marked fragility, deeper ulcers, and spontaneous bleeding

have inflammation only in the region surrounding the appendiceal orifice, without involving the rest of the colon. The appendiceal orifice inflammation (AOI) also shows erythema, edema, granularity, fragility, and ulceration. Among the several reports to evaluate the prevalence of AOI in total colonoscopy, Byeon et al. reported 51% (48/98) prevalence in newly-diagnosed distal UC patients [4]. The clinical significance of how inflammation around the appendiceal orifice varies is controversial [5].

7.2.3 Small Bowel and Upper Gastrointestinal Manifestation

Generally, the small intestine is not involved in UC, but backwash ileitis, which is defined by endoscopic and/or histological inflammation extending from the cecum into the terminal ileum, commonly by a few centimeters, is observed among 10% of patients with diffuse colitis. Although its etiology is still unknown, its association with concurrent primary sclerosing cholangitis has been suggested [6]. Whether patients who have backwash ileitis are more likely to develop colon cancer is still controversial [6].

7.3 Recent Advances in Endoscopic Imaging for IBD

Despite the recent high-quality endoscopic imaging, pathological findings still play an important role in diagnosing IBD. Neumann et al. introduced endocytoscopy as a new endoscopic imaging modality to evaluate in-vivo microscopic imaging within the mucosal layer of the IBD patients at a magnification up to 1,400-fold. They reported high concordance between endocytoscopy and histopathology for grading intestinal disease activity [7].

7.4 Summary

Despite many differential diagnoses, to diagnose UC by the typical colonoscopic findings in patients who have chronic diarrhea is not difficult. However, we should also keep in mind that atypical findings such as rectal sparing are not uncommon in the initial presentation to avoid inappropriate diagnosis.

References

1. Park SH, Yang SK, Park SK, Kim JW, Yang DH, Jung KW, Kim KJ, Ye BD, Byeon JS, Myung SJ, Kim JH. Atypical distribution of inflammation in newly diagnosed ulcerative colitis is not rare. Can J Gastroenterol Hepatol. 2014;28(3):125–30.
2. Gumaste V, Sachar DB, Greenstein AJ. Benign and malignant colorectal strictures in ulcerative colitis. Gut. 1992;33(7):938–41.
3. Bernstein CN, Shanahan F, Anton PA, Weinstein WM. Patchiness of mucosal inflammation in treated ulcerative colitis: a prospective study. Gastrointest Endosc. 1995;42(3):232–7.
4. Byeon JS, Yang SK, Myung SJ, Pyo SI, Park HJ, Kim YM, Lee YJ, Hong SS, Kim KJ, Lee GH, Jung HY, Hong WS, Kim JH, Min YI. Clinical course of distal ulcerative colitis in relation to appendiceal orifice inflammation status. Inflamm Bowel Dis. 2005;11(4):366–71.
5. Park SH, Loftus Jr EV, Yang SK. Appendiceal skip inflammation and ulcerative colitis. Dig Dis Sci. 2014;59(9):2050–7. doi:10.1007/s10620-014-3129-z.
6. Navaneethan U, Jegadeesan R, Gutierrez NG, Venkatesh PG, Arrossi AV, Bennett AE, Rai T, Remzi FH, Shen B, Kiran RP. Backwash ileitis and the risk of colon neoplasia in ulcerative colitis patients undergoing restorative proctocolectomy. Dig Dis Sci. 2013;58(7):2019–27. doi:10.1007/s10620-013-2571-7.
7. Neumann H, Vieth M, Neurath MF, Atreya R. Endocytoscopy allows accurate in vivo differentiation of mucosal inflammatory cells in IBD: a pilot study. Inflamm Bowel Dis. 2013;19(2):356–62. doi:10.1002/ibd.23025.

Chapter 8
Typical Endoscopic Findings and Diagnostic Criteria for Crohn's Disease

Tadakazu Hisamatsu

Abstract Crohn's disease (CD) is a chronic inflammatory disorder whose etiology remains unknown. CD irregularly affects the entire gastrointestinal tract, and causes intestinal complications such as fistula and stricture. CD is diagnosed by integration of physiological, radiological, endoscopic, serological, and histological findings. In particular, typical endoscopic findings of ileocolonoscopy such as "cobblestone appearance" and "longitudinal ulcer" are the gold standard for diagnosis of CD. Development of new techniques such as balloon endoscopy and capsule endoscopy yield more information with regard to small intestinal lesions. The importance of upper gastrointestinal endoscopy has been reported, and it often detects lesions in the esophagus, stomach, and duodenum in patients with CD. Endoscopic examination is important to exclude infectious disease, especially when immunosuppressive therapy is considered.

Keywords Aphthous erosion • Bamboo-like appearance • Cobblestone appearance • Crohn's disease • Fissuring ulcer • Granuloma • Longitudinal ulcer • Skip lesion

8.1 Introduction

Crohn's disease (CD) is a chronic inflammatory disorder whose etiology remains unknown. CD irregularly affects the entire gastrointestinal tract, unlike ulcerative colitis (UC), which is restricted to the colon and rectum. CD is often aggressive and causes intestinal complications such as fistula and stricture. Cumulative operative risk is ~50% within 10 years after diagnosis [1], and multiple bowel resections can cause short-bowel syndrome and malnutrition. Therefore, in recent years, it has been proposed that CD is a progressive disorder. Although sufficient evidence has not been shown, early diagnosis followed by intervention (i.e., tumor necrosis factor monoclonal antibodies) is expected to change the natural history and improve long-term prognosis of CD.

T. Hisamatsu
Division of Gastroenterology and Hepatology, The Third Department of Internal Medicine, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka-shi, Tokyo 181-8611, Japan
e-mail: thisamatsu@ks.kyorin-u.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_8

CD is diagnosed by integration of physiological, radiological, endoscopic, serological and histological findings. Because of the lack of specific disease markers, typical endoscopic findings are the gold standard for diagnosis of CD. In addition, development of balloon endoscopy and capsule endoscopy yields much information with regard to small intestinal lesions.

8.2 Typical Endoscopic Findings of CD

8.2.1 Role of Endoscopy in Diagnosis of CD

Although CD can affect the entire gastrointestinal tract, the most commonly affected areas are the small intestine (ileum) and colon. In particular, the terminal ileum is frequently affected in ileocolonic CD. Therefore, ileocolonoscopy is the gold standard for diagnosis and evaluation of CD. In the consensus regarding endoscopy of the European Crohn's and Colitis Organization (ECCO), ileocolonoscopy is proposed as the most important and powerful method in the diagnosis of inflammatory bowel disease (IBD) [2]. The consensus recommends that ileocolonoscopy should be performed before the initiation of any medical treatment.

8.2.2 Typical Endoscopic Findings of CD in the Small Intestine and Colon

The typical endoscopic findings of CD are the patchy distribution of inflammation with skip lesions (areas of inflammation interposed between normal-appearing mucosa) [2]. Typical CD lesions are "cobblestone appearance" (Fig. 8.1a) and "longitudinal ulcers" (Fig. 8.1b, c). In endoscopic and radiological examinations, longitudinal ulcers in the small intestine are located at the site of mesenteric attachment. Anal lesions are also important for diagnosis of CD. In CD, intestinal complications such as fistula and stricture are often observed. Endoscopy sometimes detects the primary lesions of perianal fistula (Fig. 8.2). Histologically, transmural inflammation and deep ulcers (fissuring ulcers) are observed in surgical specimens. Histological examination of biopsy specimens taken from the ulcers and aphthous erosions is useful for detecting noncaseating granuloma [3, 4].

Aphthous erosions in the small intestine, colon, and upper gastrointestinal (GI) tract are often observed in CD. These lesions could be endoscopic features of the early phase of CD. Granuloma is often detected by biopsy in aphthous lesions. Tsurumi et al. retrospectively investigated the incidence of aphthous-type CD in 649 patients diagnosed between 1985 and 2011. The incidence of aphthous-type CD was 5.2% (1985–2004) and 8.5% (2005–2011), respectively. With regard to the clinical course, 59.3% of cases of aphthous-type CD progressed to typical CD [5].

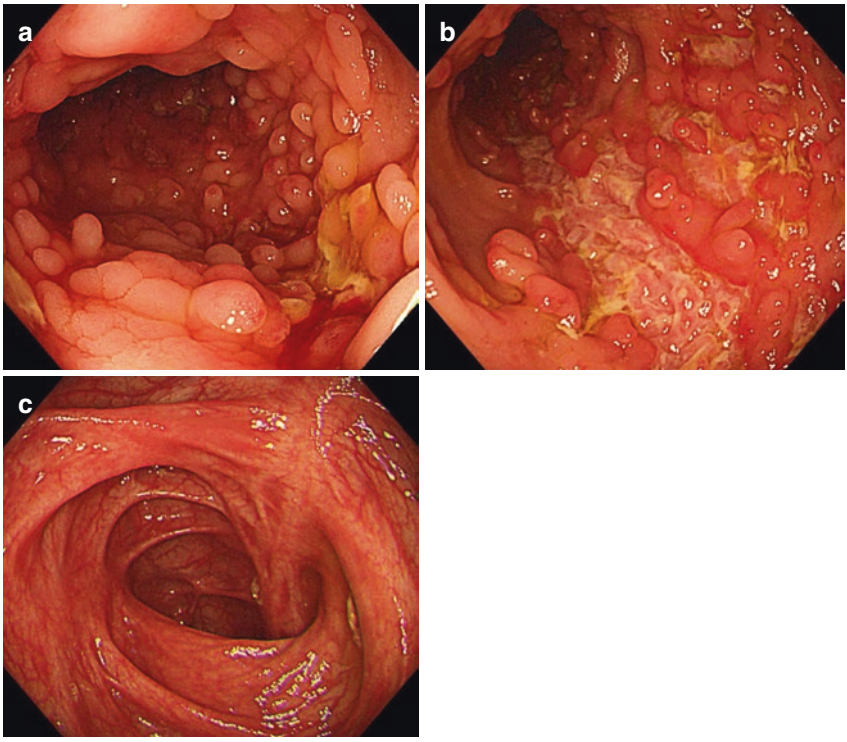


Fig. 8.1 Typical endoscopic findings of CD. Cobblestone appearance in the colon (**a**). Longitudinal ulcer in the colon (**b**). Scar formation of longitudinal ulcers (mucosal healing) (**c**)

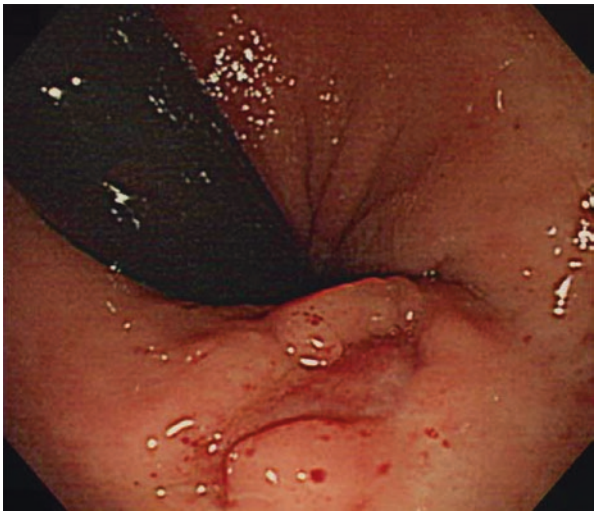


Fig. 8.2 Endoscopic examination can detect the primary lesion of perianal fistula

The role of endoscopy for diagnosis and management of fistulizing CD has been discussed [6]. An expert panel concluded that the highest diagnostic accuracy of fistulizing CD can only be established if a combination of modalities is used. Endoscopic assessment of the rectum is recommended as an essential procedure to determine the most appropriate management strategy.

8.2.3 Importance of Upper GI Endoscopy in CD

The upper GI tract including the stomach and duodenum is also involved in CD. Upper GI endoscopy plays an important role in the diagnosis of pediatric CD. Lenaerts et al. reported the results of a retrospective study of CD in 230 children and adolescents with a mean age of 12.5 years at the time of diagnosis. During an average follow-up of 6.6 years, 30% of patients had lesions of the esophagus, stomach, and duodenum [7]. A prospective observational study of 56 children and adolescents with CD showed a high incidence (71%) of upper GI involvement [8]. In a study of childhood-onset IBD in Scotland (276 CD, 99 UC, 41 IBD of unclassified type, diagnosed before aged 17 years), at the time of diagnosis, CD involved the upper GI tract in 51% of cases, as well as the small bowel and colon in 51%, colon in 36%, and ileum in 6% [9]. A survey of a Belgian registry for pediatric CD also demonstrated a high frequency of upper GI involvement in pediatric CD patients [10]. The incidence of esophageal involvement in pediatric CD was ≤43%, while in adults it was only 0.2–11.2% [11]. Histopathological examination of the upper GI is useful for the diagnosis of CD. In comparison between 24 pediatric patients with CD and 28 age-matched patients without CD, histological abnormalities including noncaseating granulomas in the stomach and duodenum were more frequent in CD patients [12]. Hummel et al. also reported the importance of histopathological examination for the diagnosis of CD. In 11% of children with CD, diagnosis was based solely on granulomatous inflammation in the upper GI tract. Focal cryptitis of the duodenum and focally enhanced gastritis were found significantly more frequently in children with CD compared to those with UC and non-IBD [13]. Thus, discrimination between UC and CD may sometimes be difficult with ileocolonoscopy alone because of a lack of definitive lesions, especially in patients with newly diagnosed IBD and indeterminate colitis. Upper GI endoscopy should be performed as the first-line investigation in those patients.

Various endoscopic findings in the upper GI tract are observed in patients with CD. Solitary or longitudinal ulcers and erosions of the esophagus can be seen (Fig. 8.3). Intestinal Behcet's disease can also involve the esophagus, therefore it should be ruled out. Aphthous erosions in the gastric antrum and

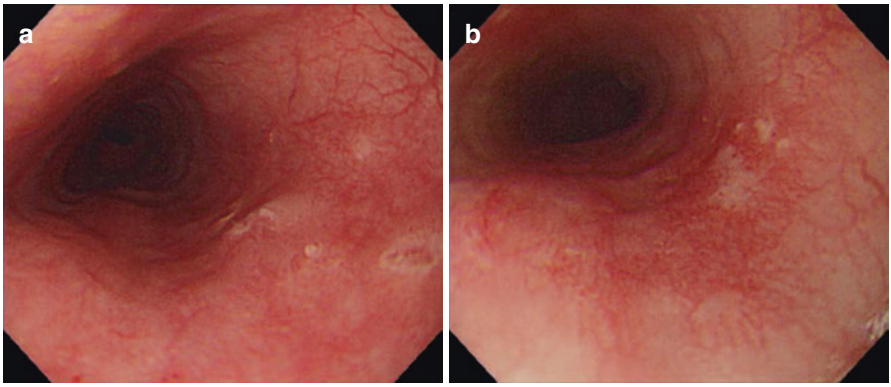


Fig. 8.3 Esophageal lesions in CD. Solitary small ulcers (**a**) and erosions with redness (**b**)

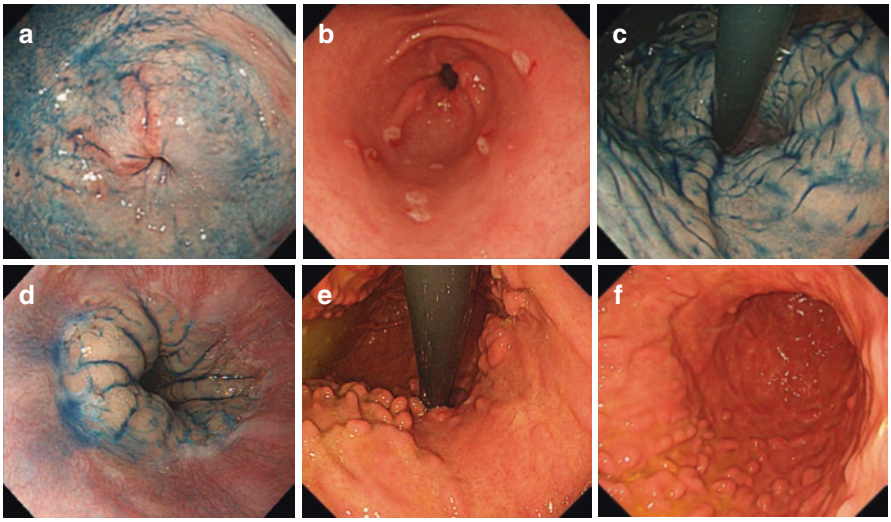


Fig. 8.4 CD lesions in the stomach. Aphthous erosions in the antrum (**a**, **b**). Bamboo-joint like appearance in upper portion of the gastric corpus (**c**, **d**). Cobblestone appearance in the stomach (**e**, **f**)

bamboo-joint like appearance in the upper portion of the gastric corpus are often seen in CD [14] (Fig. 8.4a–f). Observation of the duodenum is also important for the diagnosis of CD. Various endoscopic findings including aphthous erosions, cobblestone appearance, and longitudinal ulcers are seen. Notch signs in the second portion of the duodenum are typical findings of CD (Fig. 8.5a–f).

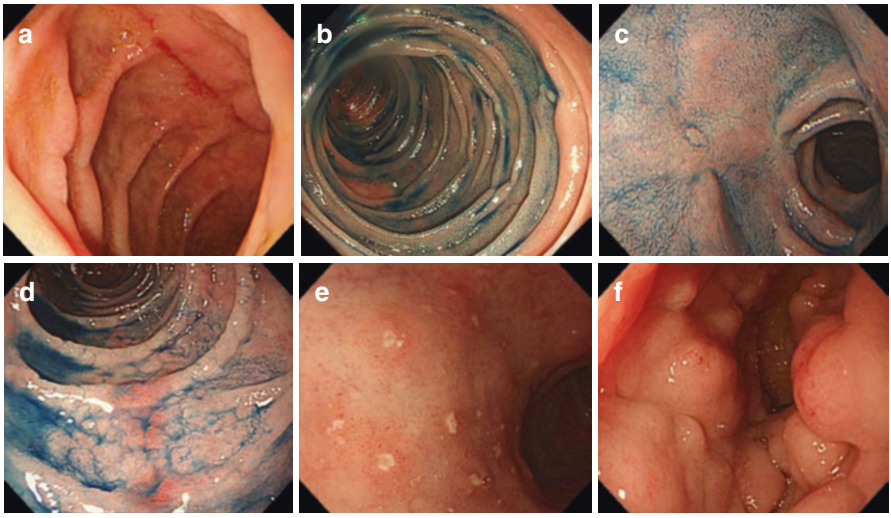


Fig. 8.5 Various CD lesions in the duodenum. Notch signs in the second portion (**a**, **b**). Longitudinal ulcer scar (**c**). Aphthous erosions (**d**, **e**). Cobblestone appearance (**f**)

8.3 Role of Endoscopic Findings in Diagnostic Criteria

Although there is no gold standard of IBD diagnostic criteria, several consensuses and criteria have been proposed [15–18]. As described above (Sect. 8.2.1), ECCO recommend ileocolonoscopy for the diagnosis of CD [2]. Although the diagnosis of CD should be performed comprehensively, typical endoscopic and radiological findings such as skip lesions with longitudinal ulcers and cobblestone appearance are important. In the diagnostic criteria for CD in Japan [19], longitudinal ulcer, cobblestone appearance, and noncaseating granuloma are defined as major findings. Aphthous lesions, anal lesions, and upper GI lesions are defined as supplementary findings. Hisabe et al. evaluated the Japanese diagnostic criteria for CD [20]. The survey included 579 patients with a definitive diagnosis of CD, and 59 with a suspected diagnosis of CD. In that survey, a total of 87.4% of definitive diagnoses of CD were based on the findings of longitudinal ulcer or cobblestone appearance. In the Asia–Pacific region, the importance of exclusion of infectious diseases, including intestinal tuberculosis, has been emphasized [21]. Understanding of typical endoscopic and radiological findings must be helpful to exclude various non-IBD diseases.

8.4 Summary

In this chapter, typical endoscopic findings of CD were reviewed. Ruling out differential diagnoses, especially infectious disease such as intestinal tuberculosis, is important. Morphological characteristics and distribution are important for endoscopic diagnosis. It is assumed that the endoscopic findings of early CD are already established, and earlier diagnosis and therapeutic intervention could be practical.

References

1. Peyrin-Biroulet L, Loftus Jr EV, Colombel JF, et al. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol. 2010;105:289–97. doi:10.1038/ajg.2009.579.
2. Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7:982–1018. doi:10.1016/j.crohns.2013.09.016.
3. Geboes K, Ectors N, D'Haens G, et al. Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of inflammatory bowel disease? Am J Gastroenterol. 1998;93:201–6.
4. Van Assche G, Dignass A, Panes J, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. J Crohns Colitis. 2010;4:7–27.
5. Tsurumi K, Matsui T, Hirai F, et al. Incidence, clinical characteristics, long-term course, and comparison of progressive and nonprogressive cases of aphthous-type Crohn's disease: a single-center cohort study. Digestion. 2013;87:262–8. doi:10.1159/000350615.
6. Gecse KB, Bemelman W, Kamm MA, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. Gut. 2014;63:1381–92. doi:10.1136/gutjnl-2013-306709.
7. Lenaerts C, Roy CC, Vaillancourt M, et al. High incidence of upper gastrointestinal tract involvement in children with Crohn disease. Pediatrics. 1989;83:777–81.
8. Cameron DJ. Upper and lower gastrointestinal endoscopy in children and adolescents with Crohn's disease: a prospective study. J Gastroenterol Hepatol. 1991;6:355–8.
9. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135:1114–22. doi:10.1053/j.gastro.2008.06.081.
10. De Greef E, Mahachie John JM, Hoffman I, et al. Profile of pediatric Crohn's disease in Belgium. J Crohns Colitis. 2013;7:e588–98. doi:10.1016/j.crohns.2013.04.016.
11. Ramaswamy K, Jacobson K, Jevon G, et al. Esophageal Crohn disease in children: a clinical spectrum. J Pediatr Gastroenterol Nutr. 2003;36:454–8.
12. Schmidt-Sommerfeld E, Kirschner BS, Stephens JK. Endoscopic and histologic findings in the upper gastrointestinal tract of children with Crohn's disease. J Pediatr Gastroenterol Nutr. 1990;11:448–54.
13. Hummel TZ, ten Kate FJ, Reitsma JB. Additional value of upper GI tract endoscopy in the diagnostic assessment of childhood IBD. J Pediatr Gastroenterol Nutr. 2012;54:753–7. doi:10.1097/MPG.0b013e318243e3e3.
14. Yokota K, Saito Y, Einami K. A bamboo joint-like appearance of the gastric body and cardia: possible association with Crohn's disease. Gastrointest Endosc. 1997;46:268–72.
15. Calkins BM, Lilienfeld AM, Garland CF. Trends in incidence rates of ulcerative colitis and Crohn's disease. Dig Dis Sci. 1984;29:913–20.
16. Lennard-Jones JE. Classification of inflammatory bowel disease. Scand J Gastroenterol Suppl. 1989;170:2–19.
17. Myren J, Bouchier IA, Watkinson G. The OMGE multinational inflammatory bowel disease survey 1976–1986. A further report on 3175 cases. Scand J Gastroenterol Suppl. 1988;144:11–9.
18. Shivananda S, Hordijk ML, Ten Kate FJ. A comparison of various diagnostic classifications. Scand J Gastroenterol. 1991;26:167–73.
19. http://www.nanbyou.or.jp/entry/219.
20. Hisabe T, Hirai F, Matsui T. Evaluation of diagnostic criteria for Crohn's disease in Japan. J Gastroenterol. 2014;49:93–9. doi:10.1007/s00535-013-0798-x.
21. Ouyang Q, Tandon R, Goh KL. Management consensus of inflammatory bowel disease for the Asia–Pacific region. J Gastroenterol Hepatol. 2006;21:1772–82.

Chapter 9
Differential Diagnosis of Inflammatory Bowel Disease: Endoscopic Findings and Diagnosis of Intestinal Behçet's Disease and Simple Ulcer Syndrome

Jae Hee Cheon

Abstract Intestinal Behçet's disease (BD) can be diagnosed if characteristically shaped ulcers are observed in the small or large intestine, and other clinical findings meet the BD diagnostic criteria. Intestinal BD and inflammatory bowel diseases (IBDs), including Crohn's disease and ulcerative colitis, have many overlapping clinical manifestations and similarities. They share fluctuating clinical courses with repeated remission and relapse, similar extraintestinal manifestations, and similar gastrointestinal symptoms.

Gastrointestinal involvement in BD may affect the entire gastrointestinal tract from the mouth to the anus. Intestinal BD ulcers vary in shape, number, and distribution, but a typical endoscopic feature of intestinal BD is a few round or oval-shaped, deeply penetrating ulcers with discrete margins at the ileocecal area. Intestinal BD patients often require surgical interventions owing to frequent complications, such as massive bleeding, fistula formation, and free bowel perforation. Another disease entity, simple ulcer syndrome, has been described as deep, discrete ulcerations with a "punched-out," round or oval appearance in the ileocecal region. They are similar to ulcers seen in intestinal BD but do not fulfill the clinical criteria of BD. Recently, novel diagnostic criteria encompassing patients with ileocolonic ulcers who do not fully satisfy the diagnostic criteria for systemic BD were proposed.

Keywords Intestinal Behçet's disease • Diagnostic criteria • Simple ulcer • Inflammatory bowel disease

J.H. Cheon
Department of Internal Medicine and Institute of Gastroenterology, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea
e-mail: geniushee@yuhs.ac

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_9

9.1 Introduction

9.1.1 Clinical Characteristics of Intestinal Behçet's Disease

Behçet's disease (BD) is a chronic, immune-mediated, multisystemic disorder characterized by recurrent oral and/or genital ulcers, arthritis, skin manifestations, and ocular, vascular, neurological, or intestinal involvement. Intestinal BD is a specific subtype of BD; if gastrointestinal symptoms are predominant, and typical ulcerative lesions are objectively documented in patients with BD, the condition is termed "intestinal BD" [1]. Similar to inflammatory bowel disease (IBD), intestinal BD is considered a chronic IBD characterized by a heterogeneous range of clinical courses and symptoms [2]. Intestinal BD shares many clinical features with IBD [3].

The frequency of gastrointestinal involvement varies depending on geographic location, ranging 3–50%. Symptomatic or documented intestinal involvement is common in East Asian countries such as Korea and Japan, whereas intestinal involvement is rare in Mediterranean patients [4–7]. Intestinal BD is one of the major causes of morbidity and mortality due to BD, since it often leads to severe complications such as bowel perforation or massive bleeding. Unfortunately, clinical data have been relatively limited because of the rarity of the disease. Moreover, since intestinal BD manifests similarly to colitides such as Crohn's disease (CD) or intestinal tuberculosis (TB), it is still challenging for gastroenterologists to accurately diagnose intestinal BD in patients with ileocolonic ulcers [8].

9.1.2 Signs and Symptoms

Patients with intestinal BD typically present with abdominal pain, abdominal distension, nausea, diarrhea, bowel habit changes, weight loss, and bleeding, similarly to patients with IBD [9–12]. Gastrointestinal involvement may affect all areas from the mouth to the anus, and the nature of pain is usually correlated with disease location. Cramping in the right lower quadrant is a common pain pattern in intestinal BD, because the ileocecal valve is most frequently involved.

The gastrointestinal manifestations usually appear 4.5–6 years after the onset of oral ulcers, but the gastrointestinal manifestations can also appear before the onset of any other BD symptoms. Similar to other IBDs, the clinical features of intestinal BD vary over time and with the course of the disease [13]. Even though a large proportion of intestinal BD patients experience only mild clinical manifestations, it should not be underestimated as a mild disease. The first year after diagnosis influences the clinical course of the following years in intestinal BD [14, 15]. The clinical course of intestinal BD can be divided into two types: a severe clinical course versus remission or a mild clinical course. Younger age, elevated erythrocyte sedimentation rate, elevated C-reactive protein level, lowered albumin level, and higher disease activity at diagnosis are associated with a severe clinical course of intestinal

BD. Among these factors, a high disease activity index score for intestinal BD at diagnosis is regarded as the most important independent predictive factor for requiring an operation at some point [16]. Volcano-type ulcers, an absence of mucosal healing, a history of previous bowel surgery, and initial nonresponse to medical therapy have also repeatedly been poor prognostic factors in patients with intestinal BD [17].

9.1.3 Diagnosis of Intestinal Behçet's Disease

Empirically and historically, patients were generally diagnosed with intestinal BD if they had both intestinal ulcerations and clinical manifestations that met the diagnostic criteria of BD. The diagnostic criteria for systemic BD were suggested by the Behçet's Disease Research Committee of Japan or the International Study Group for Behçet's Disease; however, adequate diagnosis of intestinal BD using these criteria is often limited because of various extraintestinal manifestations and fluctuating disease courses of intestinal BD. As a result, novel diagnostic criteria encompassing patients with ileocolonic ulcers who do not otherwise fully satisfy the diagnostic criteria for systemic BD were recently proposed. The criteria are composed of two aspects: colonoscopic findings and extraintestinal systemic manifestations. Patients are categorized into four groups, including definite, probable, suspected, and nondiagnostic for intestinal BD (Fig. 9.1). The diagnosis should be confirmed based not only on the endoscopic findings, but also on histopathologic findings, radiologic findings, and clinical course.

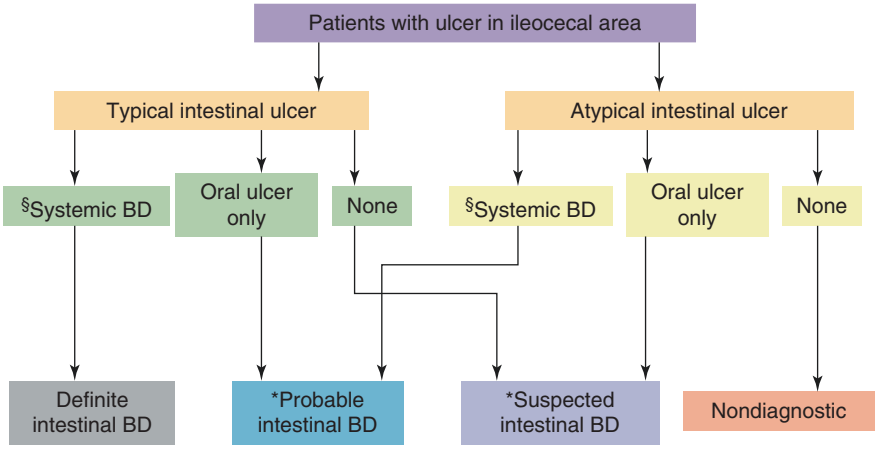


Fig. 9.1 Algorithm for the diagnosis of intestinal Behçet's disease based on types of ileocolonic ulcerations and clinical manifestations. §Complete, incomplete, and suspected subtypes of systemic BD were classified according to the diagnostic criteria of the Research Committee of Japan. *Close follow-up is necessary [25]

9.2 Case Presentations

9.2.1 Characteristic Case of Intestinal BD

Intestinal BD most commonly manifests in the terminal ileal and cecal regions (80–95%), but it can affect any part of the gastrointestinal tract, from the oral cavity to the anus. Multiple ulcerations tend to show localized distribution in the ileocecal area, whereas multisegmental or diffuse distributions of lesions are relatively uncommon [11]. Rectal and anal lesions are rare in intestinal BD patients [3, 18–20]. The distribution pattern of lesions is characterized into localized single, localized multiple, multisegmental, and diffuse appearance with the rates being 67%, 27%, 2%, and 4% in order of frequency, respectively [11].

The typical endoscopic findings are focal, segmental mucosal inflammation and punched-out fissuring-type or aphthoid ulcers in the ileocecal area (Table 9.1). Ulcers are deep, and tend to be round or ovoid. The presence of five or fewer intestinal or focal ulcers is a common endoscopic feature of intestinal BD. The majority of patients have only a single or a few ulcers (60–65%); however, multiple ulcers can also be present (Fig. 9.2). Ulcer sizes vary from small to large. When the ulcer

Table 9.1 Endoscopic findings typical of intestinal Behçet's disease

Typical findings
Single or a few (<5) large ulcers in the ileocecal area
Round or oval shape
Deep ulcerations
Discrete and elevated borders
Ulcer base covered with exudates
Atypical findings
Aphthoid or geographic ulcers
Multisegmental or diffuse distribution
Esophageal ulcers

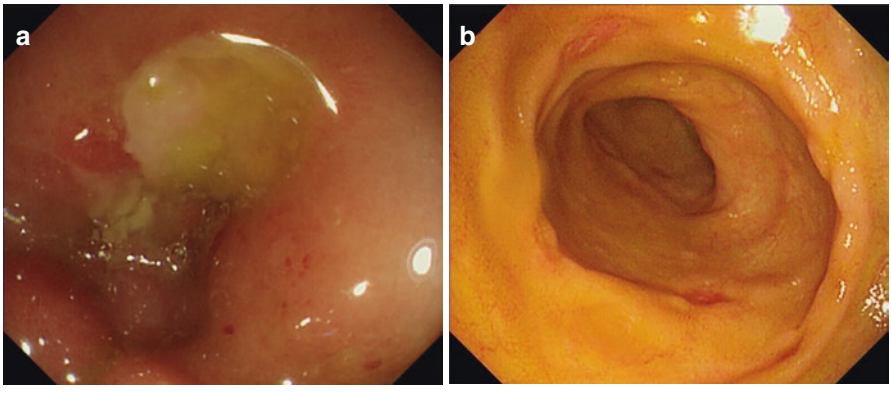


Fig. 9.2 Single and multiple ulcers in intestinal BD. **(a)** A single, round, active ulcer in the terminal ileum. **(b)** Multiple irregularly shaped small ulcers in the terminal ileum

is small, it appears aphthoid; that is, having a small, well-demarcated circular or ovoid shape (Fig. 9.3). The smaller ulcers have a similar appearance to the oral aphthoid ulcers of BD patients (Fig. 9.4). Small, well-demarcated circular or oval ulcers with normal adjacent mucosa are commonly presented. Larger ulcers typically seen in intestinal BD are usually oval or round. In particular, an ulcer with large, well-demarcated nodular margins and deep penetration is known as a volcano-type ulcer (Fig. 9.5). Ulcers with converging folds in this lesion can be regarded as chronic lesions. Owing to the elevated surrounding mucosa, this lesion can be misdiagnosed as ulcerofungating cancer; however, in contrast to a malignant ulcer, the margin in a volcano-type ulcer is clear, and no mucosa friability is noted. Volcano-type ulcers accompany fibrosis, and patients with these ulcers are less responsive to medical treatments and more frequently require surgery [21]. In large ulcer cases, the ulcer's margin is commonly discrete and clear, and the surrounding mucosa appears normal. A thick, whitish exudate is often observed at the ulcer's base (Fig. 9.6). Marginal elevation or erythema is also seen in intestinal BD patients. Longitudinal ulcers are rarely seen. As mentioned earlier, ulcerations of intestinal BD can be present at any site along the gastrointestinal tract. Therefore, when gastrointestinal ulcers with

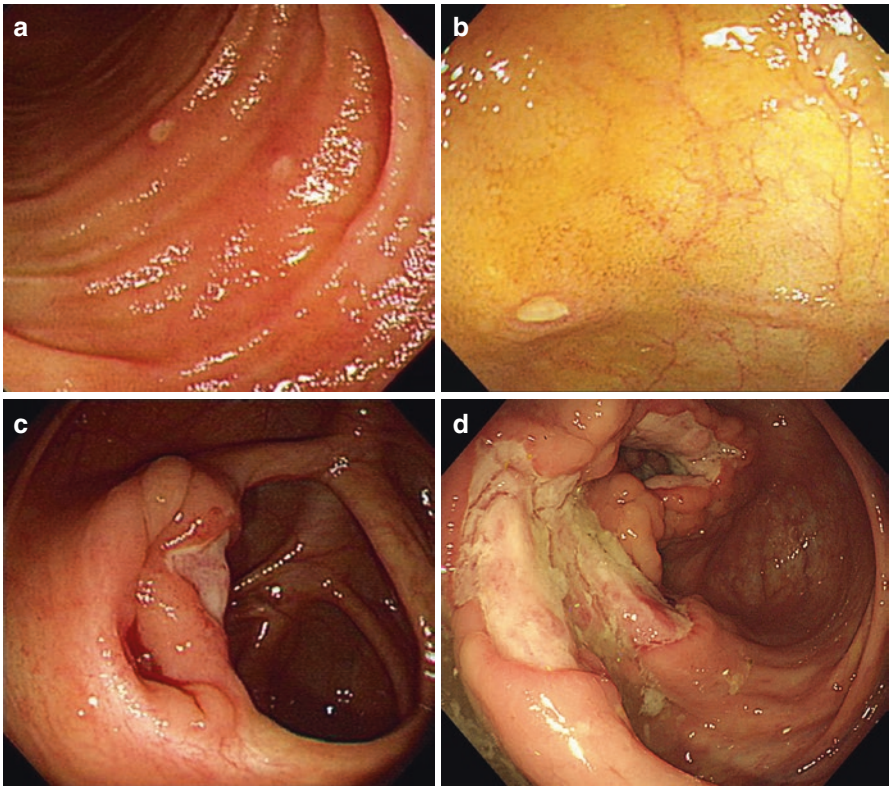


Fig. 9.3 Ulcers with variable sizes in intestinal BD. **(a)** Two aphthoid lesions in the terminal ileum. **(b)** Small oval-shaped or round ulcer in the terminal ileum. **(c)** A cecal ulcer with whitish exudate. **(d)** Huge cecal ulcers accompanying nodular margins and whitish surface exudate

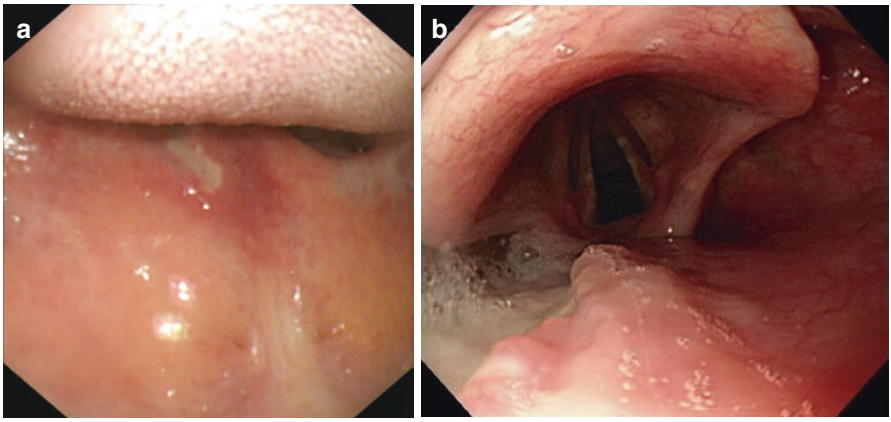


Fig. 9.4 Oral aphthoid ulcers in patients with intestinal BD. **(a)** Small round ulcer in the oral cavity. **(b)** Huge oral ulcer

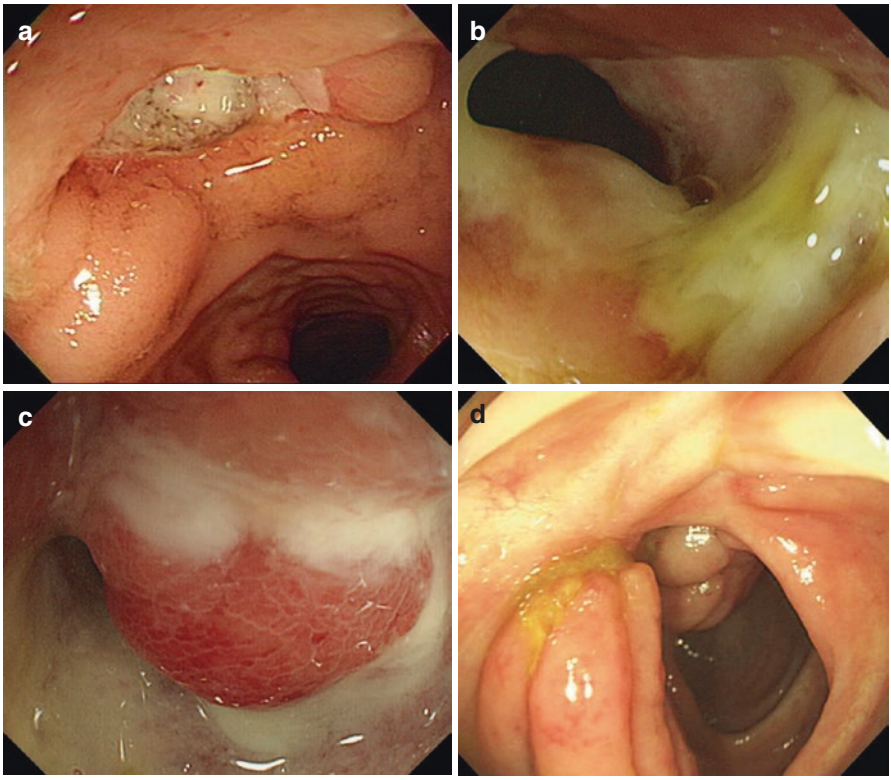


Fig. 9.5 Volcano-type ulcers in intestinal BD. **(a)** Deep, penetrating ulcer with nodular margins in the terminal ileum. **(b)** Deep, penetrating, encircling ulcer in the terminal ileum. **(c)** Deep terminal ileal ulcer with nodular erythematous margin. **(d)** Ileocecal ulcer with converging folds

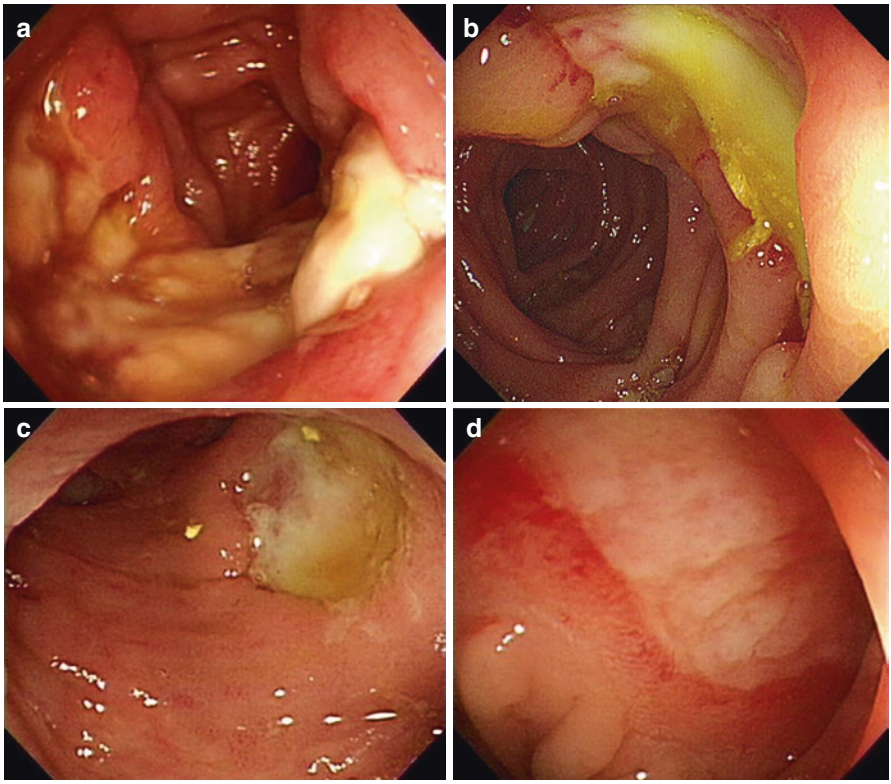


Fig. 9.6 Typical intestinal ulcers in intestinal BD. **(a)** Large, deep ulcer in the terminal ileum accompanying a sharply demarcated, elevated border and whitish thick exudate. **(b)** Large ulcer with discrete border in the ascending colon. **(c)** Deep round-shaped ulcer covered with thick exudate in the terminal ileum. **(d)** Ulcers with hyperemic rim in the terminal ileum

typical BD features are observed in patients with compatible clinical backgrounds, intestinal BD-related ulcerations should be suspected. The stomach is the least frequently involved part of the gastrointestinal tract (<5%), while esophageal involvement is diverse and nonspecific. The lesions are generally seen in the middle of the esophagus, although diffuse esophagitis and stenosis have also been reported (Fig. 9.7), Punched-out ulcers are sometimes seen in the perianal area (Fig. 9.8).

As a result of inflammation or scarring after ulcer healing, the adjacent mucosa may shrink, resulting in ileocecal valve deformity and scars. Luminal stricture can also follow during the healing process. The major endoscopic aspects of patients with intestinal BD and healed lesions with medical therapy are presented in Fig. 9.9.

9.2.2 A Case of Simple Ulcer Syndrome

The prevalent intestinal BD ulcer characteristics can be summarized as an oval or round shape and punched-out, deep, discrete ulcerations, mainly present in the

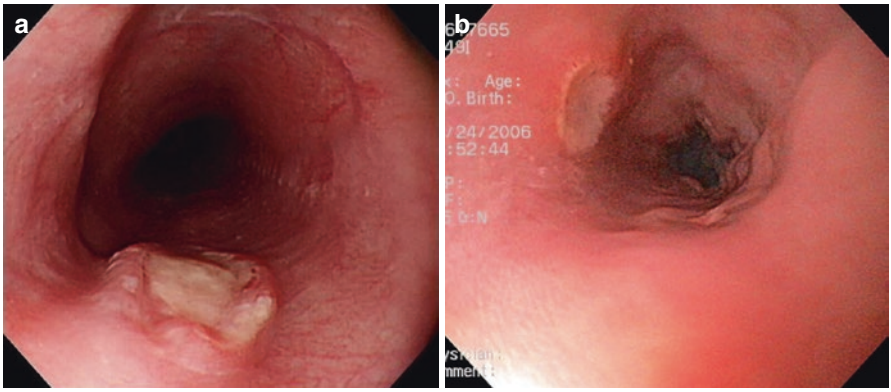


Fig. 9.7 Esophageal involvement in intestinal BD. **(a)** Oval-shaped midesophageal ulcer with a discrete margin. **(b)** Several shallow ulcers in the midesophagus

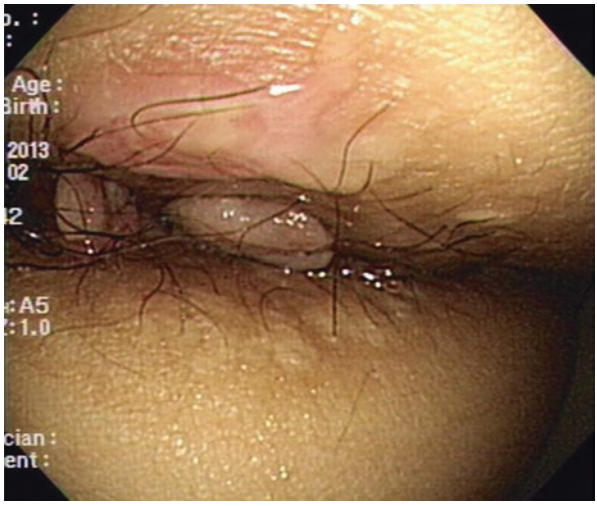


Fig. 9.8 Punched-out ulcer in the perianal area

ileocecal area. Another disease entity, simple ulcer syndrome, has also been characterized by deep, discrete ulcerations with a punched-out, round or oval appearance in the ileocecal region. The ulcer characteristics are similar to that of intestinal BD, but do not otherwise clinically fulfill the criteria for BD (Fig. 9.10) [22]. In fact, simple ulcer syndrome shows macroscopic and microscopic similarities to intestinal BD. As a result, some authors have proposed that intestinal BD and simple ulcer syndrome could be considered the same disease entity [23]. Whether these two diseases are actually the same disease or separate disease

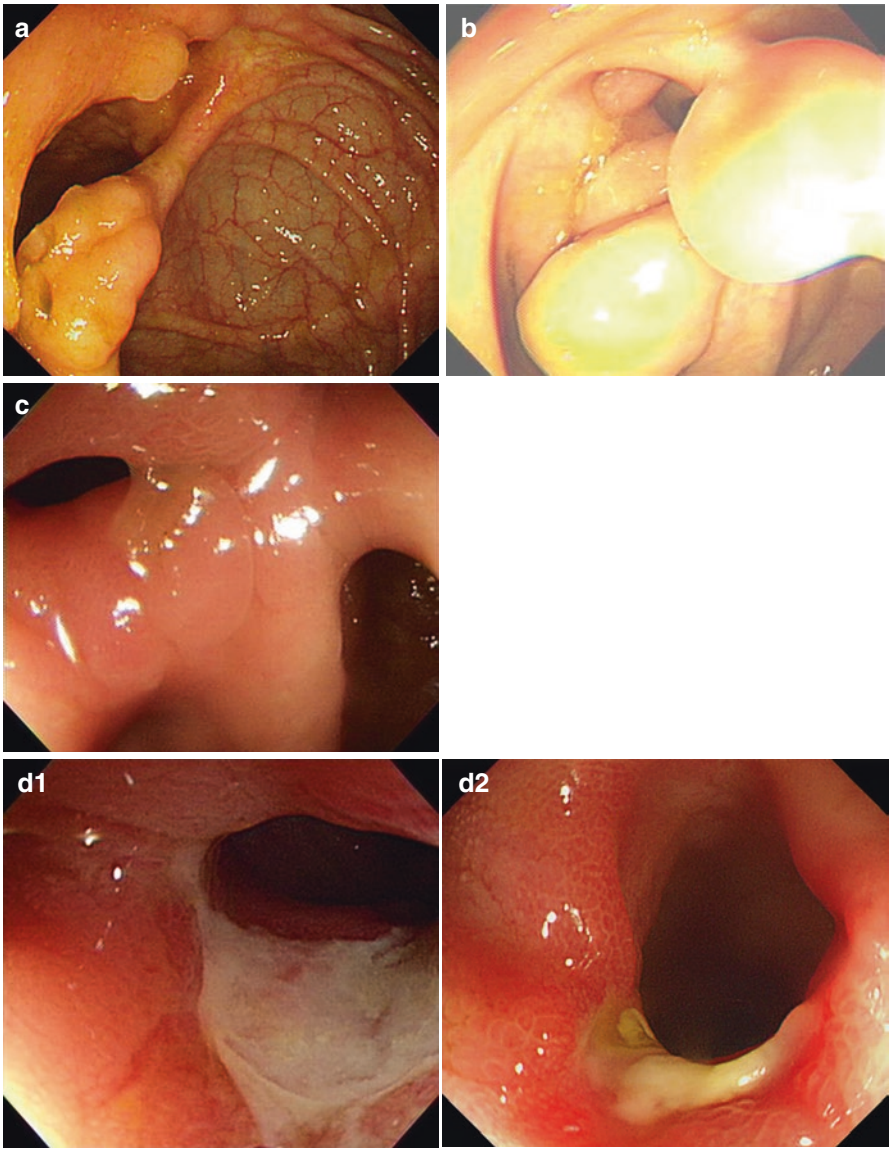


Fig. 9.9 Various findings of healing active ulcers, scars, and deformities. **(a)** After healing, patulous ileocecal valve with scar is observed. **(b)** After healing of ulcer, scar with luminal deformity is noted. **(c)** Scarring change with ileocecal valve stricture. **(d)** After medical therapy, a huge ulcer (**d1**) is substantially improved into shallow ulcer (**d2**)

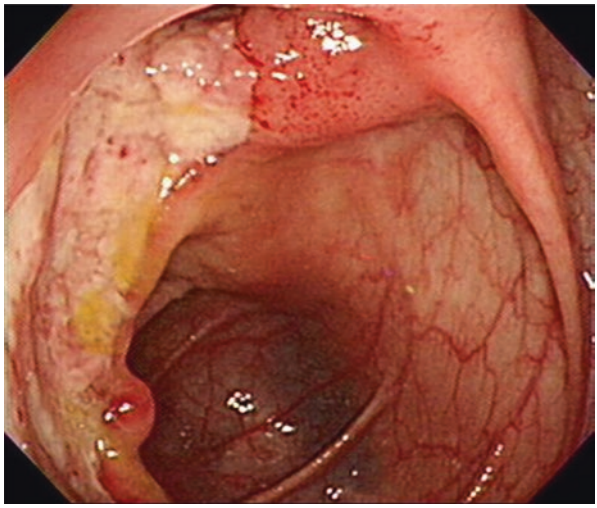


Fig. 9.10 Simple ulcer in the ileocecal area

entities, however, is still controversial. Both diseases may present with a simple ulcer at the onset, followed by the systemic manifestations of BD. For this reason, simple ulcer syndrome and intestinal BD could be variations on the same disease spectrum [24]. On the other hand, at some points during its clinical course, simple ulcer is typically confined to the ileocecal area, while intestinal BD generally presents multiple ulcerations at any point along the gastrointestinal tract during the entire clinical course (unless it is an atypical presentation). Moreover, it is rare for simple ulcer to definitively progress into intestinal BD, making it more difficult to see both diseases as part of the same spectrum. Although these controversies exist, it might be appropriate, based on the observation that the treatment, progress, and recurrence of these diseases are similar, to clinically categorize the two diseases as components of the same entity. The recent diagnostic guideline suggests that simple ulcer syndrome corresponds to suspected-type intestinal BD [25].

9.2.3 Characteristic Complications

Complications such as stricture, fistula, hemorrhage, or perforation occur in approximately 50% of cases involving the intestine (Fig. 9.11), often leading to surgery [26–28]. The recurrence and surgical intervention rates are reported to be even higher in patients with intestinal BD than in those with CD [3]. Compared to CD, bowel perforation is more common than fistula formation in intestinal BD. At the anastomotic site or within the vicinity of the surgical site, the recurrence of active ulcers or penetrating discrete ulcers is easily observed (Fig. 9.12).

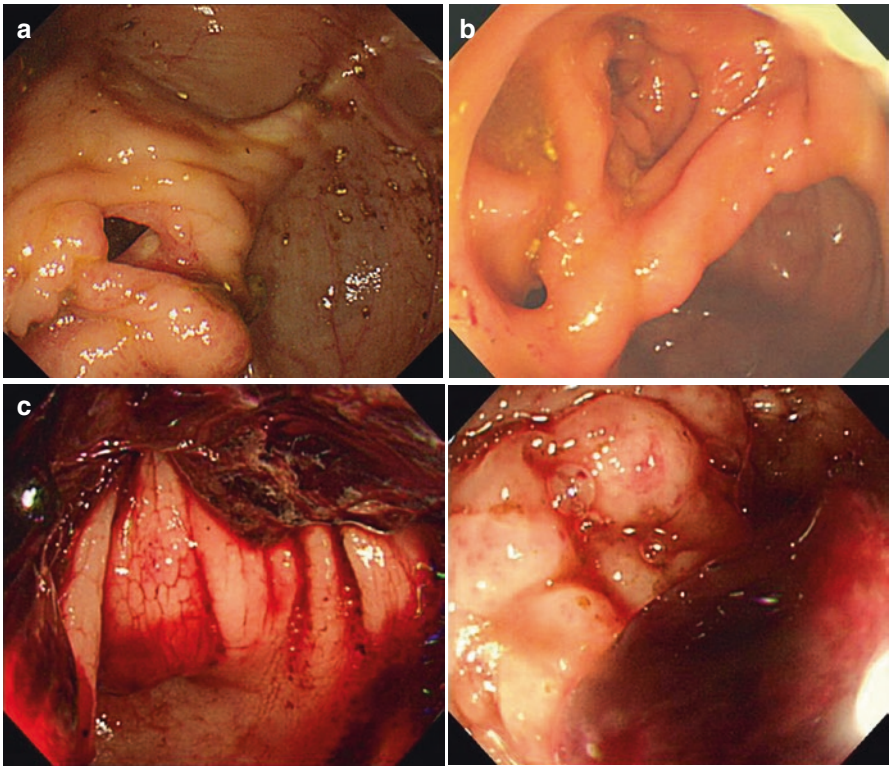


Fig. 9.11 Complications of intestinal BD. **(a)** Ileocecal stricture with ulceration. **(b)** Opening of fistula is seen in the terminal ileum. **(c)** Active ulcer presented with hematochezia

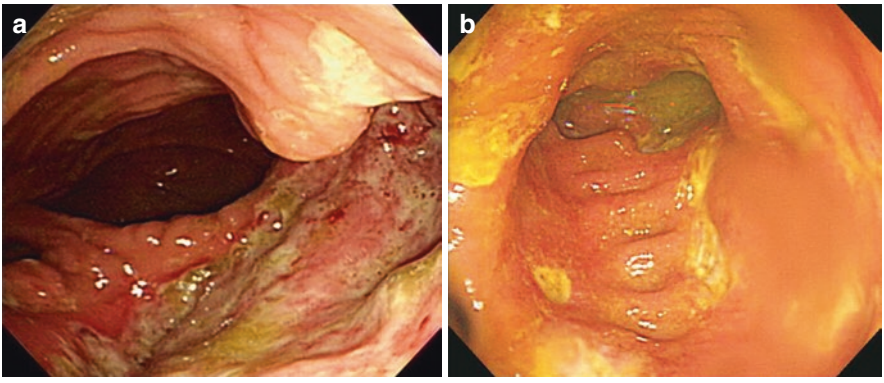


Fig. 9.12 Anastomotic recurrence. **(a)** Deeply penetrating discrete ulcer on the anastomotic site after ileocecectomy. **(b)** Multiple, variably shaped, active ulcers are noted in the neoterminal ileum

9.3 Differential Diagnostic Considerations

Due to the similar extraintestinal manifestations and complications such as fistulas, hemorrhage, and perforations, intestinal BD can be misdiagnosed as CD or TB during endoscopic examinations. It is important to make the diagnosis with full consideration of endoscopic, pathologic, radiologic, and clinical findings. To achieve definite differentiation, long-term follow up is sometimes needed. Longitudinal ulcers, a cobblestone appearance, and diffuse or segmental involvement are more frequent in CD than in intestinal BD, while localized focal involvement is more common in intestinal BD than in CD. In addition, anorectal involvement is more frequently observed in CD than intestinal BD. Multiple ulcers are commonly seen in CD, while a single or fewer than five ulcers are a typical feature of intestinal BD. The larger, deeper, and well-demarcated ulcers usually seen in intestinal BD are relatively rare in CD (Table 9.2). Based on these findings, a simple two-characteristic distinguishing strategy including ulcer shape (round, irregular/geographical, longitudinal) and lesion distribution (focal single/focal multiple, segmental/diffuse) has been proposed, correctly diagnosing 92% of intestinal BD or CD cases (Fig. 9.13) [20]. Finally, it is important, but sometimes problematic, for physicians to differentiate intestinal BD from intestinal TB, since the immunosuppressive therapeutic approach for intestinal BD may worsen the disease course of intestinal TB. Annular ulcers and scarred areas with discoloration are typically observed endoscopic features of intestinal TB. Some diagnostic methods, such as tissue culture, tissue polymerase chain reaction, and interferon-gamma release assay, can be helpful for making that differential diagnosis, in conjunction with general examinations such as chest radiography and a tuberculin test [29].

Table 9.2 Differential features between intestinal BD and Crohn's disease

Endoscopic findings	Intestinal Behçet's disease	Crohn's disease
Distribution	Mostly ileocecal area	Panintestinal
Anorectal involvement	Rare	Common
Ulcer	One or several	Several, multiple
Size	Usually large	Various
Depth	Deep, penetrating	Shallow or transmurally inflamed
Shape Margin	Round, oval Thick mucus in base and nodular margin	Longitudinal, various shape, cobblestone appearance Sharply outlined, discretely inflamed, nodular heaped-up borders
Border	Discrete, elevated	Relatively irregular, ill-defined

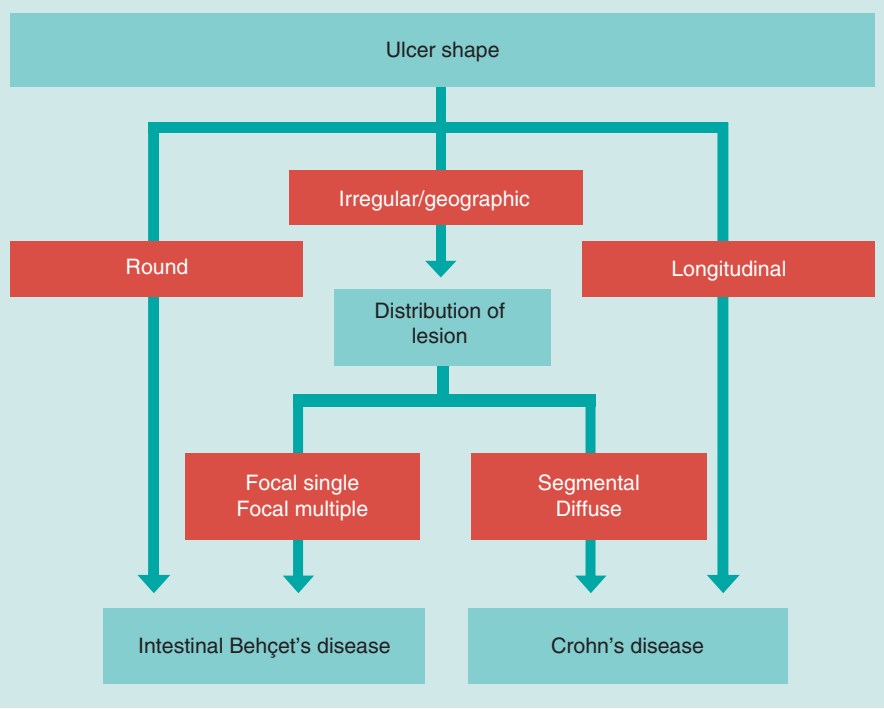


Fig. 9.13 The simple decision tree model for endoscopic differentiation of intestinal BD and Crohn's disease

9.4 Summary

Intestinal BD, a specific subtype of BD, can lead to severe morbidity and mortality. Intestinal BD can be diagnosed in the presence of typical endoscopic findings and clinical features meeting the diagnostic criteria of BD. With recent diagnostic advances and increasing awareness of intestinal BD, diagnostic algorithms continue to evolve, but patient prognosis is still challenging.

References

1. Tsukada S, Yamazaki T, Iyo S, Nishio I, Hashimoto K, Matsubara F. Neuro-Behçet's syndrome: report of two cases and review of the literature. Saishin Igaku. 1964;19:1533–41.
2. Ebert EC. Gastrointestinal manifestations of Behcet's disease. Dig Dis Sci. 2009;54(2):201–7. doi:10.1007/s10620-008-0337-4.

3. Grigg EL, Kane S, Katz S. Mimicry and deception in inflammatory bowel disease and intestinal Behcet's disease. Gastroenterol Hepatol. 2012;8(2):103–12.
4. Mizuki N, Ohno S. Immunogenetic studies of Behcet's disease. Rev Rhum Engl Ed. 1996;63(7–8):520–7.
5. Kaklamani VG, Vaiopoulos G, Kaklamanis PG. Behcet's Disease. Semin Arthritis Rheum. 1998;27(4):197–217.
6. Shimizu T, Ehrlich GE, Inaba G, Hayashi K. Behcet disease (Behcet syndrome). Semin Arthritis Rheum. 1979;8(4):223–60.
7. Yazici Y, Yurdakul S, Yazici H. Behcet's syndrome. Curr Rheumatol Rep. 2010;12(6):429–35. doi:10.1007/s11926-010-0132-z.
8. Cheon JH, Shin SJ, Kim SW, Lee KM, Kim JS, Kim WH. Diagnosis of intestinal Behcet's disease. Korean J Gastroenterol. 2009;53(3):187–93.
9. Kim WH, Lee S. Diagnostic challenges in Asia: intestinal Behcet's disease. In: Falk Symposium. Kluwer Academic Publishers; 2006. p 46.
10. Choi IJ, Kim JS, Cha SD, Jung HC, Park JG, Song IS, Kim CY. Long-term clinical course and prognostic factors in intestinal Behcet's disease. Dis Colon Rectum. 2000;43(5):692–700.
11. Lee CR, Kim WH, Cho YS, Kim MH, Kim JH, Park IS, Bang D. Colonoscopic findings in intestinal Behcet's disease. Inflamm Bowel Dis. 2001;7(3):243–9.
12. Kim D, Yang S, Byeon J, Myung S, Jo J, Choi K. Clinical manifestations and course of intestinal Behcet's disease: an analysis in relation to disease subtypes. Intest Res. 2005;3(1):48–54.
13. Jung YS, Cheon JH, Park SJ, Hong SP, Kim TI, Kim WH. Clinical course of intestinal Behcet's disease during the first five years. Dig Dis Sci. 2013;58(2):496–503. doi:10.1007/s10620-012-2351-9.
14. Munkholm P, Langholz E, Davidsen M, Binder V. Disease activity courses in a regional cohort of Crohn's disease patients. Scand J Gastroenterol. 1995;30(7):699–706.
15. Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. Gastroenterology. 1994;107(1):3–11.
16. Jung YS, Yoon JY, Hong SP, Kim TI, Kim WH, Cheon JH. Influence of age at diagnosis and sex on clinical course and long-term prognosis of intestinal Behcet's disease. Inflamm Bowel Dis. 2012;18(6):1064–71. doi:10.1002/ibd.21833.
17. Park JJ, Kim WH, Cheon JH. Outcome predictors for intestinal Behcet's disease. Yonsei Med J. 2013;54(5):1084–90. doi:10.3349/ymj.2013.54.5.1084.
18. Wu QJ, Zhang FC, Zhang X. Adamantiades-Behcet's disease-complicated gastroenteropathy. World J Gastroenterol. 2012;18(7):609–15. doi:10.3748/wjg.v18.i7.609.
19. Lee HJ, Kim YN, Jang HW, Jeon HH, Jung ES, Park SJ, Hong SP, Kim TI, Kim WH, Nam CM, Cheon JH. Correlations between endoscopic and clinical disease activity indices in intestinal Behcet's disease. World J Gastroenterol. 2012;18(40):5771–8. doi:10.3748/wjg.v18.i40.5771.
20. Lee SK, Kim BK, Kim TI, Kim WH. Differential diagnosis of intestinal Behcet's disease and Crohn's disease by colonoscopic findings. Endoscopy. 2009;41(1):9–16. doi:10.1055/s-0028-1103481.
21. Kim ES, Chung WC, Lee KM, Lee BI, Choi H, Han SW, Choi KY, Chung IS. A case of intestinal Behcet's disease similar to Crohn's colitis. J Korean Med Sci. 2007;22(5):918–22.
22. Iida M. Clinical course of intestinal lesions in patients with intestinal disease and simple ulcer. Stomach Intest. 1992;27:287–302.
23. Hayasaki N, Ito M, Suzuki T, Ina K, Ando T, Kusugami K, Goto H. Neutrophilic phlebitis is characteristic of intestinal Behcet's disease and simple ulcer syndrome. Histopathology. 2004;45(4):377–83. doi:10.1111/j.1365-2559.2004.01954.x.
24. Jung HC, Rhee PL, Song IS, Choi KW, Kim CY. Temporal changes in the clinical type or diagnosis of Behcet's colitis in patients with aphthoid or punched-out colonic ulcerations. J Korean Med Sci. 1991;6(4):313–8.
25. Cheon JH, Kim ES, Shin SJ, Kim TI, Lee KM, Kim SW, Kim JS, Kim YS, Choi CH, Ye BD, Yang SK, Choi EH, Kim WH. Development and validation of novel diagnostic criteria for

intestinal Behcet's disease in Korean patients with ileocolonic ulcers. Am J Gastroenterol. 2009;104(10):2492–9. doi:10.1038/ajg.2009.331.
26. Kasahara Y, Tanaka S, Nishino M, Umemura H, Shiraha S, Kuyama T. Intestinal involvement in Behcet's disease: review of 136 surgical cases in the Japanese literature. Dis Colon Rectum. 1981;24(2):103–6.
27. Sayek I, Aran O, Uzunalimoglu B, Hersek E. Intestinal Behcet's disease: surgical experience in seven cases. Hepato-Gastroenterology. 1991;38(1):81–3.
28. Bradbury AW, Milne AA, Murie JA. Surgical aspects of Behcet's disease. Br J Surg. 1994;81(12):1712–21.
29. Hisamatsu T, Naganuma M, Matsuoka K, Kanai T. Diagnosis and management of intestinal Behcet's disease. Clin J Gastroenterol. 2014;7:205–12. doi:10.1007/s12328-014-0488-0.

Chapter 10
Differential Diagnosis of Inflammatory Bowel Disease: Endoscopic Findings and Diagnosis of Intestinal Tuberculosis

Jeung Hui Pyo, You Sun Kim, Young Sook Park, and Young-Ho Kim

Abstract The diagnosis of intestinal tuberculosis (TB) must consider the clinical, laboratory, endoscopic, and histological features, and should be categorized as a definitive or probable diagnosis. Definitive intestinal TB can be diagnosed based on the presence of acid-fast bacilli, caseating granulomas, or *M. tuberculosis* in culture. A diagnosis of probable intestinal TB is justified in a patient with appropriate clinical, endoscopic, or histologic findings and response to anti-TB treatment (Marshall, Am J Gastroenterol 88(7):989–999, 1993).

Keywords Intestinal tuberculosis • Crohn's disease • Colonoscopy

10.1 Introduction

TB remains a major infectious disease with high morbidity and mortality rates among adult patients [1]. Approximately 8.6 million people developed TB worldwide in 2012. There were 1.3 million deaths from TB, with the highest incidence in Africa and Asia [2]. Extrapulmonary TB usually involves the gastrointestinal tract, vertebrae and other bones, meninges, pericardium, and genitourinary tract, and accounts for 10–15% of all cases of TB [3]. Abdominal TB may involve the peritoneum, mesenteric lymph nodes, and any part of the gastrointestinal tract from the mouth to the anus.

Active intestinal TB is defined as a microbiologically proven *M. tuberculosis* infection involving the gastrointestinal tract, or clinical, endoscopic, or histological

J.H. Pyo • Y.-H. Kim (✉)
Sungkunkwan University School of Medicine,
81 Irwon-ro, Gangnam-Gu, Seoul 135-710, South Korea
e-mail: bowelkim@gmail.com

Y.S. Kim
Inje University College of Medicine, Seoul, South Korea

Y.S. Park
Eulji University School of Medicine, Seoul, South Korea

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_10

findings compatible with intestinal TB and responsiveness to anti-TB treatment [4]. The pathophysiology of intestinal TB may originate from exposure to infected liquid droplets with direct seeding, contiguous spread from adjacent organs, hematogenous spread from active primary or miliary TB, or ingestion of contaminated milk from cows infected with bovine TB [5, 6]. Intestinal TB has been known since antiquity. After about 1950, effective anti-TB chemotherapy and improved standards of living reduced the incidence of all forms of TB, including abdominal TB [1]. However, there is now a resurgence of TB due to the increasing prevalence of acquired immunodeficiency syndrome and increased use of immunosuppressive drugs [7]. The differential diagnosis of Crohn's disease and intestinal TB can be very challenging, particularly in Asian countries, where intestinal TB remains common and the incidence of Crohn's disease is increasing, as these conditions exhibit overlapping clinical presentations and shared colonoscopic findings [8–11]. We review the diagnosis of intestinal TB and differential diagnosis from Crohn's disease, focusing on the usefulness of colonoscopy.

10.1.1 Clinical Presentation

Intestinal TB occurs most frequently in patients aged 20–50 years old. Symptoms are non-specific, and the condition usually has an insidious onset. Some patients have had symptoms for years by the time that intestinal TB is suspected. Even some have few or no symptoms and they are diagnosed during screening colonoscopy [12].

Abdominal pain, diarrhea, and weight loss are common symptoms. Fever, loss of appetite, nausea, vomiting, and hematochezia may also occur [13, 14]. In patients who are suspected of having intestinal TB, documented concomitant active TB in other sites would permit a probable diagnosis. About one third of patients have concomitant extra-intestinal TB involving the lung or peritoneum [15]. A past history of pulmonary TB, incomplete treatment [16, 17], or, less commonly, a family history of active TB may provide useful clues toward the diagnosis [18].

10.1.2 Laboratory Findings

Laboratory findings for intestinal TB may include anemia, leukocytosis, elevated erythrocyte sedimentation rate, elevated CRP, and hypoalbuminemia [13, 14, 19]. In HIV-infected patients with TB who have CD4+ cell counts of 200 or more per cubic millimeter, findings are similar to those of HIV-negative patients with TB. However, in HIV-infected patients with fewer than 200 CD4 + cells per cubic millimeter, extrapulmonary TB, including intestinal TB or TB lymphadenitis, is common [7].

Stool cultures for acid-fast bacilli have limited diagnostic value. How often one obtains a positive culture in the absence of active pulmonary TB is not clear, but it

is likely to be infrequent. Positive cultures are more likely to occur in patients with active pulmonary disease who swallowed infected sputum, and are not recommended [1]. A specific fecal polymerase chain reaction (PCR) product was noted in 16 of 18 patients with untreated intestinal TB, but was negative in all 30 control subjects and eight treated gastrointestinal TB patients. Thus, fecal PCR has a sensitivity of 88% and specificity of 100% for diagnosing intestinal TB [20]. Although this is an attractive test, the actual utility remains unknown and requires further study.

10.1.3 Colonoscopic Findings

The most valuable approach for diagnosing intestinal TB is colonoscopy with a corresponding biopsy [20], [21]. The most frequent site of intestinal TB is the ileocecal region [14] due to the predilection of lymphoid tissue and the relative physiological stasis of the ileocecum. Other commonly involved sites are the ascending colon, transverse colon, jejunum, sigmoid colon, descending colon, and rectum [14].

The most characteristic colonoscopy findings for intestinal TB are transverse ulcers, in contrast to the longitudinal ulcers observed in Crohn's disease (Fig. 10.1). Colonoscopy shows the presence of large, deep circumferential ulcers, small, shallow serpiginous ulcers, or small, shallow ulcers in a circumferential arrangement (Fig. 10.2) [12]. However, transverse ulcers are sometimes absent in intestinal TB (Fig. 10.3), and longitudinal ulcers are not always present in Crohn's disease. The ulcers in Crohn's disease can occur on a normal-appearing mucosa, whereas the mucosa surrounding the ulcer in intestinal TB can have features of inflammation, such as erythema, nodularity, or edema (Fig. 10.4). Small aphthous ulcers are distinctly uncommon in intestinal TB [20–27].

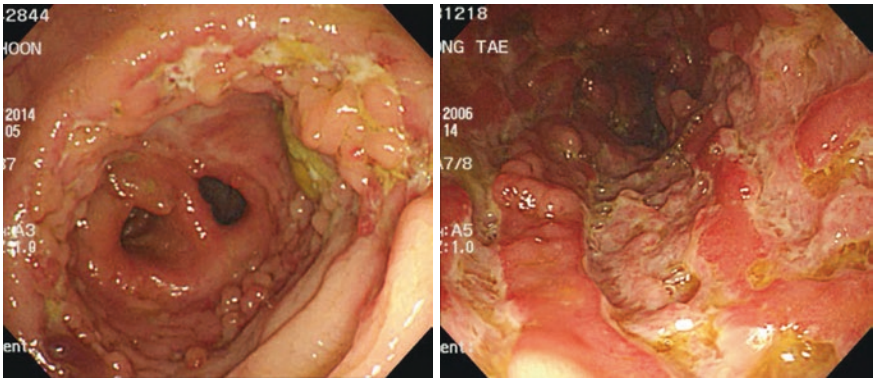


Fig. 10.1 Transverse versus longitudinal ulcer. The most characteristic colonoscopic findings for intestinal TB are transverse ulcers (10.1.1), in contrast to the longitudinal ulcers observed in Crohn's disease (10.1.2)

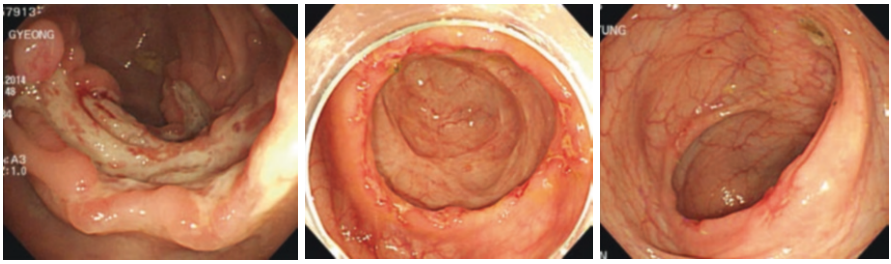


Fig. 10.2 Typical colonoscopic findings of intestinal TB. Colonoscopy reveals large deep circumferential ulcers (10.2.1), small, shallow serpiginous ulcers (10.2.2), small shallow ulcers in a circumferential arrangement (10.2.3)

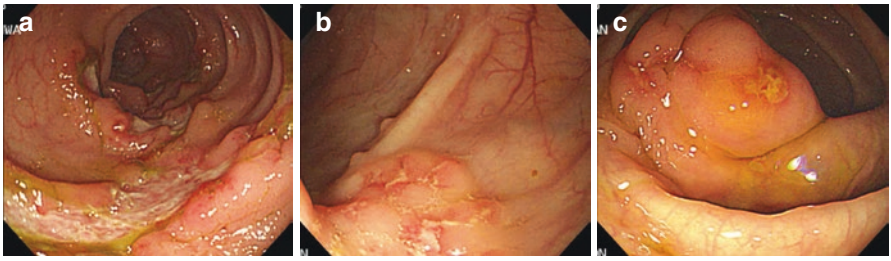


Fig. 10.3 Atypical colonoscopic findings of intestinal TB. Colonoscopy doesn't show any transverse ulcers. However, *M.tuberculosis* was isolated in these cases and the lesions were improved after anti-TB medication

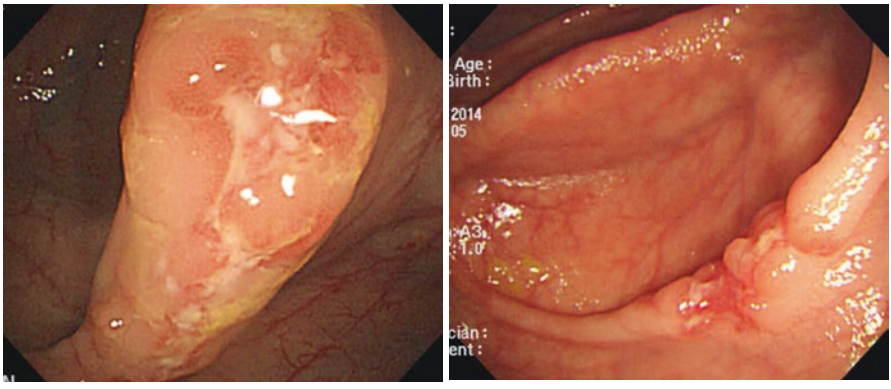


Fig. 10.4 The mucosa surrounding the ulcer in intestinal TB. Colonoscopy shows erythema, nodularity or edema in the mucosa surrounding the ulcer

Colonoscopy often reveals scarring and fibrosis in the ileocecal area. Pseudopolyps, a patent ileocecal valve, and strictures are also commonly seen in intestinal TB (Fig. 10.5). In such cases, there is usually a past history of pulmonary TB. Gastrointestinal or constitutional symptoms are rare. Although evidence is

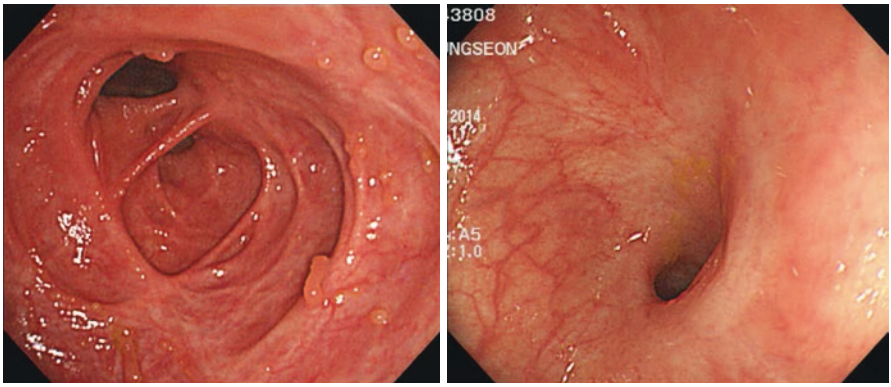


Fig. 10.5 Sequelae of intestinal TB. Colonoscopy reveals scars, pseudopolyps, patulous IC valve (10.5.1), and stricture (10.5.2)

lacking, inactive intestinal TB does not require anti-TB treatment or diagnostic tests to prove TB.

According to a prospective trial comparing the characteristic colonoscopic findings of intestinal TB with the characteristic colonoscopic findings of Crohn's disease [28], four parameters (involvement of fewer than four segments, a patulous ileocecal valve, transverse ulcers, and scars or pseudopolyps) were observed more frequently in patients with intestinal TB than in patients with Crohn's disease. Thus, describing the direction of ulcers, location and number of involved segments, presence of pseudopolyps or scarring, and involvement of the ileocecal valve is important during colonoscopic exams of patients suspected of having intestinal TB. A systematic analysis according to the characteristic colonoscopy findings during the differential diagnosis between intestinal TB and Crohn's disease showed 94.9% positive predictive value for Crohn's disease, and 88.9% positive predictive value for TB. However, the limitation of that study was the relatively small sample size at a single center; thus, further studies are needed to validate this system.

Endoscopically obtained mucosal biopsies have a limited amount of tissue, making differential diagnosis difficult. Colonic mucosa reveals only a few acid-fast bacilli; thus, biopsies from endoscopically abnormal and normal sites are needed for an accurate diagnosis [29]. Biopsies of both the ulcer base and margin should be obtained for ulcerative lesions [17]. Considering the predominance of granulomas in the ulcer base, deep and adequate biopsies from the ulcer base should improve the diagnostic yield [22]. Although evidence remains lacking, taking at least six biopsies from the lesion is recommended [24].

The histological parameters of intestinal TB are caseating granulomatous inflammation and acid-fast bacilli. However, examining the sum of the literature, an educated guess is that fewer than 30% of cases can be diagnosed based on the finding of caseating granulomas or acid-fast bacilli [22, 29, 30]. Features that were frequently found in intestinal TB included confluent granulomas, granulomas exceeding 10 μm in size, ulcers lined by bands of epithelioid histiocytes, disproportionate submucosal inflammation, and submucosal granulomas [29–31].

The use of a TB PCR assay of colonoscopy mucosal biopsies for the diagnosis of intestinal TB increases specificity but lacks sensitivity. Although PCR is not the confirmatory method for differentiating between intestinal TB and Crohn's disease, it may be of value as a supplementary tool [22, 32–35].

In contrast to pulmonary TB, the presence of only a small number of *M.tuberculosis* in intestinal TB gives a low positive rate of 14% to 36% [13, 15, 22] and requires a long time (several weeks) to grow in culture. Colonic mucosal tissues stored in the refrigerator and contained in normal saline are sent to the laboratory. Three to four biopsy specimens should be taken for *M.tuberculosis* cultures. These biopsies are then crushed and inoculated into media [36]. *M.tuberculosis* is isolated using solid (egg-based and agar-based) or liquid growth media. Drug susceptibility testing should be performed in cases with positive cultures to assess the possibility of first-line drug-resistant TB.

10.1.4 Skin Test and Serological Test

In the tuberculin skin test (TST), a substance called purified protein derivative (PPD), which is derived from tuberculin, is injected under the skin. Typically, PPD produces a T-cell-mediated delayed-type hypersensitivity reaction if the person has been infected with *M. tuberculosis*. This should produce a wheal reaction. The reaction to the TST should be assessed 48–72 h after the injection. The TST is read by palpating the site of injection to find an area of induration (firm swelling); the diameter of the indurated area should be measured across the forearm. Erythema (redness) should not be measured [35]. The traditional cut-off is 10 mm. The sensitivity is near 100% in immunocompetent patients infected with *M.tuberculosis*. However, there is a possibility of false-positive testing by cross-reactivity of PPD antigens present in the *Mycobacterium bovis* strain used for BCG vaccination and in non-tuberculosis mycobacteria (NTM). Sensitivity can also be reduced in patients with other infections, malnutrition, lymphoma, or other immunocompromised conditions. The actual cut-off value that constitutes a positive TST remains controversial due to the cross-reactivity of PPD antigens present in the *Mycobacterium bovis* strain used for BCG vaccination and in NTM [35].

The use of TST as a diagnostic tool in patients with ileo-colonic inflammation has limitations. Cross-reactivity with BCG, a high prevalence of environmental mycobacteria, and widespread latent *M. tuberculosis* infection makes interpretation of a positive TST difficult. Anergy in HIV, primary TB, and disseminated TB limits the diagnostic utility of this test. Anergy has also been demonstrated in untreated patients with Crohn's disease [37]. A prospective evaluation of the differential diagnosis between intestinal TB and Crohn's disease using a cut-off value of 10 mm achieves 68% sensitivity, 84% specificity, 81% positive predictive value, and 72% negative predictive value [38].

Interferon-gamma release assays (IGRAs) detect the presence of *M. tuberculosis* infection by measuring the immune response to TB proteins in whole blood. IGRAs

offer the possibility of detecting *M. tuberculosis* infection with greater specificity than TST as *M. tuberculosis* antigens used in IGRA don't cross-react with BCG and NTM. IGRAs do not boost subsequent test results and can be completed following a single patient visit. Laboratory tests are not affected by the perceptions or biases of health-care workers in contrast to TST, but results can be dependent on the batching and transport of specimens.

A positive reaction to IGRA also cannot differentiate a latent TB infection (LTBI) from an active TB infection such as TST. Further, a negative reaction to IGRA does not exclude the diagnosis of LTBI or TB disease, and negative predictive value decreases when TB is clinically suspected. As in TST, clinicians should be cautious in interpreting test results in patients with HIV or those who are taking immunosuppressive drugs. A prospective evaluation of the differential diagnosis between intestinal TB and Crohn's disease using a IGRA shows 67% sensitivity, 90% specificity, 87% positive predictive value, and 73% negative predictive value [38].

10.1.5 Empirical Anti-TB Treatment

Definitive intestinal TB can be diagnosed based on the finding of acid-fast bacilli, caseating granulomas, or *M. tuberculosis* in culture. A diagnosis of probable intestinal TB is justified in a patient with appropriate clinical manifestations and gross endoscopic findings and evidence of a response to anti-TB treatment (Fig. 10.6) [1, 39]. Although the follow-up period has not been determined, follow-up colonoscopy exams should be performed within 2 to 3 months after initiating anti-TB treatment. If follow-up colonoscopy reveals significant resolution, anti-TB treatment

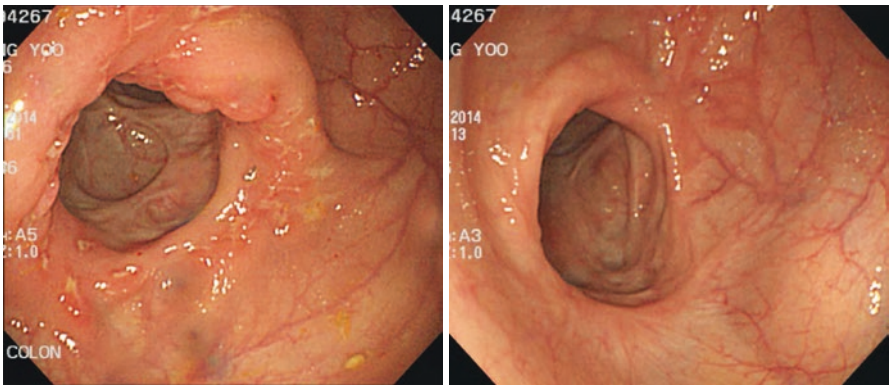


Fig. 10.6 Colonoscopic findings before (10.6.1) and after (10.6.2) empirical anti-TB treatment. The patient didn't have the presence of acid-fast bacilli, caseating granulomas, or *M. tuberculosis* in culture. The colonoscopic finding was improved 2 months later after empirical anti-TB treatment

should be maintained for 6 months to treat pulmonary TB [40–42]. After 1 month of treatment, CRP usually recedes to a normal level [19, 43].

In patients who failed to respond to primary anti-TB therapy, the rare possibility of drug-resistant TB must be considered [15, 44, 45]. However, in the absence of acid-fast bacilli, caseating granulomas, or *M. tuberculosis* in culture, it is difficult to determine which drug-resistant TB is present. In patients who fail to improve after empirical therapy, delayed response to anti-TB treatment may be considered, although this is rare [40]. It is practically difficult to decide to continue anti-TB treatment in cases for which the diagnosis of intestinal TB is not definite and colonoscopy findings fail to show response to anti-TB therapy. Anti-TB response should be interpreted with caution in patients with Crohn's disease. In some Crohn's disease patients, anti-TB chemotherapy might be effective in improving particular symptoms, laboratory findings, or colonoscopy findings although it is incomplete or temporary [19, 42]. In cases that lack a treatment response, clinicians should consider other diagnoses, including Crohn's disease.

10.2 Summary

TB remains an unresolved infectious disease throughout the world. Differentiating between intestinal TB and Crohn's disease is a major diagnostic challenge. This is particularly true in Asian countries, which show increasing incidence of inflammatory bowel disease, such as Crohn's disease. Definite diagnosis of intestinal TB is often difficult to achieve with histological or microbiological proof alone; thus, understanding the endoscopic features is potentially important for differentiating intestinal TB from Crohn's disease.

References

1. Marshall JB. Tuberculosis of the gastrointestinal tract and peritoneum. Am J Gastroenterol. 1993;88(7):989–99.
2. Frieden TR, Brudney KF, Harries AD. Global tuberculosis: perspectives, prospects, and priorities. JAMA. 2014;312(14):1393–4. doi:10.1001/jama.2014.11450.
3. Mehta JB, Dutt A, Harvill L, Mathews KM. Epidemiology of extrapulmonary tuberculosis. A comparative analysis with pre-AIDS era. Chest. 1991;99(5):1134–8.
4. Jakubowski A, Elwood RK, Enarson DA. Clinical features of abdominal tuberculosis. J Infect Dis. 1988;158(4):687–92.
5. Horvath KD, Whelan RL. Intestinal tuberculosis: return of an old disease. Am J Gastroenterol. 1998;93(5):692–6. doi:10.1111/j.1572-0241.1998.207_a.x.
6. Myers AL, Colombo J, Jackson MA, Harrison CJ, Roberts CR. Tuberculous colitis mimicking Crohn's disease. J Pediatr Gastroenterol Nutr. 2007;45(5):607–10. doi:10.1097/MPG.0b013e3180335b9a.
7. Barnes PF, Bloch AB, Davidson PT, Snider Jr DE. Tuberculosis in patients with human immunodeficiency virus infection. N Engl J Med. 1991;324(23):1644–50. doi:10.1056/nejm199106063242307.

8. Yang SK, Loftus Jr EV, Sandborn WJ. Epidemiology of inflammatory bowel disease in Asia. Inflamm Bowel Dis. 2001;7(3):260–70.
9. Thia KT, Loftus Jr EV, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol. 2008;103(12):3167–82. doi:10.1111/j.1572-0241.2008.02158.x.
10. Ng SC, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, Wong TC, Leung VK, Tsang SW, Yu HH, Li MF, Ng KK, Kamm MA, Studd C, Bell S, Leong R, de Silva HJ, Kasturiratne A, Mufeena MN, Ling KL, Ooi CJ, Tan PS, Ong D, Goh KL, Hilmi I, Pisespongsa P, Manatsathit S, Rerknimitr R, Aniwan S, Wang YF, Ouyang Q, Zeng Z, Zhu Z, Chen MH, Hu PJ, Wu K, Wang X, Simadibrata M, Abdullah M, Wu JC, Sung JJ, Chan FK. Incidence and phenotype of inflammatory bowel disease based on results from the Asia–Pacific Crohn's and Colitis Epidemiology Study. Gastroenterology. 2013;145(1):158.e2–65.e2. doi:10.1053/j.gastro.2013.04.007.
11. Ng SC. Epidemiology of inflammatory bowel disease: focus on Asia. Best Pract Res Clin Gastroenterol. 2014;28(3):363–72. doi:10.1016/j.bpg.2014.04.003.
12. Sato S, Yao K, Yao T, Schlemper RJ, Matsui T, Sakurai T, Iwashita A. Colonoscopy in the diagnosis of intestinal tuberculosis in asymptomatic patients. Gastrointest Endosc. 2004;59(3):362–8.
13. Hwang KE, Jang NS, Park CY, Lym SY, Kim BI, Jeon WK, Jung ES, Lee SJ. Significance of colonoscopy in the early diagnosis of intestinal tuberculosis. Korean J Gastroenterol. 1997;29(4):449–56.
14. Choi SM, Yang SK, Jung HY, Ha HK, Yu CS, Kim JC, Kim HK, Won SY, Lee MH, Jung SA, Kim HR, Hong WS, Kim YI. Clinical features of intestinal tuberculosis with special reference to risk factors for complication. Korean J Gastroenterol. 1997;30(4):462–71.
15. Lee YJ, Yang SK, Myung SJ, Byeon JS, Park IG, Kim JS, Lee GH, Jung HY, Hong WS, Kim JH, Min YI. The usefulness of colonoscopic biopsy in the diagnosis of intestinal tuberculosis and pattern of concomitant extra-intestinal tuberculosis. Korean J Gastroenterol. 2004;44(3):153–9.
16. Leung VK, Law ST, Lam CW, Luk IS, Chau TN, Loke TK, Chan WH, Lam SH. Intestinal tuberculosis in a regional hospital in Hong Kong: a 10-year experience. Hong Kong Med J. 2006;12(4):264–71.
17. Patel N, Amarapurkar D, Agal S, Baijal R, Kulshrestha P, Pramanik S, Gupte P. Gastrointestinal luminal tuberculosis: establishing the diagnosis. J Gastroenterol Hepatol. 2004;19(11):1240–6. doi:10.1111/j.1440-1746.2004.03485.x.
18. Khan R, Abid S, Jafri W, Abbas Z, Hameed K, Ahmad Z. Diagnostic dilemma of abdominal tuberculosis in non-HIV patients: an ongoing challenge for physicians. World J Gastroenterol. 2006;12(39):6371–5.
19. Park SH, Yang SK, Myung SJ, Byeon JS, Ye B, Kwon S, Kim B, Yoon SM, Do MY, Kim DH, Kim SH, Kim JH. Usefulness of C-reactive protein level before and during antimycobacterial therapy in the differential diagnosis between Crohn's disease and intestinal tuberculosis. Int Rescuer. 2007;5(1):19–25.
20. Kalvaria I, Kottler RE, Marks IN. The role of colonoscopy in the diagnosis of tuberculosis. J Clin Gastroenterol. 1988;10(5):516–23.
21. Aoki G, Nagasako K, Naker Y, Suzuki H, Endo M, Takemoto T. The fibercolonoscopic diagnosis of intestinal tuberculosis. Endoscopy. 1975;7(3):113–21.
22. Kim KM, Lee A, Choi KY, Lee KY, Kwak JJ. Intestinal tuberculosis: clinicopathologic analysis and diagnosis by endoscopic biopsy. Am J Gastroenterol. 1998;93(4):606–9. doi:10.1111/j.1572-0241.1998.173_b.x.
23. Alvares JF, Devarbhavi H, Makhija P, Rao S, Kottoor R. Clinical, colonoscopic, and histological profile of colonic tuberculosis in a tertiary hospital. Endoscopy. 2005;37(4):351–6. doi:10.1055/s-2005-861116.
24. Shah S, Thomas V, Mathan M, Chacko A, Chandy G, Ramakrishna BS, Rolston DD. Colonoscopic study of 50 patients with colonic tuberculosis. Gut. 1992;33(3):347–51.
25. Singh V, Kumar P, Kamal J, Prakash V, Vaiphei K, Singh K. Clinicocolonoscopic profile of colonic tuberculosis. Am J Gastroenterol. 1996;91(3):565–8.

26. Makharia GK, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, Deo V, Aggarwal A, Tiwari RP, Sreenivas V, Gupta SD. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. Am J Gastroenterol. 2010;105(3):642–51. doi:10.1038/ajg.2009.585.
27. Naga MI, Okasha HH, Ismail Z, El-Fatatry M, Hassan S, Monir BE. Endoscopic diagnosis of colonic tuberculosis. Gastrointest Endosc. 2001;53(7):789–93.
28. Lee YJ, Yang SK, Byeon JS, Myung SJ, Chang HS, Hong SS, Kim KJ, Lee GH, Jung HY, Hong WS, Kim JH, Min YI, Chang SJ, Yu CS. Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. Endoscopy. 2006;38(6):592–7. doi:10.1055/s-2006-924996.
29. Pulimood AB, Peter S, Ramakrishna B, Chacko A, Jeyamani R, Jeyaseelan L, Kurian G. Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. J Gastroenterol Hepatol. 2005;20(5):688–96. doi:10.1111/j.1440-1746.2005.03814.x.
30. Kirsch R, Pentecost M, Hall Pde M, Epstein DP, Watermeyer G, Friederich PW. Role of colonoscopic biopsy in distinguishing between Crohn's disease and intestinal tuberculosis. J Clin Pathol. 2006;59(8):840–4. doi:10.1136/jcp.2005.032383.
31. Pulimood AB, Ramakrishna BS, Kurian G, Peter S, Patra S, Mathan VI, Mathan MM. Endoscopic mucosal biopsies are useful in distinguishing granulomatous colitis due to Crohn's disease from tuberculosis. Gut. 1999;45(4):537–41.
32. Lee TK, Kim YH, Chang UI, Jun EJ, Kim JI, Park SH, Han JY, Kim JK, Chung KW, Sun HS. The diagnostic value of polymerase chain reaction in intestinal tuberculosis. Korean J Gastrointest Endosc. 2003;26(2):79–83.
33. Gan H, Ouyang Q, Bu H, Li S, Chen D, Li G, Yang X. Value of polymerase chain reaction assay in diagnosis of intestinal tuberculosis and differentiation from Crohn's disease. Chin Med J. 1995;108(3):215–20.
34. Hillemann D, Galle J, Vollmer E, Richter E. Real-time PCR assay for improved detection of mycobacterium tuberculosis complex in paraffin-embedded tissues. Int J Tuberc Lung Dis. 2006;10(3):340–2.
35. Korean Academy of Tuberculosis and Respiratory Diseases. Guideline for the management of tuberculosis. Seoul: Korean Academy of Tuberculosis and Respiratory Diseases; 2005.
36. Bhargava DK, Kushwaha AK, Dasarathy S, Shriniwas CP. Endoscopic diagnosis of segmental colonic tuberculosis. Gastrointest Endosc. 1992;38(5):571–4.
37. Epstein D, Watermeyer G, Kirsch R. Review article: the diagnosis and management of Crohn's disease in populations with high-risk rates for tuberculosis. Aliment Pharmacol Ther. 2007;25(12):1373–88. doi:10.1111/j.1365-2036.2007.03332.x.
38. Kim BJ, Choi YS, Jang BI, Park YS, Kim WH, Kim YS, Jung SA, Han DS, Kim JS, Choi JH, Choi CH, Jeen YT, Cheon JH, Ye BD, Yang SK, Kim YH. Prospective evaluation of the clinical utility of interferon-gamma assay in the differential diagnosis of intestinal tuberculosis and Crohn's disease. Inflamm Bowel Dis. 2011;17(6):1308–13. doi:10.1002/ibd.21490.
39. Lingenfelser T, Zak J, Marks IN, Steyn E, Halkett J, Price SK. Abdominal tuberculosis: still a potentially lethal disease. Am J Gastroenterol. 1993;88(5):744–50.
40. Park SH, Yang SK, Yang DH, Kim KJ, Yoon SM, Choe JW, Ye BD, Byeon JS, Myung SJ, Kim JH. Prospective randomized trial of six-month versus nine-month therapy for intestinal tuberculosis. Antimicrob Agents Chemother. 2009;53(10):4167–71. doi:10.1128/AAC.00874-09.
41. Youn JE, Park IB, Kwon SY, Kim JS, Byun KS, Bak YT, Kim JG, Lee CH, Kim JH. Follow-up colonoscopy at 3 months of therapy in patients with tentative diagnosis of intestinal tuberculosis. Korean J Med. 1996;50(2):227–33.
42. Kim SG, Kim JS, Jung HC, Song IS. Is a 9-month treatment sufficient in tuberculous enterocolitis? A prospective, randomized, single-centre study. Aliment Pharmacol Ther. 2003;18(1):85–91.

43. Lawn SD, Obeng J, Acheampong JW, Griffin GE. Resolution of the acute-phase response in West African patients receiving treatment for pulmonary tuberculosis. Int J Tuberc Lung Dis. 2000;4(4):340–4.
44. Ko BS, Kim BG, Kim JS, Jung HC, Song IS. A case of cure with secondary rescue regimen of tuberculosis in a patient with tuberculous colitis that failed to respond to primary drugs. Korean J Gastroenterol. 2002;39(4):299–303.
45. Yun SK, Jung IK, Kim HS, Park SH, Lee MH, Kim SJ, Kim DJ. A case of colonic tuberculosis cured by secondary anti–tuberculosis medicine. Korean J Gastrointest Endosc. 1998;18(4):591–6.

Chapter 11
Endoscopic Findings and Diagnosis of Other Inflammatory Bowel Diseases of the Lower GI Tract

Takayuki Matsumoto

Abstract While Crohn's disease is the representative and the most frequent inflammatory bowel disease of the small bowel, there are other diseases characterized by small bowel mucosal lesions. Cryptogenic multifocal ulcerous stenosing enteritis is one of those diseases, initially reported in the European area in the 1970s and becoming widely recognized in the beginning of this century. The disease has been characterized by chronic or relapsing ulcers of nonspecific histology in the jejunum and the ileum, and it has been suggested that it may be associated with vasculitis. There has also been a clinical entity of chronic small bowel ulcers referred to as chronic nonspecific multiple ulcers of the small intestine (CNSU). The disease has become widely accepted as a clinical entity in the Japanese population. CNSU is clinically characterized by chronic and obscure intestinal bleeding and extraordinarily peculiar small-bowel ulcers of nonspecific pathology. The ileum other than the terminal ileum is affected by sharply demarcated, ill-shaped shallow ulcers restricted to the submucosal layer. These conditions should seriously be considered in patients with chronic and intractable small-bowel ulcers.

Keywords Crohn's disease • Cryptogenic multifocal ulcerous stenosing enteritis • Nonspecific multiple ulcers of the small intestine

11.1 Introduction

While Crohn's disease and ulcerative colitis are the major two diseases belonging to the category of inflammatory bowel disease, there are other conditions characterized by chronic and persistent inflammation of the small and large bowel. In

T. Matsumoto
Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan
e-mail: tmatsumo@iwate-med.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_11

Table 11.1 Small-bowel enteropathy

Etiology known
– Infection
– Small intestinal ischemia
– Ulcer in Meckel's diverticulum
– Drug-induced enteropathy
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Anti-cancer drugs
– Radiation enteritis
– Enteritis in association with systemic diseases
– Inherited human cPLA2a deficiency
– Chronic duodenojejunoileitis associated with celiac disease
– Others
Etiology unknown
– Crohn's disease
– Behçet's disease/simple ulcer of the small intestine
– Cryptogenic multifocal ulcerous stenosing enteritis (CMUSE)
– Chronic nonspecific multiple ulcers of the small intestine (CNSU)
– Others

addition to colonoscopy, the widespread application of capsule endoscopy (VCE) or balloon-assisted endoscopy (BAE) has enabled us to examine an extensive area of the small intestine by endoscopy. In recent years, colonoscopic and enteroscopic findings of relatively rare but clinically significant diseases as summarized in Table 11.1. have been specified.

In this chapter, the clinical features and endoscopic findings of chronic nonspecific multiple ulcers of the small intestine (CNSU) and cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) will be discussed. These diseases have become the topics of this chapter because they are characterized by clinical features and endoscopic findings mimicking Crohn's disease.

11.2 Chronic Nonspecific Multiple Ulcers of the Small Intestine (CNSU)

CNSU is a chronic and recurrent small intestinal disease initially identified in Japan in the 1960s [1–5]. The disease is characterized by chronic and occult gastrointestinal bleeding and histologically nonspecific ileal ulcers in multiplicity. However, some gastroenterologists have misinterpreted CNSU as a small intestinal pathology of nonspecific pathology without taking clinical features into consideration. The misinterpretation has led to heterogeneity in descriptions of clinicopathologic features of CNSU. Because chronic, recurrent clinical

Table 11.2 Diagnostic criteria of CNSU

Major criteria
A. Clinical features
(1) Positive fecal occult blood in multiple sampling
(2) Microcytic, hypochromic anemia for a prolonged period
B. Findings obtained by small-bowel radiography and/or enteroscopy
(1) Neighboring and non-concentric stenosis in multiplicity (radiography)
(2) Sharply demarcated shallow multiple ulcers in circumferential or oblique alignment (enteroscopy)
C. Macroscopic and microscopic findings of the small intestine
(1) Sharply demarcated flat ileal ulcers
(2) Circular or oblique ulcer in geographical or tape-like configuration
(3) Histologically nonspecific ulcer restricted to the submucosal layer
Diseases to be excluded
(1) Intestinal tuberculosis
(2) Crohn's disease
(3) Intestinal Behçet's disease/simple ulcer of the small intestine
(4) Drug-induced enteritis
Definite diagnosis of CNSU should satisfy following (1) or (2)
(1) Positive for major criteria A and B-(1) or B-(2) or any one of C
(2) Positive for all of major criteria C
Cases which satisfy major criteria A but do not satisfy B or C should be regarded as having suspected CNSU

course is a diagnostic feature of CNSU, and since the phenotype of CNSU can easily progress to the diaphragm by treating patients with total parenteral nutrition, Yao proposed a modified diagnostic criteria of CNSU in 2004 [1]. The criteria have recently been revised, with an emphasis on enterosocopic findings (Table 11.2.).

The symptoms of CNSU are characterized by those attributed to chronic and persistent blood loss from the intestine occurring early in their life. Thus patients manifest fatigue, edema, and growth retardation, and they usually have repeated episodes of treatment for anemia. However, the patients rarely manifest diarrhea, hematochezia, or fever. Based on these manifestations, patients visit gastroenterologists long after the onset of symptoms. As well as the symptoms, the physical examination reveals anemia, but the abdomen is unremarkable.

Although the small intestinal ulcers in CNSU occur predominantly in the ileum, the terminal ileum is usually spared. The ulcers usually count more than 20 in number, each of which is characterized by discrete margin and shallow and flat ulcer bed. Each ulcer appears as a linear or tall triangle in configuration, which align in a circular or oblique fashion. The ulcers occasionally fuse, thus showing geographic configuration. Even though the ulcers develop into luminal narrowing, the small intestinal lesions in CNSU never progress to cobblestone appearance, fissure or fistula formation, or adhesion. In more advanced cases, however, small intestinal stenoses are the major manifestation. Because of the

oblique nature of the pre-existing ulcers, the stenoses are not always concentric, but rather they may show spiral patterns.

The depth of ulcers is restricted to the mucosa or the submucosa, and they never extend to the proper muscular layer. The mucosal defect is accompanied by mild infiltration of plasma cells, lymphocytes, and eosinophils. Lymph follicles may also be seen. Even in histology, the margin of the ulcer is clearly demarcated by the surrounding villous mucosa. Although submucosal fibrosis occurs in the healing stage, it is restricted to the area of mucosal defect, with minimal epithelial repair and restitution.

11.2.1 Genetic Background

We have recently reviewed family histories of 13 patients with CNSU, and found six patients who were offspring of consanguineous marriage of three or five degrees. In addition, three of 13 patients had siblings showing enteropathy, and two of them were siblings of consanguineous marriage. Based on such segregation in offspring from consanguinity, we speculated that CNSU is an autosomal recessive disorder. According to the present case series of CNSU, eight of 16 patients were offspring of consanguinity marriage. In addition, four of the other eight patients who denied consanguinity in their family pedigrees had siblings of CNSU. Such dense inheritance again reconfirms that CNSU is distinctive of hereditary disease. More recently, it has been reported that homozygous mutations or compound heterozygous mutations of SLCO2A1 gene encoding a prostaglandin transporter are closely associated with the pathogenesis of the disease [21].

11.2.2 Clinicopathologic Features of CNSU

The disease occurs predominantly in females. While the ages of onset ranged from ten to 52 years, most of the patients manifest anemia during their second or third decade of life. The patients had histories of long-term anemia, and they had usually suffered from the symptoms for more than ten years before confirmation of small intestinal lesions.

There are no specific laboratory tests for the diagnosis of CNSU. The feces are continuously positive for occult blood. Peripheral blood test reveals hypochromatic and microcytic anemia. However, leukocyte and platelet counts are within normal ranges. Serum iron level is markedly decreased unless the patient is treated by iron supplementation. In addition to anemia, most patients manifest hypoproteinemia and hypoalbuminemia. However, acute inflammatory reactions such as C-reactive protein, a1-, and a2-globulins are usually within their normal ranges or slightly increased. Unlike intestinal tuberculosis, intradermal tuberculin test is negative in most cases.

11.2.3 Small-Bowel Radiography

While double-contrast barium study (DCBS) is the first choice of procedure for the diagnosis of CNSU, it is not easy for radiologists to depict the small intestinal lesions as barium flecks, because the ulcers are extremely shallow. The ulcers are usually shown as asymmetric and multiple rigid or eccentric deformities. When examined precisely by DCBS together with compression procedure, linear or tall-triangle mucosa defects may be depicted as sharply demarcated barium flecks. In cases treated by total enteral or parenteral nutrition, the ulcer heals with stricture formation.

11.2.4 Endoscopy

With the development of BAE, we were recently able to confirm enteroscopic features of CNSU. Among 15 patients with CNSU diagnosed at out institution, we attempted DBE in six patients. Based on the results, the enteroscopic features of CNSU are sharply demarcated linear (Fig. 11.1) or geographical ulcers (Fig. 11.2), which are located in circular or oblique alignment. The intervening mucosa is apparently normal without any diminutive lesions. Even though the ulcers may be accompanied by fold convergency or severe stenosis, thus mimicking diaphragms as seen in NSAIDs enteropathy, most of the ulcers have thin and faint exudates (Figs. 11.3

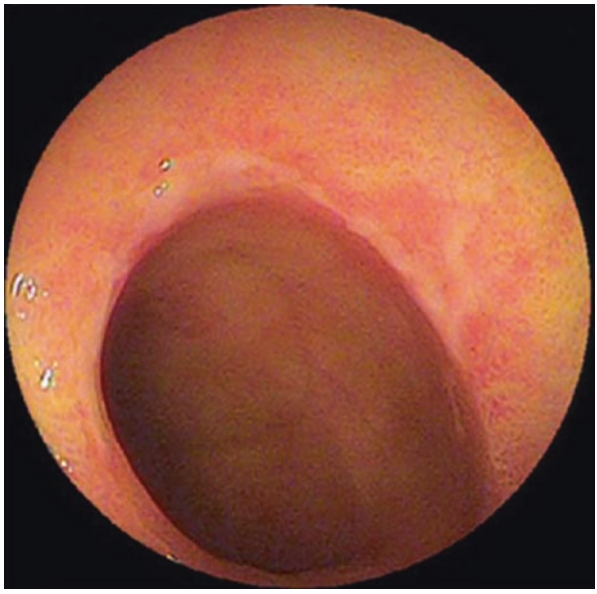


Fig. 11.1 Enteroscopic findings of CNSU. Retrograde BAE shows a thin and circular ulcer in the ileum

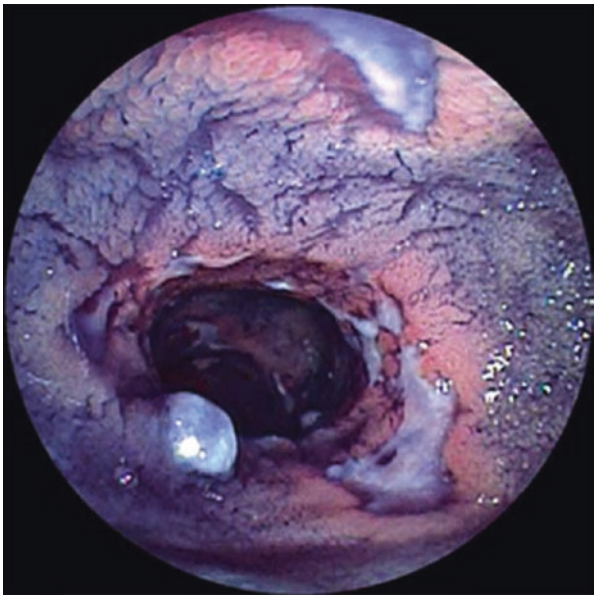


Fig. 11.2 Retrograde BAE with dye-spraying reveals a shallow and geographical ulcer in the ileum

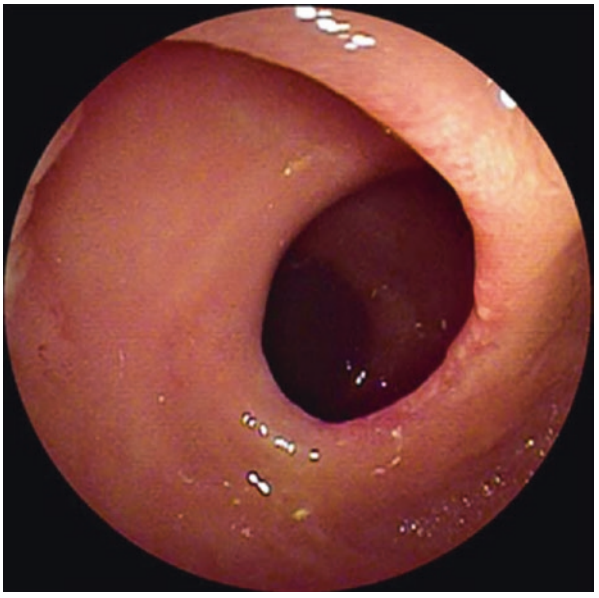


Fig. 11.3 Retrpgrade BAE shows a healing ulcer in the ileum. As a consequence, there is a deformity mimicking a spiral

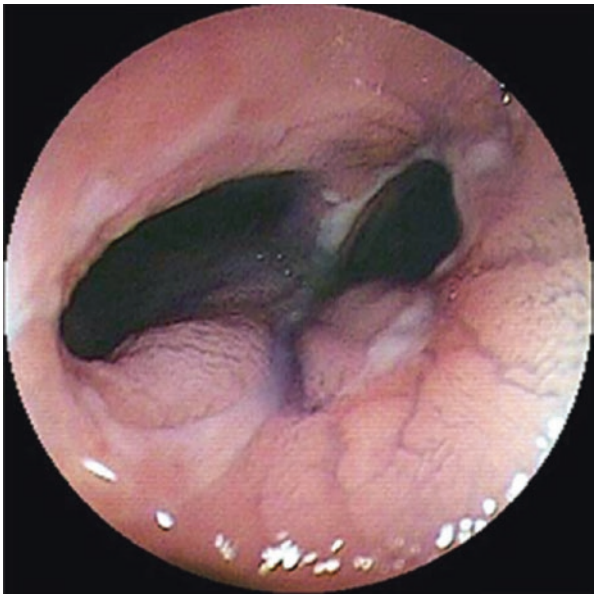


Fig. 11.4 Retrograde BAE with dye-spraying shows a shallow and branching ulcer in the ileum. There is a conspicuous and unique deformity, which partly resembles a diaphragm-like stricture

and 11.4). The enteroscopic features again indicate that the ulcers in CNSU are intractable. The VCE findings of CNSU have not been reported to date.

There have been cases of duodenal and colonic involvement of CNSU. Gastroduodenal ulcers were found in seven of our 15 cases, and colonic ulcers in three cases. One of the former cases had intractable ulcer at the gastroduodenal anastomosis, and another in the latter cases had concentric ulcers with severe stenosis in the right side of the colon. These endoscopy findings suggest CNSU to be a disease which involves any site within the GI tract.

11.2.5 Clinical Course

CNSU is characterized by recurrence of small intestinal ulcers and stenoses even after surgery. Enteral or parenteral nutrition coupled with iron supplementation is transiently effective, but the small intestinal ulcers recur within a short period of time. Although all of our patients were treated by oral 5-aminosalicylic acid, six patients by oral prednisolone, and one patient by oral azathioprine, those medications failed to induce mucosal healing or to prevent recurrence of small intestinal ulcers. Our patients have been under observation

for periods ranging from 4 to 43 years, during which ten of 15 patients required twice or more ileal resections. Histological examination of the resected specimens showed exactly the same findings as found in the initial surgical specimens. It should also be noted that our patients have been free from any extraintestinal manifestations, such as oral, skin, joint, genital, or perianal lesions, as found in Crohn's disease or Behcet's disease.

11.3 Cryptogenic Multifocal Ulcerous Stenosing Enteritis (CMUSE)

There have recently been case descriptions in the West which show small intestinal pathology, which is presumed to be similar to CNSU. In 2001, Santolaria et al. [6] reported on a peculiar small intestinal pathology. The male patient initially manifested diarrhea, weight loss, and edema, and later complained of recurrent intestinal obstruction which had occurred over a 25-year period of his life. Even though the patient had been treated three times by surgery, the small intestinal lesion recurred with a feature compatible with diaphragm disease. What should be noted in this case is the fact that the patient was completely free from NSAID use. There has also been a clinicopathologic entity characterized by nonspecific ulcers of the small intestine, which has been referred to as cryptogenic multifocal ulcerous stenosing enteritis (CMUSE) [7]. The disease was first reported by Debray et al. [8] in 1964, when the first case of CNSU was reported in the Japanese literature. Since then, 18 cases of CMUSE have been reported, mainly in French literature [7–18]. Perlemuter et al. [7, 18] reviewed cases of CMUSE in 1996, and subsequently attempted a multicenter retrospective analysis of 12 cases in 2001. In those articles, the clinicopathological features of CMUSE have been summarized as: (1) unexplained small intestinal strictures found in adolescents and in middle-aged subjects, (2) superficial ulceration of the mucosa and submucosa, (3) chronic or relapsing clinical course even after surgery, (4) no biological signs of systemic inflammatory reaction, and (5) beneficial effect of steroids. Perlemuter et al. [7, 18] hypothesized that CMUSE is closely associated with vasculitis, because stenosis and aneurysm were verified in superior mesenteric arteries and steroid is efficacious in a certain proportion of the subjects.

It has recently been reported that CMUSE may be a hereditary disorder. Brooke et al. [19] demonstrated a homozygous deletion in *PLA2G4A* encoding cPLA2αin a family pedigree of patients with CMUSE by means of whole-exam sequencing. Homozygous mutation of cPLA2α has previously been shown to result in impaired production of eicosanoids such as PGE2 and thromboxane A2, and as a consequence, in the occurrence of multiple ulcers of the small intestine and platelet dysfunction [20]. These observations strongly suggest that CMUSE is a disease predisposed to chronic prostaglandin deficiency.

References

1. Yao T, Iida M, Matsumoto T, Yao T. Chronic hemorrhagic ulcers of the small intestine or chronic nonspecific multiple ulcers of the small intestine. In: Yao T, Iida M, editors. Diseases of the small intestine. Tokyo: Igaku-Shoin; 2004. p. 176–86.
2. Matsumoto T, Iida M, Matsui T, Yao T, Watanabe H, Yao T, et al. Non-specific multiple ulcers of the small intestine unrelated to non-steroidal anti-inflammatory drugs. J Clin Pathol. 2004;57:1145–50.
3. Matsumoto T, Nakamura S, Esaki M, Yada S, Koga H, Yao T, et al. Endoscopic features of chronic nonspecific multiple ulcers of the small intestine: comparison with nonsteroidal anti-inflammatory drug-induced enteropathy. Dig Dis Sci. 2006;51:1357–163.
4. Matsumoto T, Iida M, Matsui T, Yao T. Chronic nonspecific multiple ulcers of the small intestine: a proposal of the entity from Japanese gastroenterologists to western enteroscopists. Gastrointest Endosc. 2007;66:s99–s100.
5. Matsumoto T, Kubokura N, Matsui T, Iida M, Yao T. Chronic nonspecific multiple ulcer of the small intestine segregates in offspring from consanguinity. J Crohns Colitis. 2011;5:559–65.
6. Santolaria S, Cabezali R, Ortego J, et al. Diaphragm disease of the small bowel. A case without apparent nonsteroidal anti-inflammatory drug use. J Clin Gastroenterol. 2001;32:344–6.
7. Perlemuter G, Guillevin L, Legman P, Weiss L, Couturier D, Caoussade S. Cryptogenic multifocal ulcerous stenosing enteritis. An atypical type of vasculitis or a disease mimicking vasculitis. Gut. 2001;48:333–8.
8. Debray C, Besançon F, Hardoin JP, et al. Entérite sténosante ulcéreuse plurifocate cryptogénétique. Arch Fr Mal App Dig. 1964;53:193–206.
9. Rocha A, Artigas V. La maladie ulcéreuse sténosante du hehuno-iléon. Arch Fr Mal App Dig. 1959;10:1230–6.
10. Gauthier AP, Rampal M, Lieutaud R, et al. Sténoses multiples “ideopathiques” de l’intestin gréle. A propos de deux observations. Arch Fr Mal Dig. 1966;55:31–43.
11. Paille F, Champigneulle B, Brucker P, et al. L’enteérite sténosante ulcéreuse plurifocale cryptogénetique. A propos de deux observations. Ann Gastroenterol Hepatol. 1981;17:405–9.
12. Macinot C, Lorenzini C, Ravey M, et al. Entérite segmentaire sténosante plurifocale. Semin Hop Paris. 1974;50:2518–20.
13. Lescut J, Grégoire L, Weisemburger JP. Sténoses multiples cryptogénétiques de l’intestin gréle. A propos d’une nouvelle observation. Lille Med. 1969;14:602–6.
14. Chagnon JP. Devars du Mayne JF, Marche C, et al. L’entérite sténosante ulcéreuse multifocale cryptogénétique. Une entitéautonome? Gastroenterol Clin Biol. 1984;8:808–13.
15. Doute LP, Paccalin J, Périssat J, et al. Entérite sténosante ulcéreuse plurifocale. Une nouvelle observation. Arch Fr Mal App Dig. 1966;55:537–40.
16. Harrop Shoesmith J, Tate GT, et al. Multiple strictures of the jejunum. Gut. 1964;5:132–5.
17. Bokemeyer B, Schmidt FW, Galanski M. Kryptogene multifokale stenosierende enteritis. Z Gastroenterol. 1987;25:745–8.
18. Perlemuter G, Chaussade S, Soubrane O, et al. Multifocal stenosing ulcerations of the small intestine revealing vasculitis associated with C2 deficiency. Gastroenterology. 1996;100:1628–32.
19. Brooke MA, Longhurst HJ, Plagnol V, Kirkby NS, Mitchell JA, Rüschendorf F, et al. Cryptogenic multifocal ulcerating stenosing enteritis associated with homozygous deletion mutations in cytosolic phospholipase A2-α. Gut. 2014;63:96–104.
20. Adler DH, Cogan JD, Phillips JA, Schnetz-Boutaud N, Milne GL, Iverson T, et al. Inherited human cPLA(2alpha) deficiency is associated with impaired eicosanoid biosynthesis, small intestinal ulceration, and platelet dysfunction. J Clin Invest. 2008;118:2121–31.
21. Umeno J, Hisamatsu T, Esaki M, Hirano A, Kubokura N, Asano K, et al. A hereditary enteropathy cause by mutations in SLCO2A1gene, encoding PGE transporter. PLoS Genet. 2015;11:e1005581.

Chapter 12
Endoscopic Findings and Diagnosis of Other Inflammatory Diseases of the Lower GI Tract (Except for Infectious): Vascular, Eosinophilic, Inflammation Associated with Other Diseases, etc.

Naoki Ohmiya, Tomomitsu Tahara, Mitsuo Nagasaka, Yoshihito Nakagawa, and Tomoyuki Shibata

Abstract The diagnostics of small-bowel diseases has evolved since the advent of videocapsule endoscopy and balloon-assisted enteroscopy. In this chapter, we state pathophysiology, clinical manifestations, and endoscopic diagnosis of vascular, eosinophilic diseases, and inflammation associated with other diseases in the small bowel and the large bowel.

Keywords Acute mesenteric ischemia • Chronic mesenteric ischemia • Angiodysplasia • Hereditary hemorrhagic telangiectasia • Varices • Ischemic colitis • Eosinophilic gastroenteritis • Endometriosis • Mucosal prolapse and the solitary rectal ulcer syndrome

12.1 Vascular Disease of Intestine

12.1.1 Nomenclature

When the intestine is deprived of blood, histological changes follow with the acuteness and severity of the ischemia [1]. Despite the presence of collateral channels, the vasculature has several points susceptible to poor perfusion. The middle part of the small intestine, in the middle of the area perfused by the superior mesenteric artery (SMA), is far away from the collaterals from the celiac axis to the proximal SMA, and from collaterals from the inferior mesenteric artery (IMA) to the distal SMA. This area is the most vulnerable to developing ischemia from SMA occlusion. Narrow terminal branches of the SMA supply the splenic flexure, and the rectosigmoid junction is supplied by terminal branches of the IMA. These two

N. Ohmiya (✉) • T. Tahara • M. Nagasaka • Y. Nakagawa • T. Shibata
Department of Gastroenterology, Fujita Health University School of Medicine, Aichi, Japan
e-mail: nohmiya@med.nagoya-u.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_12

watershed areas are most vulnerable to developing ischemia during systemic hypotension if the collateral anastomoses are small or tenuous [2].

The considerable variation in the clinical presentation as well as the pathology are the main explanations for a confusing nomenclature covering a spectrum ranging from acute infarction, through transient subclinical episodes to the chronic evolution of a fibrotic stricture. The expressions gangrene, hemorrhagic necrosis, necrotizing enterocolitis, and ischemic enterocolitis have all been used to describe different clinicopathological manifestations of acute severe ischemia. The chronic variety of ischemia is best known as ischemic stricture. However, the histopathology of acute ischemia and ischemic stricture merge into one another, and the appearances seen in surgical specimens depend on the stage at which the operation is performed, as well as the severity and duration of the ischemic episodes. Between the clinical emergency of acute infarction and a chronic ischemic stricture exists an ill-defined stage manifest by transient ischemic episodes. These may be single subclinical reversible thrombotic events [1].

The clinical patterns of mesenteric vascular disease is classified in this chapter as follow:

1. Acute mesenteric ischemia:
   (a) arterial occlusion
   (b) arterial vasospasm
   (c) venous occlusion
2. Chronic mesenteric ischemia:
3. Angiodysplasia, hereditary hemorrhagic telangiectasia
4. Varices
5. Ischemic colitis, mesenteric phlebosclerosis

12.1.2 Acute Mesenteric Ischemia

Pathophysiology and Clinical Manifestations

Arterial embolization, thrombosis, nonocclusive mesenteric ischemia (NOMI), and venous thrombosis account for about 50%, 15%, 30%, and 5% of acute mesenteric ischemia respectively [3, 4]. Risk factors for mesenteric arterial embolism are as follows: cardiac arrhythmia, especially atrial fibrillation, myocardial dyskinesia, prosthetic valve, electroversion, cardiac catheterization, recent myocardial infarction. The sudden occurrence of abdominal pain in these settings should prompt evaluation for SMA embolization [5].

Thrombosis of SMA or celiac artery is generally associated with a preexisting stenosis, often at the origin of the arteries. Patients usually have diffuse atherosclerotic disease, with prior coronary, cerebrovascular, or peripheral arterial insufficiency [3]. However, 30% of patients have histories consistent with chronic

mesenteric ischemia, including postprandial pain, malabsorption, and weight loss before the acute episode [4].

NOMI is due to vasospasm, which can occur during periods of relatively low mesenteric flow, especially if there is underlying arterial atherosclerotic disease. Such low-flow state can result from heart failure, hypotension, or hypovolemia. Vasoconstrictive drugs, particularly alpha-adrenergic agents, vasopressin, ergotamine, diuretics, and digitalis glycosides, can contribute to NOMI [6].

Acute mesenteric venous thrombosis causes 5–10% of cases of acute mesenteric ischemia [7, 8]. Symptomatic SMV thrombosis is about 20-fold more common than symptomatic IMV thrombosis because of the larger caliber and flow of the SMV [9]. The mean reported patient age ranges from 47 to 60 years, which is younger than that for superior mesenteric arteriopathy because of the association of arterial disease with atherosclerosis [10]. Risk factors for mesenteric venous thrombosis are as follows: hypercoagulable states including protein C deficiency, protein S deficiency, and anti-phospholipid syndrome, hyperviscosity syndromes including myeloproliferative disorders and sickle cell anemia, portal hypertension, abdominal infection/inflammation including appendicitis, diverticulitis, intra-abdominal abscess, and pancreatitis, and trauma [11]. The life-threatening complications of mesenteric venous thrombosis are induced by the resulting bowel wall edema and increased outflow resistance secondary to venous occlusion and increased blood viscosity, which can impede arterial flow, leading to submucosal hemorrhage, venous capillary congestion, and bowel infarction [12].

The pain may initially be colicky but becomes constant with progression of ischemia. The pain may be localized or diffuse. The duration of pain is typically short. The symptoms of acute mesenteric venous thrombosis are usually less severe than those of acute arterial ischemia [2]. Typically, these patients have a diffuse, intermittent abdominal pain of several days or even weeks in duration. In the absence of pain, unexplained abdominal distention and gastrointestinal bleeding may be the earliest signs of ischemia [2].

Diagnosis

Laboratory tests including leukocytosis, metabolic acidosis, and elevation of serum lactate, phosphate, and alkaline phosphatase levels, high D-dimer levels are not sensitive or specific [13, 14]. Angiography detects the meniscus defect by an embolus, and the planar defect by a thrombus in cases of SMA occlusion [15]. In NOMI, angiography reveals multiple areas of narrowing and irregularity in major branches. The small and medium arterial branches may be decreased or absent, producing a “pruned” arterial tree [16]. In mesenteric venous thrombosis, selective angiograms may reveal reflux of contrast material back into the aorta, and a prolonged arterial phase with accumulation of contrast and thickened bowel walls is also characteristic [12]. Contrast-enhanced computed tomography (CECT) and volume-rendered three-dimensional CT enable the site

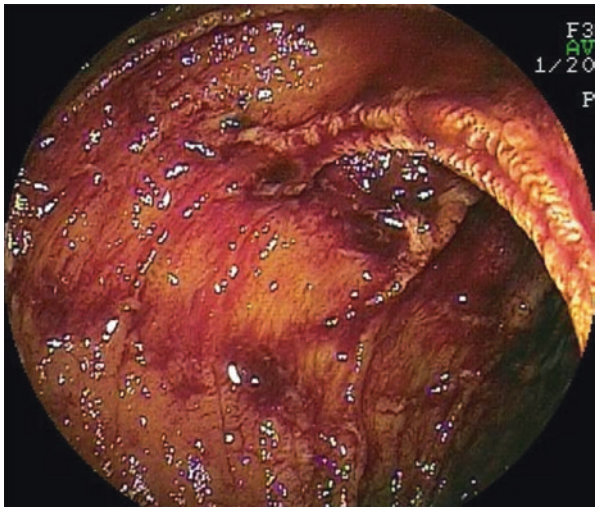


Fig. 12.1 Enteroscopic view of acute mesenteric ischemia due to aortic and SMA dissection in the proximal jejunum

of the vascular obstruction to be visualized. Enteroscopy is not necessarily used in such an emergent case. An enteroscopic view shows extensive mucosal break and oozing in the slightly dilated jejunum (Fig. 12.1).

12.1.3 Chronic Mesenteric Ischemia

Pathophysiology and Clinical Manifestations

Ischemic strictures occur in the small bowel or colon. The causes are small mesenteric vessel emboli, trauma, and the sequelae of hernia or bands. This may be the result of a slowly developing chronic ischemic process corresponding to the clinical state of intestinal angina. Partial vascular occlusion and emboli can sometimes be found. Recurrent abdominal pain and weight loss are the two primary characteristic symptoms [1].

Diagnosis

Ischemic strictures are concentric, and can be short or long, single or multiple. They produce signs and symptoms of intestinal obstruction. CT depicts concentric strictures with marked wall thickness accompanied by proximal intestinal dilation. Enteroscopy (Fig. 12.2a) and fluoroscopic enteroclysis (Fig. 12.2b) reveal concentric ulcerous stenosis, sometimes leading to longitudinal ulceration.

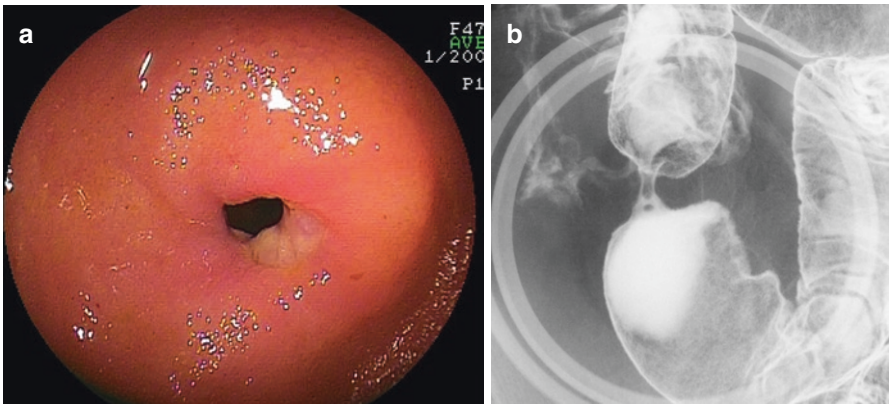


Fig. 12.2 **a** Enteroscopic view of ischemic strictures due to chronic mesenteric ischemia secondary to anti-phospholipid syndrome. **b** Fluoroscopic enteroclysis showing ischemic strictures due to chronic mesenteric ischemia secondary to anti-phospholipid syndrome

12.1.4 Angiodysplasia, Hereditary Hemorrhagic Telangiectasia

Pathophysiology and Clinical Manifestations

Angiodysplasia has been claimed to be one of the most common causes of small-bowel bleeding, and sometimes acute upper GI and colonic bleeding in the elderly [17]. The tortuously ectatic mucosal capillaries communicate with the enlarged submucosal veins and venules. The lesions are common in the jejunum, the ileum, and the right colon. They are believed to result from chronic low-grade obstruction of the submucosal veins where they traverse the muscularis propria. The resulting back-pressure causes further dilation of the mucosal vessels draining into the veins [1]. Angiodysplasia are often multiple and restricted to the mucosa and submucosa, unlike the lesions of hereditary hemorrhagic telangiectasia (HHT), which occurs in all layers of the bowel wall [18]. Histologically, angiodysplasia consists of dilated, distorted, tortuous, and thin-walled vessels lined by endothelium with little or no smooth muscle and no inflammation, fibrosis, or atherosclerosis. Initially, only submucosal veins are dilated, but in older lesions, mucosal veins and capillaries and even arteries become dilated. Congenital arteriovenous malformations that have thick-walled arteries, much larger than angiodysplasia and visible from the serosal side, also cause GI bleeding [19].

Gastrointestinal telangiectasia, which appears nearly identical to angiodysplasia, is associated with HHT, scleroderma, CREST syndrome, and possibly Turner syndrome. HHT is a genetic vascular disorder caused by mutation of the endoglin (*ENG*) gene and (type I HHT) or of the activin A receptor type II-like 1 (*ACVRL1*) gene (type II HHT) [20]. These mutations impair blood vessel growth and repair, resulting in irregular, tortuous blood spaces line by a single thin layer of endothelial cells. These mutations produce a syndrome of multiple orocutaneous telangiectasias.

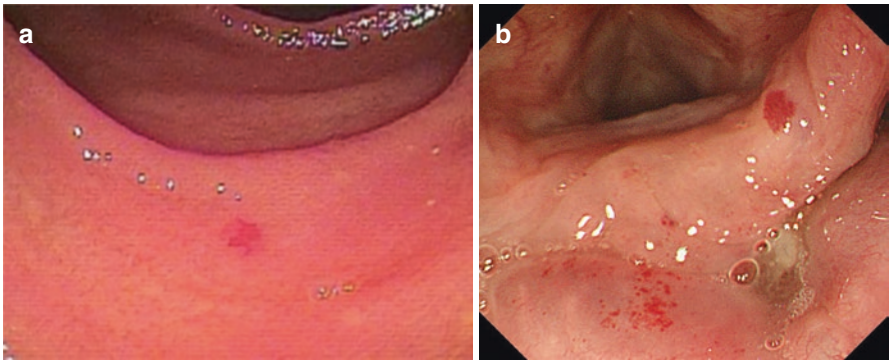


Fig. 12.3 **a** Enteroscopic view of AVM or angiodysplasia in the jejunum in a patient with hereditary hemorrhagic telangiectasia. **b** AVM or angiodysplasia in the pharynx and in the arytenoid in a patient with hereditary hemorrhagic telangiectasia

The nasal and gastrointestinal lesions frequently bleed significantly and repeatedly [21]. This bleeding tendency is explained by the thin and fragile vascular wall that lacks an elastic lamina or muscle layer and perhaps intralesional venous hypertension due to arterial shunting of blood.

Diagnosis

Endoscopy is the diagnostic procedure of choice. Angiodysplasia appears as a dense macular and reticular network of vessels, which is typically 2–8 mm wide, and intensely red because of the high oxygen content in erythrocytes within vessels supplied by arteries without intervening capillaries (Fig. 12.3a). A pale anemic mucosal halo surrounding angiodysplasia can be observed due to shunting of blood (vascular steal) from surrounding tissue by the low-resistance angiodysplastic shunt [22]. Telangiectasias in HHT are generally redder than angiodysplasias. Arteriovenous malformation is a submucosal mass covered by blueish mucosa where dilated vessels are seen through. It is sometimes pulsating and has ulceration or scarring on its surface. In patients with HHT, endoscopy shows multiple telangiectasias are visible besides gastrointestinal tract (e.g., oral cavity, pharynx, larynx; see Fig. 12.3b).

12.1.5 Varices

Pathophysiology and Clinical Manifestations

The majority of patients with duodenal varices visualized on endoscopy have extrahepatic portal hypertension. In contrast to duodenal varices, it appears that most cases of varices in other portions of the small intestine and colonic varices are seen

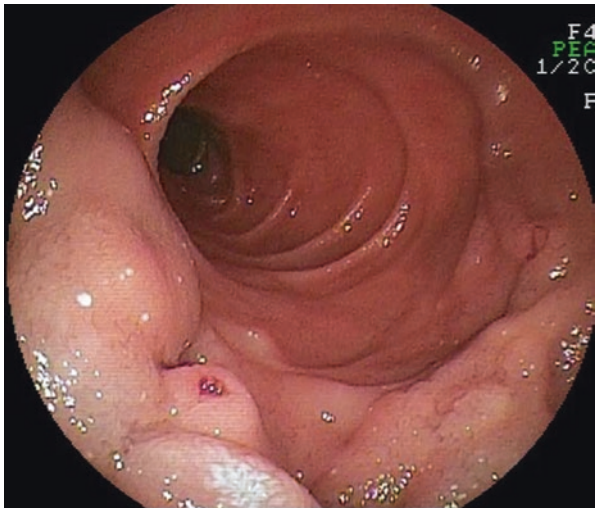


Fig. 12.4 Enteroscopic view of varix in the distal duodenum

in patients with intrahepatic portal hypertension who have previously undergone abdominal surgery [23]. Although ectopic varices can occur at several sites, bleeding ectopic varices are most commonly found in the duodenum and at sites of previous bowel surgery including stomas. In a review of 169 cases of bleeding ectopic varices, 17% occurred in the duodenum, 17% in the jejunum or ileum, 14% in the colon, 8% in the rectum, and 9% in the peritoneum [24].

Diagnosis

Contrast-enhanced CT are used to diagnose intestinal varices. Angiography provides the necessary information about the location and extent of the varices. Endoscopy reveals serpiginous vessels projecting into the lumen (Fig. 12.4).

12.1.6 Ischemic Colitis, Mesenteric Phlebosclerosis

Pathophysiology and Clinical Manifestations

Ischemic colitis is the most common form of ischemic injury to the gut, and occurs more frequently in elderly people. The disease can result from either occlusive or nonocclusive events, mainly in the territory of the inferior mesenteric artery, in colonic branches of the superior mesenteric artery, and in the superior and inferior mesenteric veins. Large arterial vessel occlusion may be caused by thrombi or atheromatous lesions. Aortic surgery can cause ischemic colitis because of unnoticed

ligation of the IMA, the occurrence of intraoperative hypoperfusion, or embolization of atheromatous debris. It has also been reported in long-distance runners. Ischemic colitis is predominantly seen in the left colon [2]. The splenic flexure and rectosigmoid junction, where low perfusion exists (watershed areas), are commonly affected, while the rectum is not usually compromised because of excellent collateral perfusion. Right colon ischemic colitis is rare, but is associated with poor prognosis. A wide spectrum of manifestations can be seen: acute transient type (reversible colopathy characterized by mucosal and submucosal hemorrhage, acute fulminant type (irreversible colopathy characterized by transmural and progression to necrosis), and chronic stenosing type (partially reversible vascular disease usually manifested by late colonic stenosis).

Mesenteric phlebosclerosis is a rare disease, characterized by thickening of the wall of the right hemicolon with calcification of mesenteric veins. Most cases have been reported from East Asia, and the long-term use of geniposide (major constituent of Gardenia fruits) in herbal medicines has been associated with its development. Some patients are asymptomatic, and others present with abdominal pain, distension, and diarrhea [25].

Diagnosis

Colonoscopy is the diagnostic procedure of choice. The endoscopic examination has to be performed with caution and minimizing air insufflation to avoid perforation. The mucosa of the affected segment usually appears edematous, hemorrhagic, and ulcerated (Fig. 12.5a). When bowel necrosis is present, colonoscopy reveals cyanotic, grey or black mucosa (Fig. 12.5b). Biopsy often demonstrates nonspecific findings of vascular congestion, submucosal hemorrhage, intestinal edema, inflammatory infiltration, loss of superficial cells, and intravascular platelet thrombi.

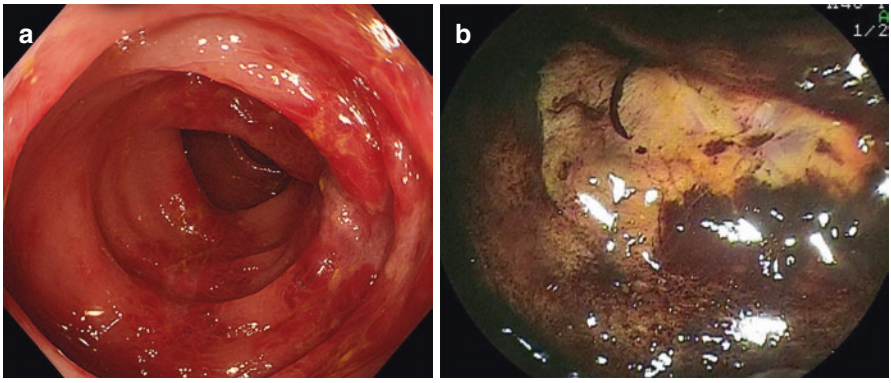


Fig. 12.5 **a** Colonoscopic view of acute transient ischemic colitis. **b** Colonoscopic view of acute fulminant ischemic colitis

In mesenteric phlebosclerosis, endoscopic reveals an edematous dark-purple mucosa with ulcerations of various sizes in the right hemicolon. Cross-sectional imaging demonstrates marked thickening of the colonic wall and linear calcification of many branches of mesenteric vein.

12.2 Eosinophilic Gastroenteritis

12.2.1 Pathophysiology and Clinical Manifestations

Eosinophilic gastroenteritis is a heterogeneous collection of disorders of varied causes with similar clinicopathological features. Allergic phenomena have been proposed to account for eosinophilic gastroenteritis. About 70% of patients have a history of allergic disorder, especially asthma, hay fever, drug sensitivity, and food hypersensitivities. The clinical manifestations of eosinophilic gastroenteritis depends on the gastrointestinal (GI) site primarily affected and the layer of bowel wall predominantly involved. The stomach and intestine are most commonly involved, but the disease may affect any part of the gastrointestinal tract as well as the pancreatic and biliary tree [26]. Klein's classification divides cases into three types: mucosal/submucosal type, muscular type, and subserosal type (Table 12.1) [27]. When the predominant involvement is mucosal, the condition behaves like other forms of inflammatory bowel diseases (IBD). If the eosinophilic infiltration is extensive, there may be malabsorption, weight loss, protein-losing enteropathy, hemorrhage, and perforation [26]. A low level of peripheral eosinophilia occurs in most cases (up to 90%) [28].

Diagnosis

Definitive diagnosis of eosinophilic gastroenteritis is made by barium radiograph and GI endoscopy with mucosal biopsy. A diffuse mucosal pattern with nodules and intraluminal masses and a sawtooth mucosal pattern may be noted in the small bowel. A widening of small-bowel segments may be seen secondary to mesenteric nodal involvement. Small-bowel biopsies may be diagnostic, showing a diffuse infiltration of the mucosa with eosinophils. When eosinophilic gastroenteritis predominantly involves the muscularis or subserosal layer of the intestine, endoscopic mucosal biopsy may not be helpful. Several diseases associated with peripheral

Table 12.1 Klein's classification of eosinophilic gastroenteritis

Types	Frequency	Clinical manifestations
Mucosal/submucosal type	60%	Diarrhea, cramping, postprandial nausea, vomiting, and periumbilical pain
Muscular type	30%	Pyloric and intestinal obstruction
Subserosal type	Rare	Eosinophilic ascites, pleural effusion

Table 12.2 Differential diagnosis of eosinophilic gastroenteritis

1	Hypereosinophilic syndrome
2	Periarteritis nodosa
3	Intestinal parasitism
	Hookworm, Ascaris, Strongiloidiasis, Toxocara, Trichuris, Capillaria, Trichinella species
4	Malignant lymphoma
5	Scirrhous carcinoma of the stomach
	Crohn's disease

eosinophilia in addition to mucosal eosinophilic infiltrates may mimic idiopathic eosinophilic gastroenteritis, and should be ruled out as in Table 12.2 [26].

Inflammation Associated With Other Diseases

12.2.2 Endometriosis

Pathophysiology and Clinical Manifestations

Endometriosis is a common disorder that occurs in approximately 15% of menstruating women [29]. Endometriosis can involve sites distant from the uterus and ovaries. Endometrial involvement of the intestinal tract occurs in 15–37% of patients with pelvic endometriosis, and is often asymptomatic. Within this group, the rectosigmoid colon is most commonly affected (95%), with more proximal locations, such as the appendix (10%) and the terminal ileum (5%), involved less frequently [30]. The usual indication for intestinal resection is chronic partial obstruction, due to the chronic inflammation and fibrosis from endometrial intestinal implants or due to a mass effect of the submucosal implant causing compression of the lumen. Symptoms of pelvic endometriosis, such as dysmenorrhea, dysfunctional uterine bleeding, are more prominent than the intestinal symptoms. Those patients with serosal implants may present with abdominal pain or cramping, abdominal bloating, low back pain, localized tenderness, change in stool caliber, diarrhea, and rectal bleeding. Intestinal symptoms do not follow the cyclic changes with the menstrual cycle, primarily because the intestinal lesions of endometriosis are not strongly influenced by hormonal changes [31].

Diagnosis

Endoscopic evaluation may be normal in the presence of noninvasive serosal implants. If hematochezia is present, invasion of the mucosa by endometrial implants may be noted on endoscopy or, in the presence of obstruction, strictures or extrinsic compression of the lumen may be noted (Fig. 12.6).

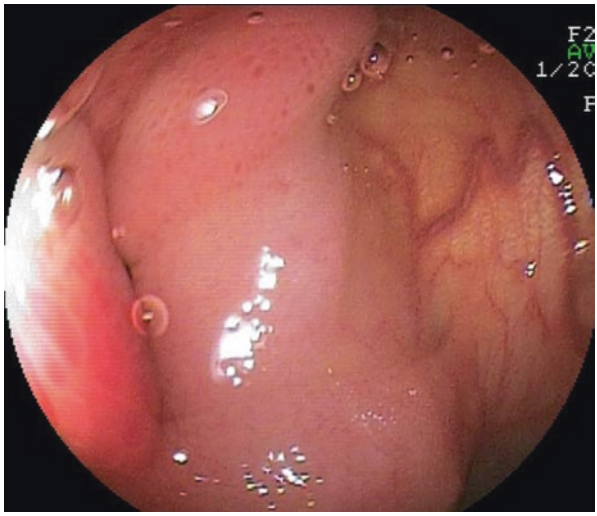


Fig. 12.6 Enteroscopic view of endometriosis in the intrapelvic ileum

12.2.3 Mucosal Prolapse and the Solitary Rectal Ulcer Syndrome

Pathophysiology and Clinical Manifestations

Mucosal prolapse (solitary rectal ulcer) syndrome typically affects young adults, presenting in the third or fourth decades [32]. Presenting symptoms are alteration of bowel habits, difficult evacuation, rectal bleeding, and mucous discharge. Tenesmus, constipation, straining, incomplete evacuation, and lower abdominal pain have been reported in most of the patients. Local trauma due to prolapse of rectal mucosa, stool impaction, as well as ischemic injury have been implicated in the pathogenesis of mucosal prolapse syndrome [31].

Diagnosis

Endoscopic appearance is variable. In classic mucosal prolapse syndrome, a single well-demarcated ulcer measuring up to 5 cm will be located at 6–10 cm from the anal verge on the anterior rectal wall (Fig. 12.7). Specific histological findings are that fibroblasts, smooth muscle, collagen replace the lamina propria, with associated hypertrophy and disorganization of the muscularis mucosa, termed fibromuscular obliteration of the lamina propria [31].

Disclosure We disclose no reports or publications that contain any materials that appear in the article. The authors report no potential conflicts of interest.

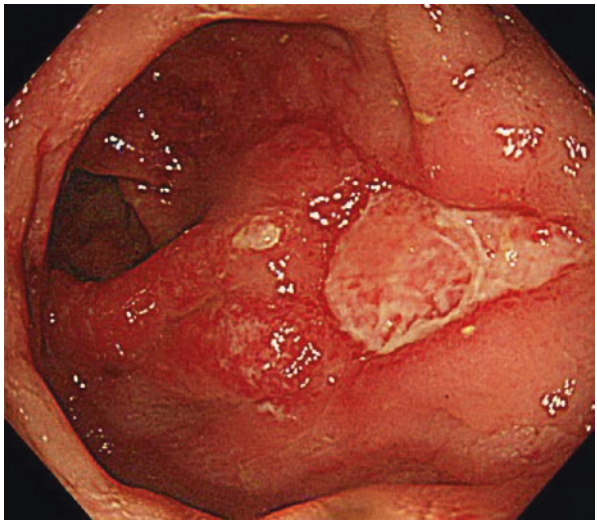


Fig. 12.7 Colonoscopic view of mucosal prolapse and the solitary rectal ulcer syndrome

References

1. Day D, Jass JR, Price AB, et al. Vascular disorders of the small intestine. In: Morson and Dawson's gastrointestinal pathology. 4th ed. Oxford: Blackwell, Massachusetts, USA. 2003. p. 345–58.
2. Panes J, Pique JM. Intestinal ischemia. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powel DW, editors. Textbook of gastroenterology. 5th ed. Hong Kong: Blackwell; 2009. p. 2811–30.
3. Acosta S, Ogren M, Sternby NH, et al. Clinical implications for the management of acute thromboembolic occlusion of the superior mesenteric artery: autopsy findings in 213 patients. Ann Surg. 2005;241:516–22.
4. Burns BJ, Brandt LJ. Intestinal ischemia. Gastroenterol Clin N Am. 2003;32:1127–43.
5. Kozuch PL, Brandt LJ. Review article: diagnosis and management of mesenteric ischaemia with an emphasis on pharmacotherapy. Aliment Pharmacol Ther. 2005;21:201–15.
6. Kim EH, Gewertz BL. Chronic digitalis administration alters mesenteric vascular reactivity. J Vasc Surg. 1987;5:382–9.
7. Moriau M, Azerad MA. Importance of a medical treatment in mesenteric vein thrombosis (MVT). Acta Gastroenterol Belg. 1996;59:146–9.
8. Rhee RY, Gloviczki P, Mendonca CT, et al. Mesenteric venous thrombosis: still a lethal disease in the 1990s. J Vasc Surg. 1994;20:688–97.
9. Acosta S, Ogren M, Sternby NH, et al. Mesenteric venous thrombosis with transmural intestinal infarction: a population-based study. J Vasc Surg. 2005;41:59–63.
10. Rhee RY, Gloviczki P. Mesenteric venous thrombosis. Surg Clin North Am. 1997;77:327–38.
11. Cappell MS. Intestinal (mesenteric) vasculopathy. I. Acute superior mesenteric arteriopathy and venopathy. Gastroenterol Clin N Am. 1998;27:783–825. vi
12. Kumar S, Sarr MG, Kamath PS. Mesenteric venous thrombosis. N Engl J Med. 2001;345:1683–8.
13. Kaleya RN, Boley SJ. Acute mesenteric ischemia. Crit Care Clin. 1995;11:479–512.
14. Murray MJ, Gonze MD, Nowak LR, et al. Serum D(−)-lactate levels as an aid to diagnosing acute intestinal ischemia. Am J Surg. 1994;167:575–8.
15. Bakal CW, Sprayregen S, Wolf EL. Radiology in intestinal ischemia. Angiographic diagnosis and management. Surg Clin North Am. 1992;72:125–41.

16. Clark RA, Gallant TE. Acute mesenteric ischemia: angiographic spectrum. AJR Am J Roentgenol. 1984;142:555–62.
17. Boley SJ, Sammartano R, Adams A, et al. On the nature and etiology of vascular ectasias of the colon. Degenerative lesions of aging. Gastroenterology. 1977;72:650–60.
18. Lewis BS. Small intestinal bleeding. Gastroenterol Clin N Am. 2000;29:67–95. vi
19. Cappell MS. Gastrointestinal vascular malformations or neoplasms: arterial, venous, arteriovenous, and capillary. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powel DW, editors. Textbook of gastroenterology. Chichester: Blackwell; 2009. p. 2785–810.
20. Jacobson BS. Hereditary hemorrhagic telangiectasia: a model for blood vessel growth and enlargement. Am J Pathol. 2000;156:737–42.
21. Guttmacher AE, Marchuk DA, White Jr RI. Hereditary hemorrhagic telangiectasia. N Engl J Med. 1995;333:918–24.
22. Marwick T, Kerlin P. Angiodysplasia of the upper gastrointestinal tract. Clinical spectrum in 41 cases. J Clin Gastroenterol. 1986;8:404–7.
23. Lebrec D, Benhamou JP. Ectopic varices in portal hypertension. Clin Gastroenterol. 1985;14:105–21.
24. Norton ID, Andrews JC, Kamath PS. Management of ectopic varices. Hepatology. 1998;28:1154–8.
25. Hiramatsu K, Sakata H, Horita Y, et al. Mesenteric phlebosclerosis associated with long-term oral intake of geniposide, an ingredient of herbal medicine. Aliment Pharmacol Ther. 2012;36:575–86.
26. Shanahan F. Gastrointestinal manifestations of immunological disorders. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powel DW, editors. . New York, NY: Blackwell; 2009. p. 2612–31.
27. Klein NC, Hargrove RL, Sleisenger MH, et al. Eosinophilic gastroenteritis. Medicine (Baltimore). 1970;49:299–319.
28. Talley NJ, Shorter RG, Phillips SF, et al. Eosinophilic gastroenteritis: a clinicopathological study of patients with disease of the mucosa, muscle layer, and subserosal tissues. Gut. 1990;31:54–8.
29. Olive DL, Schwartz LB. Endometriosis. N Engl J Med. 1993;328:1759–69.
30. Williams TJ, Pratt JH. Endometriosis in 1000 consecutive celiotomies: incidence and management. Am J Obstet Gynecol. 1977;129:245–50.
31. McNally MA, Smyrk TC, Tremaine WJ. Miscellaneous inflammatory and structural disorders of the colon. In: Yamada T, Alpers DH, Kalloo AN, Kaplowitz N, Owyang C, Powel DW, editors. Textbook of gastroenterology. 5th ed. Chichester: Blackwell; 2009. p. 1507–35.
32. Misumi A, Sera Y, Matsuda M, et al. Solitary ulcer of the rectum: report of a case and review of the literature. Gastroenterol Jpn. 1981;16:286–94.

Chapter 13
Endoscopic Findings and Diagnosis of Infectious Diseases of the Lower GI Tract: Bacterial, Pseudomembraneous, Amoebic Colitis Cytomegalovirus

Chang Soo Eun and Dong Soo Han

Abstract The clinical features of inflammatory bowel disease (IBD) may be mimicked by other infectious enterocolitides. Therefore, differential diagnosis by colonoscopic examination has an important role in the diagnosis of IBD. Infectious enterocolitis caused by salmonella, ameba, and Yersinia infection may appear to be Crohn's disease; cytomegalovirus (CMV) and enterohemorrhagic *E. coli* infection may also as appear to be ulcerative colitis at diagnosis. Nevertheless, CMV has an important role in aggravating clinical symptoms in patients with pre-existing ulcerative colitis. Careful history-taking, physical examinations, and laboratory test are helpful for differential diagnosis of colitis caused by infectious causes. Histologic findings may help to distinguish these infectious colitides.

Keywords Infectious colitis • Differential diagnosis • Endoscopy • CMV

13.1 Introduction

Infectious colitis is a common disease; it shows typical symptoms such as diarrhea, abdominal pain, hematochezia, and general symptoms such as nausea, vomiting, fever, and general weakness [1, 2]. When the typical symptoms of infectious colitis occur suddenly, it is not difficult to assess correctly. But, it can often be necessary to distinguish from other causes such as inflammatory bowel diseases and ischemic colitis [1]. For correct diagnosis, concrete history taking including immunocompromised state, physical examination, blood and stool examination, and endoscopy with biopsy are necessary [1]. Now, we are going to describe infectious colitis which should be distinguished from inflammatory bowel diseases, based on endoscopic findings.

C.S. Eun • D.S. Han
Division of Gastroenterology, Department of Internal Medicine, Hanyang University Guri Hospital, Gyungchun-ro 153, Guri-si, Gyunggi-do 11923, South Korea
e-mail: hands@hanyang.ac.kr

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_13

Endoscopic examination is not necessary for the diagnosis of infectious colitis, because these diseases are usually mild and self-limited, and have endoscopically nonspecific findings [3]. However, if there are prolonged symptoms, severe symptoms including hematochezia or dehydration, no response to empirical treatment, and the possibility of other specific causes such as pseudomembranous colitis, endoscopic examination can be helpful [3, 4]. Most of endoscopic findings of acute infectious colitis are not specific; for example, mucosal edema, erythema, hemorrhage, erosions, aphthous ulcers, exudates, and so on. Due to nonspecific findings, it is important to observe the involved area, continuity of the lesion, direction of the ulceration, and inflammatory extent of the adjacent mucosa in detail [3].

13.2 Infectious Colitis

13.2.1 Salmonellosis

Salmonellosis shows various clinical features. Non-typhoidal salmonellosis can cause colitis with diarrhea within 6–48 h after the bacteria enter the body. Usually, watery diarrhea is prolonged for 3–4 days. Occasionally, it may be accompanied with bloody or mucoid stool. It should be distinguished from shigellosis or ulcerative colitis [2, 3]. Salmonellosis can invade the small and large intestine, and it commonly involves terminal ileum or right colon, but can involve the whole colon. However, the rectum is generally preserved [4–6].

Endoscopic findings can appear as focal mucosal swelling or erythema, loss of vascularity, diffuse mucosal swelling or erythema, petechiae, granularity, or huge ulcers [5]. Severe cases, which are covered with edematous mucosa with exudates, can appear to be like pseudomembranous colitis. When well-defined multiple ulcers are seen in the right colon, it is necessary to discriminate from Crohn's disease. Salmonellosis improves rapidly within 3–4 weeks, we can discriminate from Crohn's disease by follow-up examination [3, 7].

13.2.2 Shigellosis

Typical symptoms are started within 72 h after the bacteria enter the body. For the first 24–48 h, abdominal pain, fever, and watery diarrhea occur. Thereafter, diarrhea is decreased and turns into bloody or mucoid stools, as accompanying tenesmus [2, 3].

Endoscopic findings vary from severe edema, erythema, congestion with mucous, desquamation, friability, hemorrhagic spots, aphthous ulcer to superficial ulcer or hemorrhage. In severe cases, ulcers can appear circular by fusion and enlargement [3]. Sometimes, endoscopic findings can be similar to those of ulcerative colitis, it can be distinguished from ulcerative colitis in terms of rectal mucosal preservation,

uneven distribution, and less desquamation [5, 6]. Though rectum and sigmoid colon are the most frequently involved sites, shigellosis can invade the proximal or entire colon [2].

13.2.3 Campylobacter Colitis

Camphylobacter is one of the most common causes of adult diarrhea. Usually, rectum and sigmoid colon are involved, but sometimes proximal colon can be involved [5]. Mucosal swelling, erythema, desquamation, or superficial ulcers are common endoscopic findings, so they can be similar to those of ulcerative colitis. Large but superficial ulceration on ileocecal valve can be seen commonly, but it is resolved rapidly [5]. The endoscopic finding in the involved area may be indistinguishable from ulcerative colitis, but proximal involvement is common [5, 6].

13.2.4 Yersinia Colitis

Yersinia infection may cause vaious clinical manifestations by depending on the age of affected individuals including enterocolitis, mesenteric lympadenitis and postinfectious extraintestinal symptoms [5, 7]. It frquently involves ileocecal area and right colon, but sometimes total colon can be involved [5–8]. Acute diarrhea is common, but sometimes chronic diarrhea and low abdominal pain can be appeared. Accompanied by mesenteric lymphadenitis of terminal ileum or right colon, it is necessary to distinguish it from acute appendicitis [5, 8].

Common endoscopic findings are mucosal swelling, well-defined erosions surrounded by erythema, aphthous ulcer, or octopus sucker shaped mucosal elevation in the ileocecal area [5]. Due to typical endoscopic findings and frequently involved area, it is necessary to discriminate from Crohn's disease. Sometimes, mucosal swelling, erythema, or friability without ulcers can be appeared [7].

13.2.5 Amebic Colitis

It is caused by *Entamoeba histolytica*, and involves cecum and right colon in 70%, and rectum and sigmoid colon in 30% of cases [3]. Endoscopic findings vary according to the phase. In the acute phase, diffuse mucosal swelling, erythema, friability, granularity, mucoid pus, exudates, and ulcers can appear, and they can be similar to those of ulcerative colitis [3, 5, 9]. These erosions and ulcers are accompanied by adjacent mucosal swelling [9]. In the chronic phase, multifocal small ulcers advance and invade submucosal layers radially, so they can have the appearance of flask-shaped ulcers with narrow mucosal entrance and wide base, or volcanic craters [2, 3].

It should be differentiated with Crohn's disease. Amebic cysts and trophozoites can be detected in ulcer margin and adjacent exudates by histologic examination (Fig. 13.1).

13.2.6 Enterohemorrhagic E. coli *Enterocolitis*

Enterohemorrhagic Escherichia coli (EHEC) can cause diarrhea and hemorrhagic colitis, it sometimes progresses to hemolytic uremic syndrome. *E.coli* O157:H7 infection is common in some area, but non-O157:H7 strain is also important. It occurs mostly at the terminal ileum or right colon. Endoscopic findings include severe mucosal swelling, erythema, friability, and superficial ulcers. It appears like ischemic colitis and may need to be discriminated from that, but there is a difference in frequently involved site [5] (Fig. 13.2).

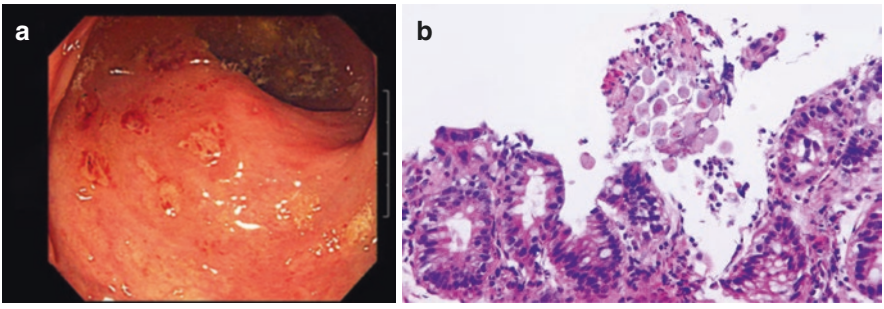


Fig. 13.1 Multiple erosions and ulcers on the mucosa of right colon. Microscopic finding of stool shows *E. histolytica* cyst

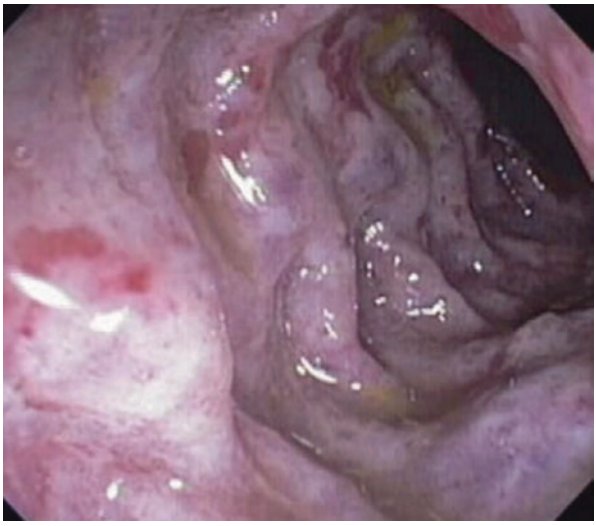


Fig. 13.2 Diffuse segmental hemorrhagic and edematous mucosa of sigmoid colon in patients with hematuria and thrombocytopenia. This patient was confirmed by Shiga toxin producing assay

13.2.7 CMV Colitis

CMV (cytomegalovirus) belongs to the herpes virus group, and can cause various diseases including gastrointestinal diseases [3]. The large intestine is one of the most frequently involved sites [3]. CMV colitis commonly occurs in immunocompromised states such as organ transplantation, and patients with hematologic malignancy, AIDS, or inflammatory bowel diseases. However, it also occurs rarely in immunocompetent patients [2, 3]. It may cause exacerbation of ulcerative colitis and failure of intensive treatment in acute severe ulcerative colitis.

Frequent symptoms are fever, diarrhea, or abdominal pain. CMV colitis can cause fatal complications such as severe hematochezia, toxic megacolon, or perforation, adequate diagnosis and management are important [3]. Endoscopic findings are varied and nonspecific. Erosions or ulcers with diffuse subepithelial hemorrhagic spots can be appeared, and ulcers [3, 5, 10]. Also, these lesions are fused and advanced to well-defined, large ulcers whose adjacent mucosa is nearly normal [3]. Sometimes, in the colon, severe erythematous and friable mucosa losing vascularity, without ulcers, appears, and can seem like ulcerative colitis [3, 5]. When CMV colitis occurs in patients with underlying severe ulcerative colitis, it can be difficult to grossly distinguish from ulcerative colitis. So, in severe ulcerative colitis, we should make sure to perform biopsy. It is important to perform the biopsy in the deep portion of ulcer bases and confirm inclusion body [2, 3, 10].

13.2.8 Pseudomembranous Colitis

Use of antibiotics can break the balance of intestinal microbiota. Then, *Clostridium difficile* can overgrow and their toxins induces intestinal mucosal cell necrosis and change intestinal permeability. Finally, antibiotic-associated colitis with ulcer can occur [2, 3, 11]. Pseudomembranous colitis is a leading and severe form of antibiotic-associated colitis, and a common cause of nosocomial diarrhea. It also aggravates clinical symptoms in patients with inflammatory bowel disease. Clinical features may appear as fever, diarrhea, and abdominal pain [12]. When diarrhea occurs in patients who recently used antibiotics, we can diagnose pseudomembranous colitis through stool toxin assay A or B, stool culture for *Clostridium difficile*, and colonoscopy [12].

Common involved sites are distal colon or left colon, but the entire large intestine can sometimes be involved. In about 20–30% of cases, there may be lesions only in the proximal colon rather than rectum. Endoscopic findings can appear as scattered yellowish white plaques which are well defined and slightly elevated [2, 3, 5]. These plaques are called pseudomembrane; they are initially only 1–3 mm in diameter, but can fuse into one another and advance to cover intestinal lumen circularly [3]. The diameter of pseudomembrane can be enlarged to 2 cm in diameter [3, 11]. The plaques are not removed by suction, and can be accompanied by erythema or swelling in adjacent mucosa [3, 11]. In one-third, nonspecific erosions or erythema can be

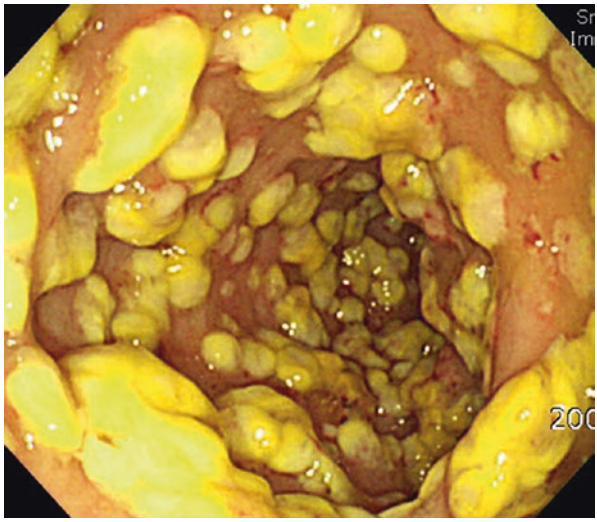


Fig. 13.3 Multiple yellowish pseudomembranes on colonic mucosa in *Clostridium difficile* toxin A positive patients

shown without the formation of pseudomembrane [5]. Meanwhile, bowel preparation for colonoscopy can cause pseudomembrane to be removed. So, sigmoidoscopy without bowel preparation is recommended preferentially, if pseudomembranous colitis is suspected [3] (Fig. 13.3).

13.3 Summary

Colitis is a nonspecific inflammation of the large intestine and results from various causes. Differential diagnosis by depending on only clinical features is difficult, but exact diagnosis is important for adequate management. When we evaluate patients with symptoms of colitis, it is very helpful to perform blood, stool, and endoscopic exams as well as careful history-taking and physical examinations. So, we should be fully aware of clinical features and endoscopic findings of various colitis and it is important to perform careful observation and adequate biopsy during endoscopic examination.

References

1. Abreu MT, Harpaz N. Diagnosis of colitis: making the initial diagnosis. Clin Gastroenterol Hepatol. 2007;5:295–301.
2. Koo JS. Endoscopic differential diagnosis for various colitis. In: 47th Seminar of Korean Society of Gastrointestinal Endoscopy.
3. Park YS. Ischemic colitis and infectious colitis. Korean J Gastrointest Endosc. 2010;42:163–9.

4. ASGE Standards of Practice Committee, Shen B, Khan K, Ikenberry SO, Anderson MA, Banerjee S, Baron T, Ben-Menachem T, Cash BD, Fanelli RD, Fisher L, Fukami N, Gan SI, Harrison ME, Jagannath S, Lee Krinsky M, Levy M, Maple JT, Lichtenstein D, Stewart L, Strohmeyer L, Dominitz JA. The role of endoscopy in the management of patients with diarrhea. Gastrointest Endosc. 2010;71:887–92.
5. Han DS. Diagnostic tips for making the diagnosis of inflammatory bowel disease. Korean J Gastrointest Endosc. 2009;38:181–7.
6. Korean Society of Gastrointestinal Endoscopy. Atlas of gastrointestinal endoscopy. 1st ed. Seoul: Daehan Medical Publishing; 2011. p. 77–101.
7. Lee JH. Inflammatory diseases of lower gastrointestinal tract. Korean J Gastrointest Endosc. 2005;30(Suppl.1):39–43.
8. Hyun KH, Jeon SM, Kim HJ, et al. A case of Yersinia enterocolitica enterocolitis accompanied by colonic adhesion after surgery for uterine myoma in an adult patient. Korean J Med. 2012;83:757–63.
9. Cheong ES, Jo YJ, An SB, Kim SH, Park YS, Lee WM, Hong YO. A case of steroid treated amebic colitis misdiagnosed as eosinophilic colitis. Korean J Gastrointest Endosc. 2011;43:42–6.
10. Huh CW, Youn YH, Jung DH, Kim DW, Kho BG, Kim JH, Park H, Lee SI. A case of cytomegalovirus colitis with endoscopic finding resembling Crohn's disease. Korean J Gastroenterol. 2012;59:303–7.
11. Hookman P, Barkin JS. Clostridium difficile associated infection, diarrhea and colitis. World J Gastroenterol. 2009;15:1554–80.
12. Park HS, Han DS. Management of antibiotics-associated diarrhea. Korean J Gastroenterol. 2009;54:5–12.

Chapter 14
Difficulty in Diagnosing Inflammatory Bowel Disease: A Case Study

Kazuo Ohtsuka

Abstract Endoscopy is an important tool for diagnosing inflammatory bowel disease (IBD). It is well known that various types of infectious colitis, such as tuberculosis, mimic Crohn's disease (CD). A broad differential diagnosis is important because IBD is a diagnosis of exclusion. On the other hand, some cases need different viewpoints in order to make the correct diagnosis. Here we present cases where the diagnoses were elusive. The first case was a very early case of ulcerative colitis (UC). The lesions did not show a typical distribution for UC. However, eventually, typical symptoms and endoscopic appearance were observed, confirming the diagnosis. The second case revealed lesions only in the upper jejunum. Capsule endoscopy and balloon-assisted enteroscopy revealed the typical appearance of CD; however, the distribution of the lesions was not typical. It took a long time to make the diagnosis. The third case involved recurrent obstruction. Mucosal healing was achieved; however, stenosis of the ileocecal valve resulted in surgery. Concomitant use of NSAIDs induced membranous stenosis, and therefore, endoscopic balloon dilation was performed.

Keywords Early stage • Obstruction • NSAIDs • Stenosis • Endoscopic balloon dilatation • Atypical distribution • Erythema nodosum • Capsule retention Longitudinal ulcers • Pseudodiverticular formations • Balloon-assisted endoscopy Patency capsule

14.1 Introduction

Morphological diagnosis of lesions is an important step for the diagnosis of inflammatory bowel disease (IBD), as mentioned in previous chapters. Cases with typical endoscopic appearances are easy to diagnose; however, some cases do not show a typical appearance. Infection and inflammation caused by systemic diseases, such

K. Ohtsuka
Department of Endoscopy, University Hospital of Medicine, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan
e-mail: kohtsuka.gast@tmd.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_14

as autoimmune diseases, often make it difficult to determine the correct diagnosis [1, 2]. Very early stage at the time of visualization, atypical distribution of lesions, and associated comorbidities also make diagnosis difficult. Here, such cases are presented.

14.2 Early-Stage Ulcerative Colitis (UC)

A woman in her 40s was referred for colonoscopy due to a history of hematochezia. She did not have symptoms of abdominal pain, fever, or weight loss. Bowel movements occurred once a day, and stools had a normal appearance. Colonoscopy revealed small white dots with hyperemia in the ascending colon (Fig 14.1a). A biopsy specimen showed non-specific inflammation. The rectum was normal in appearance. She was initially diagnosed with non-specific colitis. The symptoms soon resolved. One year later, she returned to the hospital with complaints of abdominal pain associated with frequent diarrhea and hematochezia (up to 10 times per day). Colonoscopy revealed loss of the vascular pattern, granular mucosa, diffuse hyperemia, and exudates (Fig 14.1b). She was diagnosed with pancolitis-type UC. Mesalazine was prescribed, but it did not alleviate the symptoms. The patient was admitted and treated with an infusion of prednisolone (1 mg/kg). Her symptoms improved and she was subsequently discharged. One year later, UC recurred. At that time, she developed erythema nodosum in the right lower leg. She was again treated with an infusion of prednisolone, and showed improvement.

A characteristic of UC is the specific distribution of the affected mucosa. Typically, it is continuous from the rectum up through the colon. However, some cases involve atypical distribution [3]. The present case was associated with small

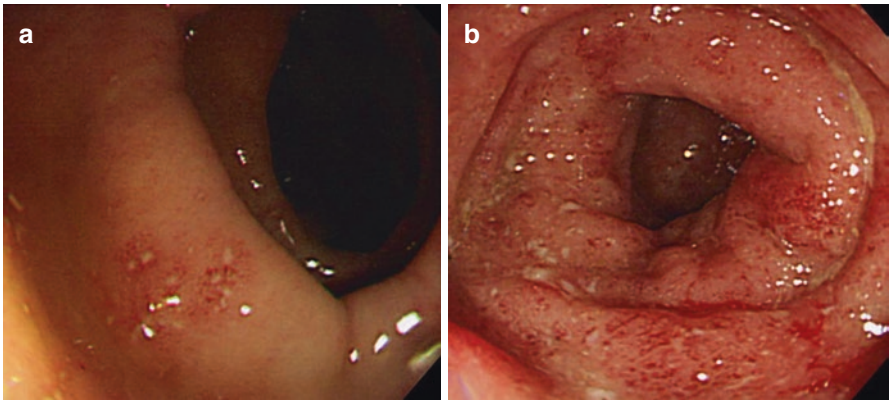


Fig. 14.1 **(a)** Colonoscopy revealed small white dots with hyperemia in the ascending colon. **(b)** Colonoscopy revealed loss of the vascular pattern, granular mucosa, and diffuse hyperemia in the sigmoid colon

and focal lesions in atypical areas in the initial presentation. However, the typical appearance and distribution of UC were observed with progression of the disease. Some UC cases may show non-specific and uncharacteristic appearance during initial presentation.

14.3 Jejunal Crohn's Disease (CD)

A man in his 50s was referred for evaluation of diarrhea. He had had diarrhea since he was a teenager. He had tested positive for fecal occult blood and undergone colonoscopy 12 years ago. Colonoscopy revealed multiple aphthae at that time. He was prescribed mesalazine; however, follow-up colonoscopy a year later revealed no difference in the aphthae, and he subsequently discontinued therapy. Recently, his diarrhea increased in frequency and he lost a total of 4 kg of body weight. Physical examination performed by his family doctor revealed the patient to have tenderness in the left upper quadrant of the abdomen; however, there were no palpable masses. Upper gastrointestinal endoscopy and ileocolonoscopy showed a normal appearance. Laboratory examination was normal. Additionally, abdominal computed tomography was negative for masses and bowel dilatation. Capsule endoscopy (CE) was performed to evaluate the small intestine, which revealed longitudinal ulcers and fold convergences (Fig 14.2a). Ninety minutes after swallow, the real-time viewer revealed food residues and stenosis in the upper jejunum (Fig 14.2b). Capsule retention then occurred. Four weeks later, the patient underwent anterograde single-balloon endoscopy. There were no lesions in the esophagus, stomach, and duodenum; however, there were several longitudinal ulcers and pseudodiverticular formations in the upper jejunum (Fig 14.3a). The retained capsule was found

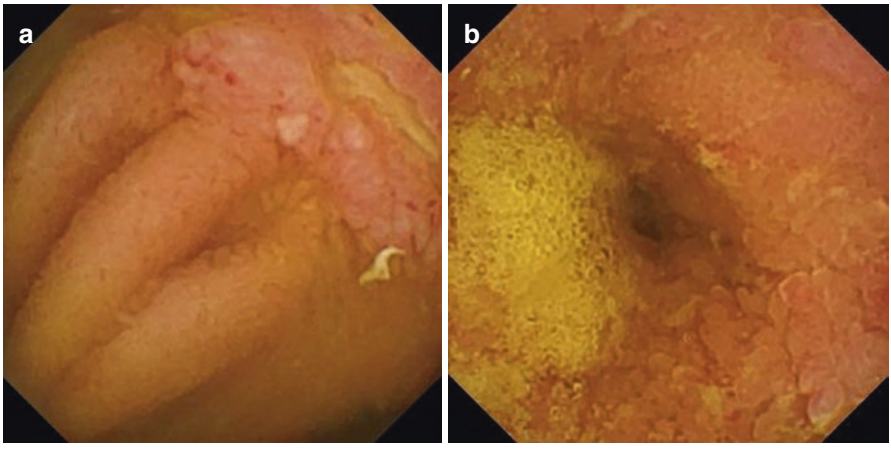


Fig. 14.2 **(a)** Capsule endoscopy revealed longitudinal ulcers and fold convergences. **(b)** There was a stenosis. Surrounding mucosa was inflamed

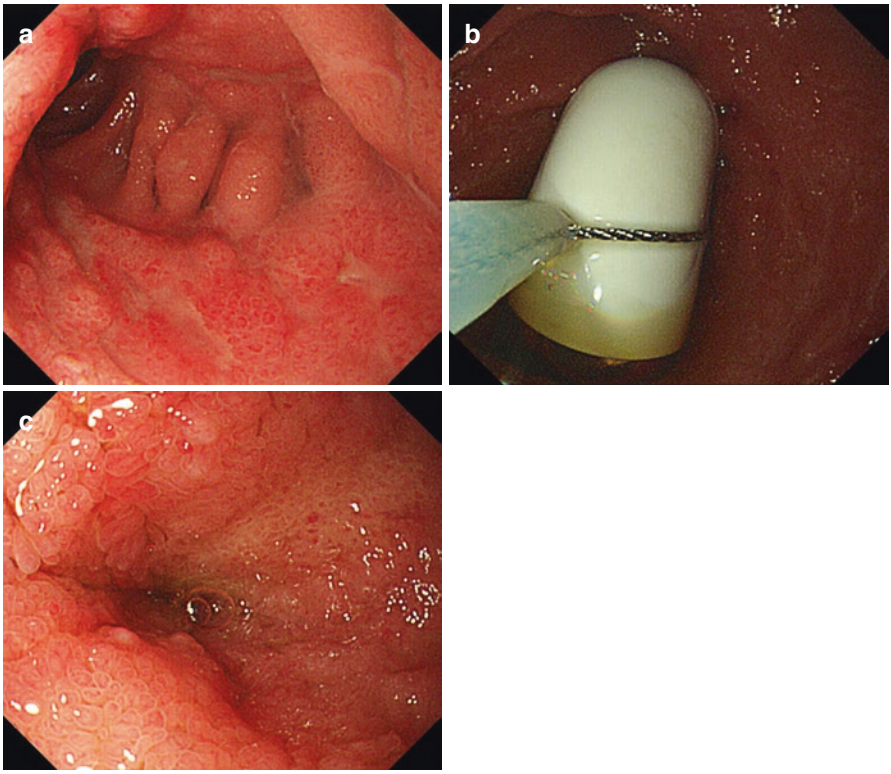


Fig. 14.3 **(a)** Single-balloon enteroscopy showed longitudinal ulcer and fold convergences similar to Figure 14.2a. **(b)** Retained capsule was retrieved. **(c)** There was a stenosis that caused capsule retention

in a stenotic area 70 cm from the pylorus (Fig 14.3b, c). The capsule was retrieved and the stenosis was dilated using a through-the-scope (TTS) balloon. After diagnosis, the patient was treated with an anti-TNF antibody.

Diagnostic delay is frequent in patients with CD [4]. In this case, the diagnosis took more than 10 years. Small intestinal lesions often cause minimal or no symptoms. Some cases are not diagnosed until the presence of severe stenosis or fistula is discovered. Ileocolonoscopy is an important tool for the diagnosis and assessment of CD [5]. Most of the cases are associated with colonic or ileal lesions; however, a few cases have only jejunal lesions. Patients with lesions in the ileum are more likely to have a stricturing behavior [6]. In the present case, CD was diagnosed in part by retention of the capsule used in CE. Capsule retention is not only an adverse event but also an important finding [7]. However, CE should be removed if it is retained in the body. Retained capsules are contraindications for magnetic resonance imaging studies. Balloon-assisted endoscopy (BAE) is a good procedure for the retrieval of retained capsules [8]; however, adhesions that are common in the patients with CD often make BAE difficult. Recently, the patency capsule has been developed and this helps avoid retention [9].

14.4 Modification by NSAID

A patient in her 20s complained of severe diarrhea and weight loss. Colonoscopy revealed typical longitudinal ulcers and a cobblestone appearance of the ascending colon (Fig. 14.4). She was diagnosed with CD and treated with an anti-TNF-alpha antibody. Mucosal healing occurred; however, she developed stenosis of the ileocecal valve (Fig. 14.5). The obstruction did not resolve despite repeated endoscopic balloon dilation. Eventually, the patient underwent an ileocecal resection. She remained asymptomatic for 6 months; however, she developed obstructive symptoms of abdominal distention and vomiting and was hospitalized. Single-balloon enteroscopy revealed no evidence of stenosis at the anastomosis (Fig 14.6a); however, membranous stenosis without ulceration was discovered in the middle ileum (Fig 14.6b, c). This was treated by balloon dilation using a 15-mm TTS balloon (Fig 14.6d). After dilation, the obstructive symptoms resolved (Fig 14.6e). As per the patient's history, she often treated her headaches with ibuprofen. After counseling her to stop taking NSAIDs, the obstructive symptoms have not returned. It was determined that NSAIDs caused enteropathy and stenosis.

Stenosis is a major complication of CD [10]. Severe inflammation and ulcer healing cause stenosis; however, there are many other causes of intestinal stenosis. NSAIDs are widely used and often cause membranous stenosis [11]. Taking the patient's history is important for the diagnosis of NSAID enteropathy. Endoscopic examination is also important for the assessment and minimally invasive treatment of stenosis [12].

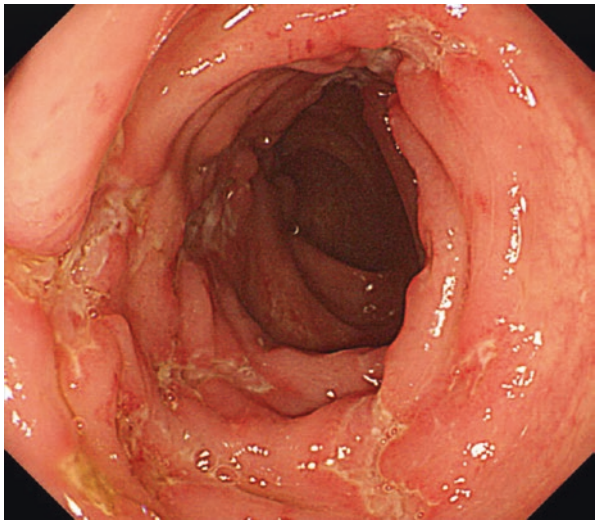


Fig. 14.4 There were longitudinal ulcers and a cobblestone appearance of the ascending colon

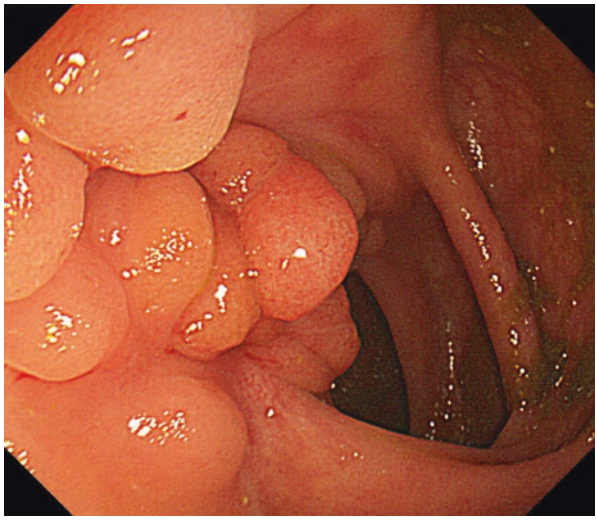


Fig. 14.5 After anti-TNF antibody therapy, there were no active lesions. However, ileocecal valve was stenotic

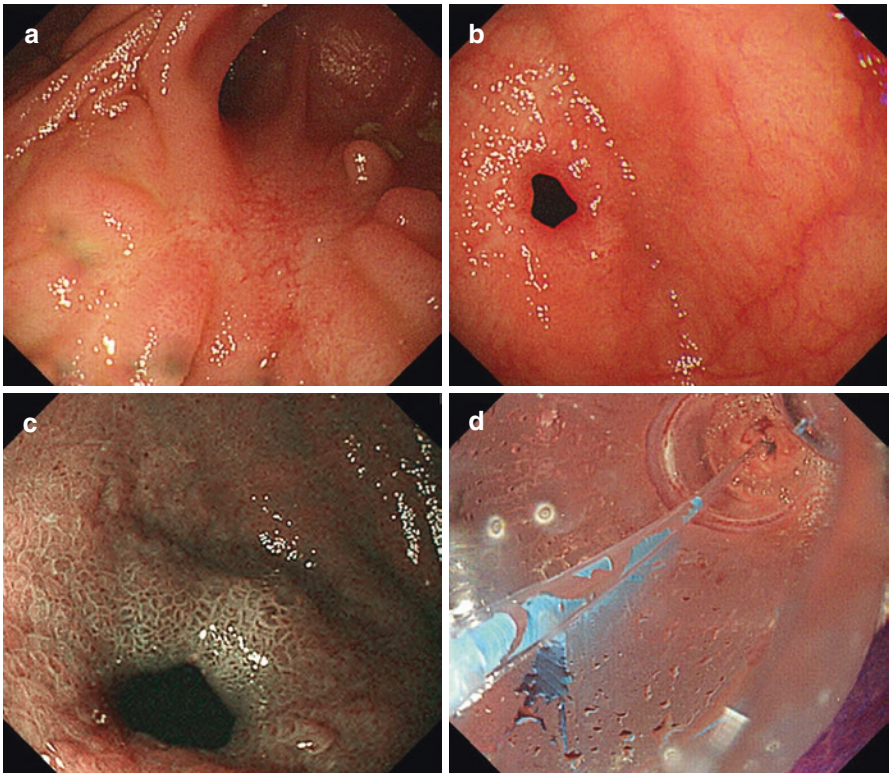
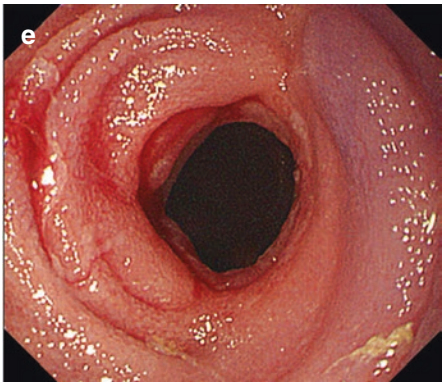


Fig. 14.6 **(a)** Mucosal healing was achieved and there was not a stenosis at anastomosis. **(b)** There was a membranous stenosis in middle ileum. **(c)** Narrow band imaging revealed no ulcerations. **(d)** Endoscopic balloon dilation (EBD) was carried out. **(e)** After EBD, the stenosis was alleviated

Fig. 14.6 (continued)



References

1. Epstein D, Watermeyer G, Kirsch R. Review article: the diagnosis and management of Crohn's disease in populations with high-risk rates for tuberculosis. Aliment Pharmacol Ther. 2007;25:1373–88.
2. Katsanos KH, Voulgari PV, Tsianos EV. Inflammatory bowel disease and lupus: a systematic review of the literature. J Crohns Colitis. 2012;6:735–42.
3. Leighton JA, Shen B, Baron TH, et al. ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease. Gastrointest Endosc. 2006;63:558–65.
4. Burgmann T, Clara I, Graf L, et al. The Manitoba Inflammatory Bowel Disease Cohort Study: prolonged symptoms before diagnosis—how much is irritable bowel syndrome? Clin Gastroenterol Hepatol. 2006;4:614–20.
5. Geboes K, Ectors N, D'Haens G, et al. Is ileoscopy with biopsy worthwhile in patients presenting with symptoms of inflammatory bowel disease? Am J Gastroenterol. 1998;93:201–6.
6. Lazarev M, Huang C, Bitton A, et al. Relationship between proximal Crohn's disease location and disease behavior and surgery: a cross-sectional study of the IBD Genetics Consortium. Am J Gastroenterol. 2013;108:106–12.
7. Cheifetz AS, Lewis BS. Capsule endoscopy retention: is it a complication? J Clin Gastroenterol. 2006;40:688–91.
8. Tanaka S, Mitsui K, Shirakawa K, et al. Successful retrieval of video capsule endoscopy retained at ileal stenosis of Crohn's disease using double-balloon endoscopy. J Gastroenterol Hepatol. 2006;21:922–3.
9. Nakamura M, Hirooka Y, Yamamura T, et al. Clinical usefulness of novel tag-less Agile patency capsule prior to capsule endoscopy for patients with suspected small bowel stenosis. Dig Endosc. 2015;27:61–6.
10. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis. 2011;17:1415–22.
11. Wang ML, Miao F, Tang YH, et al. Special diaphragm-like strictures of small bowel unrelated to non-steroidal anti-inflammatory drugs. World J Gastroenterol. 2011;17:3596–604.
12. Takenaka K, Ohtsuka K, Kitazume Y, et al. Comparison of magnetic resonance and balloon enteroscopic examination of the small intestine in patients with Crohn's disease. Gastroenterology. 2014;147:334–42.

Part III
Endoscopy in the Management of IBD

Chapter 15
Endoscopy in the Management of Inflammatory Bowel Disease: Who, When, and How

Yasuo Suzuki

Abstract In inflammatory bowel disease (IBD), confirmation of mucosal healing by endoscope has been recommended as a gold standard for complete remission.

In ulcerative colitis (UC), colonoscopic examination has been thought to be the most reliable approach to view all parts of the large intestine. Detecting the disease type of UC accurately by total colonoscope examination is very important, therefore a total colonoscope examination must be done at the time of diagnosis and starting induction therapy. And a surveillance program to detect dysplasia or early-stage colon cancer by diligent colonoscopic surveillance has been emphasized in UC.

In Crohn's disease (CD) the diagnostic relevance of endoscopy remains unclear as compared with its established value in UC. CD lesions may appear at any site from the mouth to the perianal region; therefore, thorough examination from the upper parts of digestive track to the rectum should be examined by endoscope, including the small intestine being examined by capsule endoscopy or balloon endoscopy. The confirming of mucosal healing of involved CD lesion by endoscope examination is now strongly recommended because the achievement of mucosal healing of the involved lesion affects significantly the long-term prognosis at the stage of clinical remission after treatment.

Keywords Inflammatory bowel disease • Ulcerative colitis • Crohn's disease • Endoscopy • Mucosal healing

Y. Suzuki
Internal Medicine, Sakura Medical Center, Toho University,
564-1 Shimoshizu, Sakura, Chiba 285-8741, Japan
e-mail: yasuo-suzuki@sakura.med.toho-u.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_15

15.1 Introduction

The application of the endoscope in the management of patients with inflammatory bowel disease (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) continues to increase in terms of quality, frequency and therapeutic outcomes. It may be said that the endoscope has now become the gastroenterologist's eyes and hands on gastrointestinal (GI) lesions. When considering major lesions reflecting pathological GI disorders, gastroenterologists can now directly observe the inside of the intestinal tract, which means better understanding, more correct diagnosis, and the most appropriate clinical decision-making. Of course, all this demands a high level of professional skill to make the optimal use of the endoscope in a clinical practice setting.

However, in the clinical practice setting pertaining to GI lesions requiring endoscopy, there are certain technical issues which can be challenging, including the skills needed for the gastroenterologist to efficiently and safely operate the endoscope to observe the lesions, and make a correct diagnosis. Endoscopical findings do not always reflect the exact pathogenical findings. Additionally, the patient has to ingest a large volume of laxative, which may have unpleasant taste and odor. This means that endoscopy cannot be undertaken anytime we wish; it depends on taking time to prepare both the patient and the equipment.

Hitherto, as the main assessment index to evaluate treatment efficacy in IBD patients, the degree of clinical activity has always been used, while the activity of intestinal lesions observed by a colonoscope, now known as the endoscopic index (EI), has generally not been used. The improvement or disappearance of clinical symptoms and returning to work or to normal daily life including meal consumption were thought to be the most important target of treatment. Achieving clinical goals has generally been based on global assessments consisting of several clinical symptoms, blood test results, and general physician's assessments.

In Japan, for some time, most gastroenterologists have been discussing the importance of colonoscopic findings to judge treatment efficacy, but in the global arena, colonoscopic findings have not been widely accepted as the standard for judging treatment efficacy. This is because, as stated above, the procedures for examination by a colonoscope are complicated and require skill, time, and preparation, not a simple and easy approach to assess a therapeutic effect. This is particularly serious in CD patients, in whom the IBD lesions may appear at any location, from the mouth to the perianal region. Nonetheless, recently, small intestinal lesions can be observed directly by applying newly developed equipment such as the balloon small intestinal endoscope and the capsule intestinal camera. Accordingly, confirmation of mucosal healing by directly observing intestinal lesions has been recommended as a gold standard to reflect complete remission. Further, mucosal healing is recommended as a standard for complete remission because healing of intestinal lesions can predict long-term prognosis, or a favourable long-term disease course [1]. Additionally, direct observations of intestinal lesions has an unrivalled value in surveying for cancers associated with intestinal inflammation.

There are still significant limitations and issues associated with endoscopy in IBD, like timing of endoscopy, the type of endoscope to be selected, and what

endoscopic indices to be accepted as a standard for mucosal healing. Additionally, there are major histologic differences between UC and CD lesions, which can make the meaning of endoscopic findings different for the two IBD phenotypes.

15.2 Ulcerative Colitis

In UC, colonoscopic examination has been thought to be the most reliable approach to viewing all parts of the large intestine, fully observe the lesions, and make corrective diagnosis. Therefore, UC lesions are relatively uncomplicated to view, to evaluate, and to make treatment decisions about. However, the aforementioned issues related to operational skills and preparation time require serious consideration. It is fair to say that the use of the endoscope is different at different disease levels in UC.

15.3 At the Time of Diagnosis and the Initiation of Induction Therapy

Compared with the West, and other major health service-providing countries, Japan is the country where an endoscopic examination is most frequently done. In Japan, colonoscopic examination is thought to be an essential step at the time of diagnosis, determining disease severity and deciding induction treatment for patients with active UC, instead of Ba-enema accompanied by radiation exposure, which used to be the standard in the bad old days. However, in Western countries it has been taken to be sufficient to examine the lesions from the rectum to the sigmoid colon in active UC at the time of determining disease severity and deciding induction therapy. At the time of diagnosis, determining the accurate disease feature (proctitis, left-sided colitis, or total colitis) is essential for selecting an adequate induction regimen.

Detecting the disease type of UC accurately by total colonoscope examination is very important since disease type affects disease severity and the long-term outcome of disease course. Therefore total colonoscope examination must be done at the time of diagnosis and starting induction therapy. However, there is no clear evidence about the degree of severity of mucosal damage observed by colonoscope affecting the choice of type of therapy until now.

15.4 After Induction Therapy

For confirming mucosal healing, the timing of undertaking colonoscopic examination is generally thought to be several weeks after achieving clinical remission [2], but there is no accepted consensus on the time when colonoscopic examination should be done for assessing the efficacy of a treatment intervention after starting an

induction therapy. The timing when colonoscopic examination should be done for confirming mucosal healing is differently decided depending on the type of induction therapy used. Improvement in response to tacrolimus or anti-TNF antibodies, which can rapidly induce remission, can be observed sooner (within a few weeks) endoscopically compared to other options. Mucosal healing following these treatments can be confirmed typically in 2–3 months (Colombel JF et al., Gastroenterol 2011). In contrast, colonoscopic examination to confirm response to mesalazine or cytapheresis is done relatively later due to time required to see the full efficacy of these interventions, generally 2 weeks after a whole set of cytapheresis therapy (10 times) or in a few months.

As an endoscopic activity index for UC, the Mayo endoscopic index has been widely applied among several endoscopic indices seen in the literature, but there is poor validation among observers when the Mayo endoscopic index is used. Recently, the UCIES was developed as an endoscopic index that has good validation among observers and can better express inflammatory lesions [3]. Therefore, in the near future, one may expect UCEIS to be recognized as a more reliable standard endoscopic active index for UC.

15.5 During Maintenance Period

The major aims of undertaking colonoscopic examinations during remission are to assess the efficacy of a maintenance therapy, to predict long-term clinical course, and to survey for dysplasia or cancerous lesions associated with UC. However, there is no consensus on the timing when colonoscopic examination should proceed, but during quiescent UC, colonoscopic examination is done generally once a year. Colonoscopic examination should be done soon after clinical symptoms worsen to confirm the actual UC exacerbation. I believe that in the near future, measurement of calprotectin in stool samples can become a predictor of UC relapse before clinical symptoms appear [4, 5].

15.6 Cancer Surveillance

It has been reported that the developing rate of colon cancer is high in patients with long duration of disease course. Accordingly, a surveillance program to detect dysplasia or early stage colon cancer by diligent colonoscopic surveillance has been emphasized. Indeed, definitive surveillance is warranted in high-risk cases like patients with total colitis, with a long disease duration or with long duration of active disease course [6]. Additionally, in all high-risk cases, random biopsy during surveillance colonoscopy can have added diagnostic value [7, 8]. Recently, in Japan, “target biopsy”, which is a newly developed knowledge-based approach, has been regarded as a more reliable surveillance strategy for managing colon cancer as compared with random biopsy approach during surveillance colonoscopy [9].

15.7 Crohn's Disease

The diagnostic relevance of endoscopy in CD remains unclear as compared with its established value in UC. However, although colonoscopy has had an important role for detecting mucosal changes in the colon, such as UC, the reason why the role of endoscopy still remains unclear in CD is that the diagnostic value of colonoscopy depends on the skills of the colonoscopist, generally a time-demanding and more complicated practice for CD as compared with detecting colonic lesions in UC. Needless to say that colonoscopy is not a straightforward undertaking if the patient has anal lesions as well. Colonoscopic examination is limited to observing only up to the terminal ileum. Therefore, it has been difficult to observe mucosal lesions in the small intestine by an endoscope or a colonoscope; but nowadays, mucosal lesions in the entire small intestine can be observed by the introduction of capsule endoscopy or balloon endoscopy.

Based on the above arguments, observations of intestine by an endoscope or a colonoscope is relevant only for surveying mucosal lesions, but CD has a transmural presence, which is not present patients with UC. This rises a question, can endoscopy fully detect pathological lesions in CD patients? By using MRI enterography or CT enterography, which can detect transmural changes, and it has recently been established that mucosal healing observed by an endoscope shows different conditions [10]. This indicates that we need to better understand intestinal mucosal lesions as seen by an endoscope.

15.8 At the Time of Diagnosis and the Initiation of Treatment

At the time of diagnosis and the initiation of the treatment, patients should be requested to be ready for the examination of the entire digestive track because as stated above, CD lesions may appear at any site from the mouth to the perianal region. Therefore, for a thorough examination to diagnose CD lesions, the upper parts of digestive track including esophagus, stomach and duodenum are examined by gastro-duodenal endoscopy. The segment from the terminal ileum to the rectum is examined by a colonoscope, while the small intestine can now be examined by capsule endoscopy or balloon endoscopy instead of enterolysis.

15.9 After Treatment

The goal of treatment for patients with active CD was the achievement of improving clinical symptoms, because confirming of involved lesion of whole parts of the digestive track was so difficult and the meaning of mucosal healing observed by

endoscope was not clear before. But now the confirming of mucosal healing of involved lesion by endoscope examination is strongly recommended because the realization of mucosal healing of involved lesion significantly affects long-term prognosis at the stage of clinical remission after treatment. So endoscopic examination for confirming of mucosal healing is usually done, generally within a few months after clinical remission.

15.10 During Maintenance Treatment

It is not clarified when is the best timing of doing endoscopic examination for confirming of retaining mucosal healing during maintenance treatment because endoscopic examination for confirming the existence of affected lesions in whole digestive tract is not easy, while colonoscopic examination for confirming lesions of only the colon is not so difficult in UC. In CD, endoscopic examination is not done regularly because of technical difficulties. The worsening of clinical symptoms does not always reflect exacerbation in CD, although the worsening of clinical symptoms including bloody stool relatively reflect exacerbation in UC. The best timing for doing endoscopic examination during maintenance treatment is the time when there is a possibility of relapse or appearance of new involved lesions suspected as a result of the appearance of inflammatory reactions checked by blood tests, or as a result of using other imaging techniques [11].

15.11 After Operation

There are a significant number of cases in whom operation is done for perforation, fistula, narrowing mainly at the terminal ileum, and lesions at operated anastomosis, which often appear soon after operation. The Rutgeerts score, which was developed for estimating the severity of mucosal lesions at operated anastomosis in CD by endoscopy, is generally valid for estimating the severity of recurrence of lesions after operation [12]. The existence or severity of lesions at the operated anastomosis observed by endoscopic estimation and evaluated by the Rutgeerts scoring system can predict long-term prognosis or otherwise. Fortunately, observing mucosal lesions at anastomosis between the ileum and the colon by an endoscope is practical. A very interesting paper recently reported that observation by an endoscope to detect recurrence or severity of lesions at anastomosis 6 months after operation by using the Rutgeerts scoring system was useful for predicting long-term prognosis and adding intervention to support treatment or not [13] (Fig. 15.1).

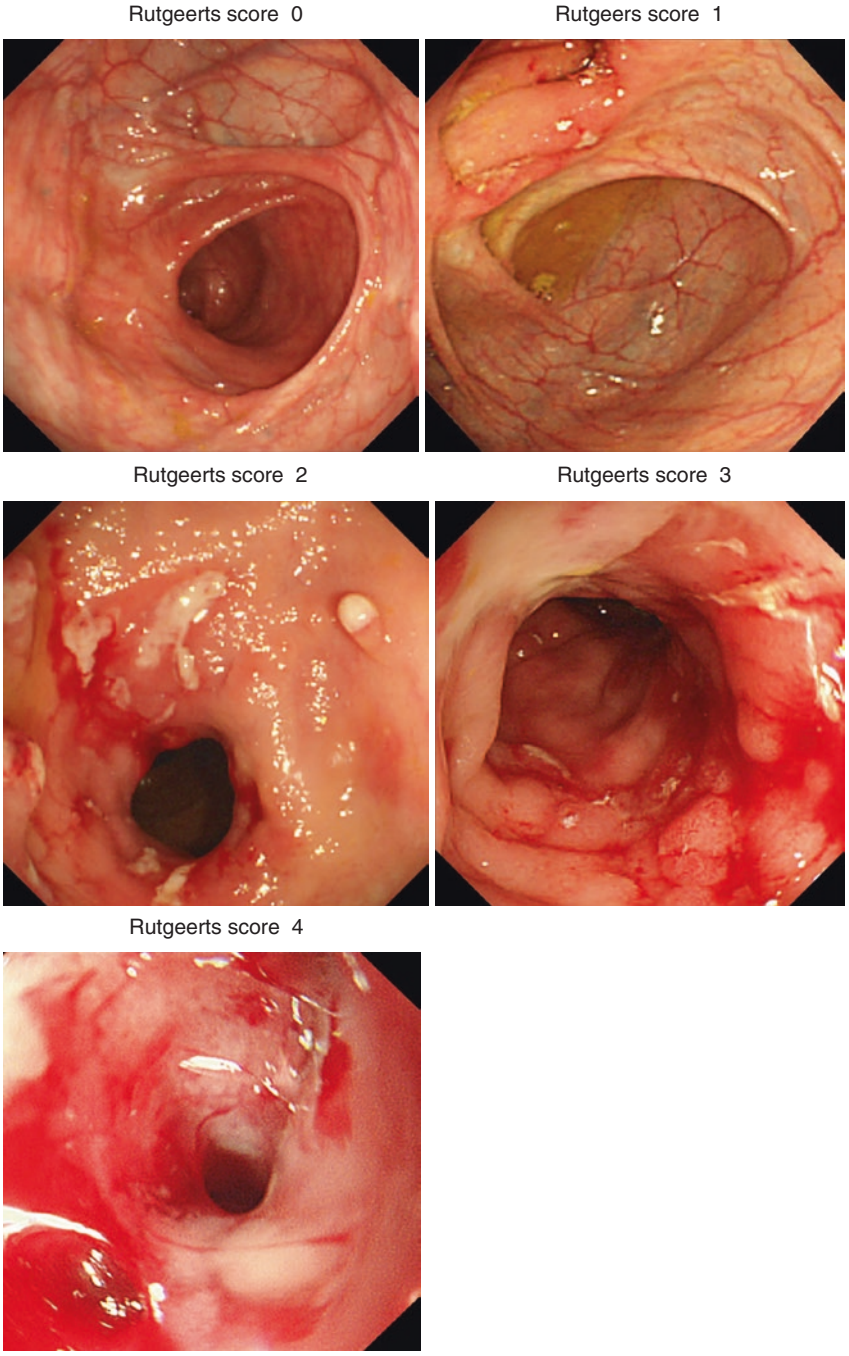


Fig. 15.1 Rutgeerts score

15.12 Summary

In patients with IBD, endoscopy is becoming an indispensable practice for detecting intestinal lesions reflecting the initiation and the progression of IBD or cancers, which may be associated with IBD lesions. However, given that UC lesions are primarily confined to the colon and the rectum, while CD lesions may appear at any location from the mouth to the perianal region, and inflammation may go beyond the mucosa, endoscopy has limitations in CD patients, but convenient and reliable in UC patients. Although currently, the significance of observing mucosal lesions during an endoscopic examination to assess mucosal condition or determine the severity of IBD is acknowledged, in the near future the endoscopic examination is expected to be performed more appropriately during disease course. This assertion will be supported by the outcomes of future work in this clinical setting, including combination of biomarkers in UC and imaging techniques like CT and MRI in CD.

References

1. Froslie KF, et al. Gastroenterology. 2007;133(2):412–22.
2. Neurath MF, Travis SPL. Gut. 2012;61:1619–35.
3. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013 Nov;145(5):987–95.
4. Taghvaei T, Maleki I, Nagshvar F, et al. Intern Emerg Med. 2014;10:321.
5. Emanuel B, et al. Dig Dis Sci. 2014;60:485.
6. Nakarai A, Kato J, Hiraoka S, et al. Am J Gastroenterol. 2013;108:83–9.
7. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48:526–35.
8. Rubin CE, et al. DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. Gastroenterology. 1992;103(5):1611–20.
9. Kiesslich R, Fritsch J, Holtmann M, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology. 2003;124:880–8.
10. Watanabe T, AjiokaY. Matsumoto T, et al. Target biopsy or step biopsy ? Optimal surveillance for ulcerative colitis: a Japanease nationwide randomized controlled trial. L Gastroenterol 2011;46:11-16
11. Takenaka K, Ohtsuka K, Kitazume Y, et al. Comparison of magnetic resonance and balloon enteroscopic examination of the small intestine in patients with Crohn's disease. Gastroenterology. 2014 Aug;147(2):334–42.
12. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99:956–63.
13. De Cruz P, Kamm MA, Hamilton AL, et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet. 2015;385:1406–17.

Chapter 16
Endoscopic Indices for Ulcerative Colitis

Taku Kobayashi

Abstract Colonoscopy is a gold standard in assessing disease severity of ulcerative colitis, and therefore efforts have been made in order to quantify the severity of inflammation by endoscopic indices. Most indices have been proposed to assess the efficacy of clinical trials, and therefore not been validated. Baron score, ulcerative colitis endoscopic index of severity (UCEIS), and ulcerative colitis colonoscopic index of severity (UCCIS) are validated. There are some scoring systems in which different factors are graded for each item separately [Baron score, Rachmilewitz score, endoscopic activity index (EAI, UCEIS and UCCIS), and others grading multiple aspects altogether (Matts' endoscopic grading, the Mayo endoscopic subscore (MES)]. It is essential to understand both strength and weakness of each index and utilize appropriately, since different indices have been developed for different purposes. It should be also noted that none of these widely used indices takes extent of inflammation into account. Currently, MES is most widely used in clinical trials for its simplicity, and UCEIS may become more common in the future because of its lower inter-observer variability. Definition of mucosal healing in each index has not been established yet.

Keywords Ulcerative colitis • Endoscopic index • Mucosal healing

T. Kobayashi
Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Insitiute Hospital, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan
e-mail: kobataku@insti.kitasato-u.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_16

16.1 Introduction

Endoscopy is a "gold standard" for assessing the severity of ulcerative colitis (UC), since the affected area is localized in the colon and therefore the entire diseased organ can be reached by conventional colonoscopy. The emerging concept of mucosal healing has made endoscopic evaluation more important. The evaluation includes disease extent, activity, phase, and response to the therapy. Difference in these aspects needs to be objectively stratified for the outcome measurement of clinical trials as well as directing the treatment strategy in clinical practice. There have been dozens of scoring systems proposed in the previous literature, however, many of them were developed for each specific clinical trial and then applied to other purposes. Therefore, there are only a few indices that have been appropriately validated. In this chapter, strength and weakness, clinical implication, and future direction of endoscopic indices currently used for UC are discussed.

16.2 Matts' Endoscopic Grading

Matts' endoscopic grading is one of the most conventional endoscopic indices, first described in 1961 and still used in clinical practice and clinical researches because of its simplicity [1]. In was originally developed to evaluate the significance of histological assessment of a biopsy specimen by looking at the correlation between endoscopic and histological grading systems. Its definition is focused on mucosal granularity and bleeding; however, it is not clear enough what the threshold is for distinguishing 'mild' granularity and bleeding from 'marked'. Furthermore, presence of ulcers appears only in grade 4; therefore, severity of ulceration cannot be reflected in this scoring system (Table 16.1).

Table 16.1 Matts' endoscopic grading [1]

1 = Normal
2 = Mild granularity of the mucosa, with mild contact bleeding
3 = Marked granularity and oedema of the mucosa, contact bleeding, and spontaneous bleeding
4 = Severe ulceration of mucosa with haemorrhage

16.3 Baron Score

Baron JH et al. reported the first validated endoscopic index in 1964 [2]. They studied the variation between observers in describing mucosal appearances in UC, and concluded that interobserver agreement was better reached based on mucosal friability and spontaneous bleeding compared with other descriptors. Based on this finding, classification of endoscopic activity using these two factors is proposed with high interobserver agreement (Table 16.2).

16.4 Mayo Endoscopic Subscore (MES)

Sutherland et al. established the Disease Activity Index using a quantitative rating scale with four variables including endoscopic mucosal appearance ranging from 0 to 3, which also utilizes friability and spontaneous bleeding [3]. A similar clinical disease activity index was defined by Schroeder et al. [4] for assessing the clinical efficacy of coated oral 5-ASA, with a more detailed description of mucosal appearance. This scoring system (called the Mayo score) is convenient for clinical trials, since it simultaneously reflects the overall clinical status as well as endoscopic mucosal appearance; however, it is of note that this endoscopic subscore itself has not been validated yet. The concept of mucosal healing is often defined as MES 0 and 1, which suggests the favorable long-term outcome (Table 16.3).

Table 16.2 Baron score [2]

	0 (normal)	1	2	3
Spontaneous bleeding	–	–	–	+
Bleeding to light touch	–	–	+	+

Table 16.3 Mayo endoscopic subscore (MES) [4]

0 = Normal of inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate diease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

16.5 Rachmilewitz Score

The confusion in the indices described above is that they are graded based on multiple different aspects of mucosal appearance, such as vascular pattern, friability, bleeding, and ulceration, which are not always altered in parallel. These different factors may appear at different levels, especially in patients who are responding to therapeutic intervention. Therefore, Rachmilewitz proposed an endoscopic index in which four descriptors are independently taken into account (Table 16.4) [5].

16.6 Endoscopic Activity Index (EAI)

Naganuma et al. developed EAI, consisting of six descriptors so that early improvement of mucosal inflammation can be more sensitively detected [6]. It has been shown that EAI is superior to Matts' score in differentiating responder and non-responder. Kobayashi et al. reported that decrease in EAI after 2-week intravenous cyclosporine inversely correlates to the first year colectomy, indicating that EAI is useful in stratifying early endoscopic improvement [7]. EAI is shown to have a wider range for severe cases, which may allow optimization of treatment based on severity even among patients graded identically as severe using the previous systems such as Matt's or MES (Table 16.5).

Table 16.4 Rachmilewitz score [5]

Endoscopic score		Score
Granulation scattering reflected light	No	0
	Yes	2
Vascular pattern	Normal	0
	Faded/disturbed	1
	Absent	2
Vulnerability of mucosa	None	0
	Contact bleeding	2
	Spontaneous bleeding	4
Mucosal damage (mucus, fibrin, erosion, ulcer)	None	0
	Slight	2
	Pronounced	4

Table 16.5 EAI [6]

Endoscopic score		Score
Size of ulcers	None	0
	Erosion/small ulcer	1
	Intermediate	2
	Wide-raged mucosal defects	3
Depth of ulcers	None	0
	Shallow	1
	Intermediate	2
	Deep	3
Redness	None	0
	Mild	1
	Marked	2
Bleeding	None	0
	Contact	1
	Spontaneous	2
	Massive bleeding	3
Mucosal edema	None	0
	Mild	1
	Moderate	2
	Severe	3
Mucous exudate	None	0
	Mild	1
	Marked	2

16.7 Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and Ulcerative Colitis Colonoscopic Index of Severity (UCCIS)

Travis SH et al. studied the intra- and inter- individual variation in ten endoscopic descriptors, and proposed UCEIS using three among them [8]. The UCEIS score incorporates vascular pattern (normal/patchy/complete obliteration), bleeding (none /mucosal/luminal mild/luminal moderate or severe), and erosions and ulcers (none/erosions/superficial/deep), each with precise definitions, which explained 90% of the variance in the overall assessment of endoscopic severity. It has been updated and validated with an independent [9] cohort of investigators, identifying it as one of the most well-validated endoscopic scores so far. One of the mechanisms helping UCEIS to avoid the variation is that each definition is very detailed, including size of the mucosal defects differentiating erosion (<5 mm) and ulcer (>5 mm).

UCCIS is another endoscopic severity index developed and validated recently. Thia et al. evaluated interobserver agreement in ten items and identified four (vascular pattern, granularity, ulcerations and bleeding–friability) as lesions demonstrating good agreements among endoscopic characteristics [10].

Table 16.6 UCEIS [8, 9]

Endoscopic score		Score
Vascular pattern	Normal	0
	Patchy obliteration	1
	Obliterated	2
Bleeding	None	0
	Mucosal	1
	Luminal mild	2
	Luminal moderate or severe	3
Erosions and ulcers	None	0
	Erosions	1
	Superficial ulcer	2
	Deep ulcer	3

UCCIS was established using these four parameters and validated in a different cohort [11]. What makes UCCIS unique is that it is the only validated index that takes into account the extent of disease, and is weighted differently to each descriptor.

The other characteristics by which UCEIS and UCCIS are considered well-validated is the strong correlation with the visual analogue scale. This demonstrates that these indices well reflect the global assessment of severity by endoscopists, which might most directly prove the feasibility of these scores (Table 16.6).

16.8 Consideration and Clinical Implication

We should keep in mind that many of the endoscopic indices currently used are developed for measuring outcomes of clinical trials, but the primary purpose was not to establish the validated endoscopic severity index. Therefore, these indices have not been appropriately validated yet, except for Baron, UCEIS, and UCCIS. However, this does not necessarily mean that other indices are not acceptable. MES is indeed the simplest and most widely used in clinical trials, and therefore there are much more data available than for others. On the contrary, MES is not sensitive enough to detect early response with relatively small changes in some cases (e.g., the case shown in Fig. 16.1), which is also important in clinical practice. This issue arises mainly because the simplest scores such as MES were developed to define the inclusion criteria of severity of the patients recruited to the clinical trials, and/or are only sensitive enough to detect significant changes responding to the therapeutic interventions after a certain period of time. Scores grading different endoscopic items (e.g., ulcer, bleeding, friability, etc.) independently, such as EAI and UCCIS, may have solved this issue, but have become less simple, requiring more effort for endoscopists to score. So far, UCEIS is considered to be most "well-balanced" between

accuracy, sensitivity, simplicity, and reproducibility. Much more clinical data are needed to make UCEIS as useful as MES in daily clinical practice.

Simpler scores such as Matts' and MES define the severity grades by multiple factors that are not always altered in parallel, especially in patients who is on the course of treatment. Furthermore, there could be a wide range of "severe" cases graded by these scores (e.g., any patients who have any ulcers should be scored as 3, since the definition only requires the presence but not the number or severity of ulceration). This lowers the potential ability to optimize the treatment options among severe cases, and the ability to detect the early response to treatment. Rachmilewitz, EAI, UCCIS, and UCEIS are theoretically expected to solve these disadvantages; however, these scores require more effort by the endoscopists than MES and other simpler scores, since there are more independent descriptors in the recent indices. An example of scoring by different systems is shown in Fig. 16.1.

There is also a discussion whether extent of disease should be included in the indices of endoscopic disease severity, especially because it is well known that extensive colitis is known to be an independent risk factor for colectomy [12, 13]. Therefore, patients with extensive colitis may need to be graded more severely compared with distally limited colitis; however, extent of disease is taken into account only in UCCIS among the indices described above. On the other hand, calculating sum of severity score from each segment of the colon makes the scoring process significantly more complicated. A list of strengths and weaknesses of each scoring system is summarized in Table 16.7.

Table 16.7 Strength and weakness of various endoscopic induces for UC

	Validation	Strength	Weakness
Matts [1]	No	Simple	Severity of ulceration not evaluated
Baron [2]	Yes	Simple	Evaluate bleeding aloine
Mayo [4]	No	Simple Simultaneously score endoscopic and clinical severity	Multiple aspects need to be graded altogether
Rachmilewitz [5]	No	Simultaneously score endoscopic and clinical severities Score items independently	Efforts necessary
EAI [6]	Incomplete	Score items independently	Efforts necessary
UCEIS [8, 9]	Yes	Score items independently	Lack of evidence in clinical trials
UCCIS [10]	Yes	Score items independently Evaluate extent	Significant efforts necessary

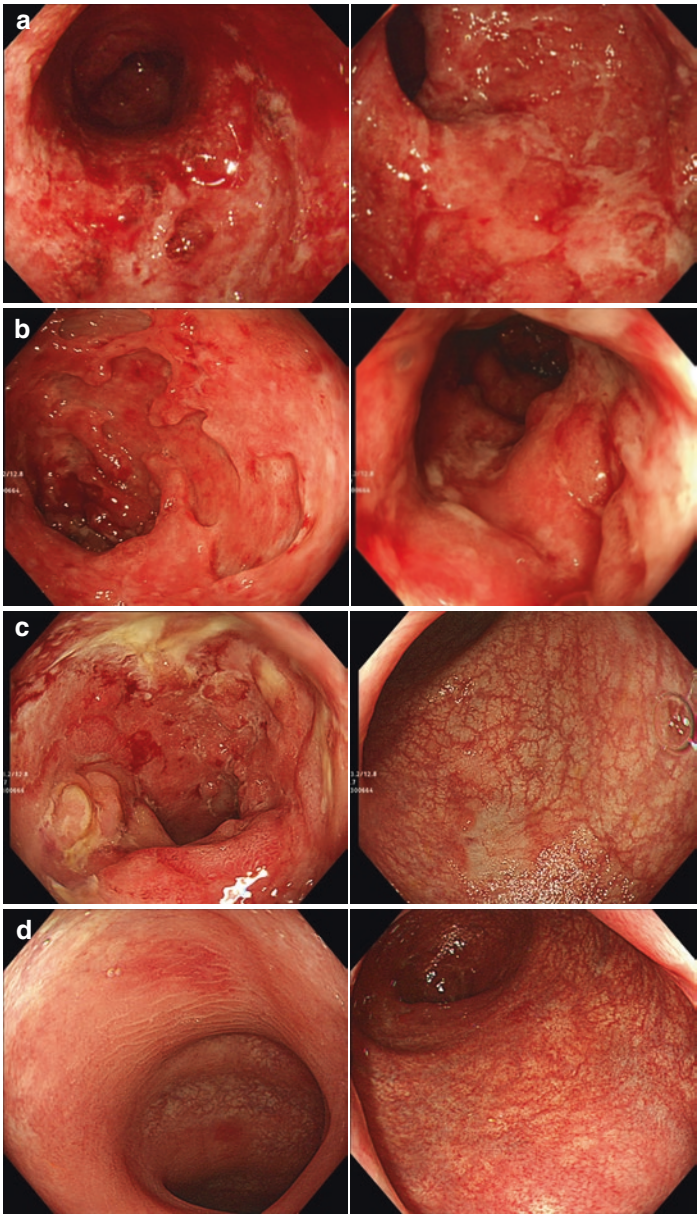


Fig. 16.1 Examples of scoring by MES, EAI, and UCEIS. **a** Endoscopic pictures of proximal (*left*) and distal (*right*) rectum of 35-year-old left-sided UC patients. MES, EAI, and UCEIS are 3, 11, and 6, respectively. **b** Endoscopic pictures of proximal (*left*) and distal (*right*) rectum of the same patient. MES, EAI, and UCEIS are 3, 14, and 7 respectively. MES is not altered, while EAI and UCEIS are higher than A because of the emergence of deep ulcers. **c** Endoscopic pictures of proximal (*left*) and distal (*right*) rectum 4 months after anti-TNF therapy and immunomodulator. MES, EAI, and UCEIS are 3, 10, and 6 respectively. MES is not altered, while EAI and UCEIS are lower than B. **d** Endoscopic pictures of proximal (*left*) and distal (*right*) rectum 10 months after continuing the treatment for a year. MES, EAI, and UCEIS are 1, 1, and 1 respectively

What is the ideal index and what is the reality? There is no gold standard yet. In general, more complicated indices tend to be more sensitive to the alteration of severity. The most well-balanced score with an appropriate validation might be UCEIS; however, its feasibility in clinical trials as well as in daily clinical practice is still unknown. The current reality might be to learn the etiology of how each index was developed, and try to choose the right scoring system for the right purpose accordingly.

References

1. Matts SG. The value of rectal biopsy in the diagnosis of ulcerative colitis. Q J Med. 1961;30:393–407.
2. Baron JH, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. Br Med J. 1964;1(5375):89–92.
3. Sutherland LR, Martin F, Greer S, Robinson M, Greenberger N, Saibil F, Martin T, Sparr J, Prokipchuk E, Borgen L. 5-aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology. 1987;92(6):1894–8.
4. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317(26):1625–9. doi:10.1056/NEJM198712243172603.
5. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ. 1989;298(6666):82–6.
6. Naganuma M, Ichikawa H, Inoue N, Kobayashi T, Okamoto S, Hisamatsu T, Kanai T, Ogata H, Iwao Y, Hibi T. Novel endoscopic activity index is useful for choosing treatment in severe active ulcerative colitis patients. J Gastroenterol. 2010;45(9):936–43. doi:10.1007/s00535-010-0244-2.
7. Kobayashi T, Naganuma M, Okamoto S, Hisamatsu T, Inoue N, Ichikawa H, Takayama T, Saito R, Sujino T, Ogata H, Iwao Y, Hibi T. Rapid endoscopic improvement is important for 1-year avoidance of colectomy but not for the long-term prognosis in cyclosporine a treatment for ulcerative colitis. J Gastroenterol. 2010;45(11):1129–37. doi:10.1007/s00535-010-0273-x.
8. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lemann M, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyshyn BR, Bernhardt CA, Mary JY, Sandborn WJ. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the ulcerative colitis endoscopic index of severity (UCEIS). Gut. 2012;61(4):535–42. doi:10.1136/gutjnl-2011-300486.
9. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, Feagan BG, Hanauer SB, Lichtenstein GR, Marteau PR, Reinisch W, Sands BE, Yacyshyn BR, Schnell P, Bernhardt CA, Mary JY, Sandborn WJ. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013;145(5):987–95. doi:10.1053/j.gastro.2013.07.024.
10. Thia KT, Loftus Jr EV, Pardi DS, Kane SV, Faubion WA, Tremaine WJ, Schroeder KW, Harmsen SW, Zinsmeister AR, Sandborn WJ. Measurement of disease activity in ulcerative colitis: interobserver agreement and predictors of severity. Inflamm Bowel Dis. 2011;17(6):1257–64. doi:10.1002/ibd.21480.
11. Samuel S, Bruining DH, Loftus Jr EV, Thia KT, Schroeder KW, Tremaine WJ, Faubion WA, Kane SV, Pardi DS, de Groen PC, Harmsen WS, Zinsmeister AR, Sandborn WJ. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. Clin Gastroenterol Hepatol. 2013;11(1):49–54. e41 doi:10.1016/j.cgh.2012.08.003.

12. Gower-Rousseau C, Dauchet L, Vernier-Massouille G, Tilloy E, Brazier F, Merle V, Dupas JL, Savoye G, Balde M, Marti R, Lerebours E, Cortot A, Salomez JL, Turck D, Colombel JF. The natural history of pediatric ulcerative colitis: a population-based cohort study. Am J Gastroenterol. 2009;104(8):2080–8. doi:10.1038/ajg.2009.177.
13. Romberg-Camps MJ, Dagnelie PC, Kester AD, Hesselink-van de Kruijs MA, Cilissen M, Engels LG, Van Deursen C, Hameeteman WH, Wolters FL, Russel MG, Stockbrugger RW. Influence of phenotype at diagnosis and of other potential prognostic factors on the course of inflammatory bowel disease. Am J Gastroenterol. 2009;104(2):371–83. doi:10.1038/ajg.2008.38.

Chapter 17
Endoscopic Indices for Crohn's Disease

Makoto Naganuma

Abstract Achieving endoscopic remission has become one of the treatment goals in Crohn's disease (CD) because recent studies have indicated that mucosal healing is associated with better CD outcomes after the initiation of medical treatment. Scoring the endoscopic disease severity is important, because endoscopy can objectively assess the severity of the disease. Crohn's disease index of severity (CDEIS), the simple endoscopic score for Crohn's disease (SES-CD), and the Rutgeerts postoperative endoscopic index are frequently used to assess endoscopic disease activity in CD. Changes in endoscopic scores are associated with clinical responses to medical treatments. CDEIS and SES-CD are clinically difficult to score. Although novel technologies to enable the diagnosis of small intestinal lesions have been developed, there have been few scoring systems to assess the severity of small intestinal lesions. The development of a simple score for both small and large intestinal lesions of CD is warranted.

Keywords Crohn's disease index of severity • Simple endoscopic score for Crohn's disease • Mucosal healing

17.1 Introduction

Conventional ileocolonoscopy is the most useful technique for assessing the extent and severity of disease in patients with inflammatory bowel disease (IBD). In the diagnosis of Crohn' s disease (CD), longitudinal ulceration and a

M. Naganuma
Center for Diagnostic and Therapeutic Endoscopy, School of Medicine, Keio University,
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: nagamakoto@z7.keio.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_17

cobblestone appearance, as well as small longitudinal erosion and aphtha, are typical findings. Although cross-sectional imaging techniques such as CT and MR enterography are critical for assessment of CD lesions, especially small intestinal lesions [1, 2], it may be difficult to detect small lesions using cross-sectional imaging. Thus, although new diagnostic devices for CD have been developed, ileocolonoscopy remains the gold standard tool for assessment of the severity of CD.

Endoscopic improvement and remission have been associated with better CD outcomes [3]; therefore, achieving endoscopic remission has become one of the treatment goals in CD [4]. Scoring endoscopic disease severity is important because endoscopy can objectively assess the severity of inflammation in patients with clinical remission after the initiation of medical treatment. Three endoscopic scores have been introduced as frequent endoscopic disease activity indices for CD [4, 5]: the Crohn's disease index of severity (CDEIS), the simple endoscopic score for Crohn's disease (SES-CD), and the Rutgeerts postoperative endoscopic index (Tables 17.1–17.3).

In this chapter, the utility and limitations of these scores are discussed, and examples of endoscopic scores for CD are also provided.

Table 17.1 Crohn's disease index of severity (CDEIS) score

	Ileum	Right colon	Transverse colon	Sigmoid/left colon	Rectum	
Deep ulceration (0 if non, 12 point if present)	(0 or 12)	(0 or 12)	(0 or 12)	(0 or 12)	(0 or 12)	Total 1
Superficial ulceration (0 if non, 6 point if present)	(0 or 6)	(0 or 6)	(0 or 6)	(0 or 6)	(0 or 6)	Total 2
Surface involved by disease (cm)[a]	0–10	0–10	0–10	0–10	0–10	Total 3
Surface involved by ulceration (cm)[a]	0–10	0–10	0–10	0–10	0–10	Total 4
Total A = Total1 + Total 2 + Total 3 + Total 4						Total A
Number of segments exposure (1–5)						*N*
Total A/N						Total B
If ulcerated stenosis is present anywhere add 3						C (0 or3)
If non-ulcerated stenosis is present anywhere add 3						D (0 or 3)
CDEIS = Total B + C + D						CDEIS

[a]The extent of disease or ulceration was quantified on a visual analogue scale from 0 to 10

17.2 Clinical Utility and Shortcomings of the Crohn's Disease Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's Disease (SES-CD)

The CDEIS has been developed to detect changes in endoscopic severity on the basis of characteristics of the ileocolonic mucosa [6]. The extent of mucosal lesions is quantified on a visual analogue scale from 0 to 10 in five sections of the bowel: ileum, right colon, transverse colon, combined sigmoid and left colon, and rectum (Table 17.1). The variables of the CDEIS are the presence of superficial ulceration, deep ulceration, the ulcerated and nonulcerated surface, and the presence of ulcerated/nonulcerated stenosis. The range of CDEIS is from 0 to 44. CDEIS is a standard, validated, and reproducible index. However, it is complex and difficult to score in clinical practice. The threshold of CDEIS for endoscopic remission is defined as CDEIS < 6, and complete endoscopic remission is defined by a value of CDEIS < 3 [7]. Mucosal healing in the study by Mary et al. was defined as only the absence of ulcers. They also defined endoscopic response as a decrease in CDEIS score >5 points. CDEIS was used as an endpoint in a clinical trial to demonstrate the efficacy of certolizumab [8]. The rates of endoscopic response, endoscopic remission, complete endoscopic remission, and mucosal healing at week 10 were 54%, 37%, 10%, and 4% respectively. At week 54, the corresponding rates were 49%, 27%, 14%, and 8% respectively, in patients who were treated with certolizumab. To date, however, there is no validated definition of endoscopic remission and mucosal healing in patients with CD.

The variables of SES-SD [9] are size of ulcers, ulcerated surface, affected surface, and the presence of narrowing (Table 17.2, Fig. 17.1). Each category is scored from 0 to 3 for the 5 bowel segments (rectum, sigmoid and descending colon, transverse colon, right colon, and terminal ileum). Thus, the total SES-CD ranges from 0 to 60. For endoscopists, the SES-CD is simpler than CDEIS for scoring the severity of disease. SES-CD is well correlated with CDEIS. Nevertheless, SES-SD has been less used than CDEIS in clinical trials, and it is also less used in clinical practice. Furthermore, only a study to validate SES-CD against CDEIS was previously conducted. There is no cutoff value of SES-CD for mucosal healing and endoscopic remission.

Table 17.2 Simple endoscopic score for Crohn's disease (SESCD)

	0	1	2	3
Size of ulcers	None	Aphthous ulcers (Ø 0.1–0.5 cm)	Large ulcers (Ø 0.5 to 2 cm)	Very large ulcers (Ø > 2 cm)
Ulcerated surface	None	<10%	10–30%	>30%
Affected surface	Unaffected	<50%	50–75%	>75%
Presence of narrowing	None	Single, can be passed	Multiple, can be passed	Cannot be passed

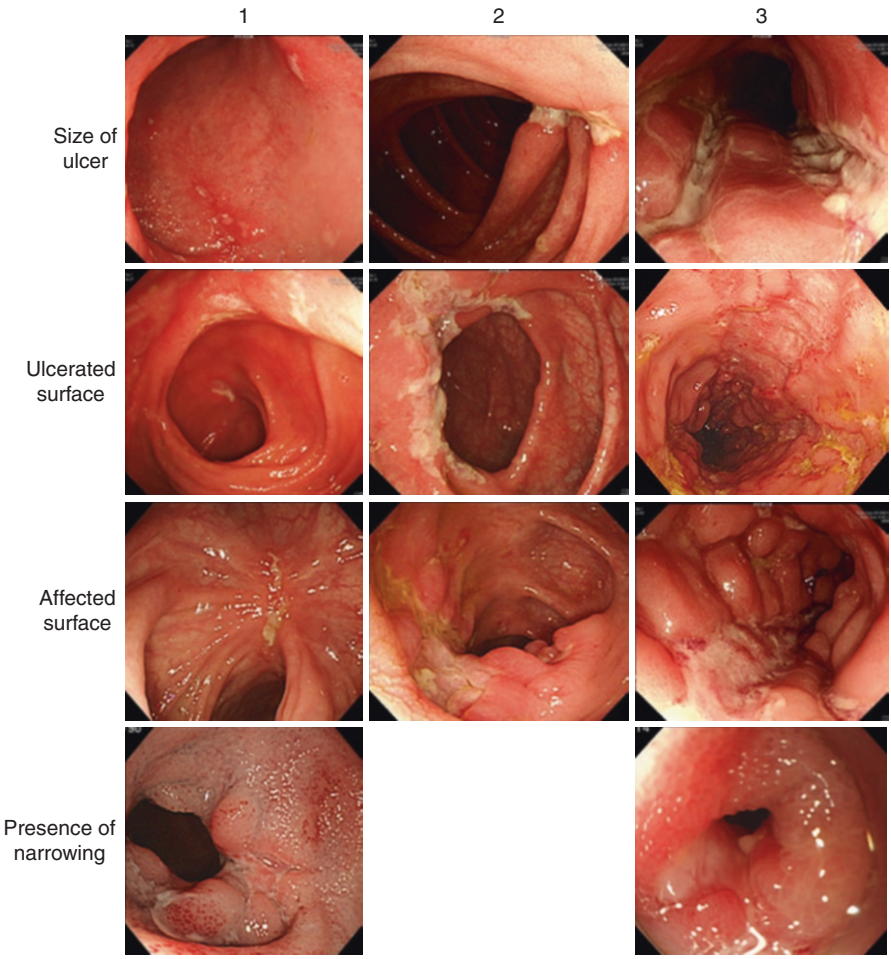


Fig. 17.1 Typical endoscopic findings of each item of simple endoscopic score for Crohn's disease (SESCD)

17.3 Examples of CDEIS and SES-CD for Patients with Crohn's Disease

Figure 17.2 indicates endoscopic findings at the terminal ileum and each segment of the colon in CD patients with abdominal pain and several diarrhea. The Crohn's disease activity index (CDAI) corresponding to those findings was 275.5. Endoscopic findings revealed deep longitudinal ulcerations and irregular ulcerations in the transverse colon and cecum (Fig. 17.2). Severe stricture with ulceration was observed at 5 cm from the ileocecal valve, and a colonoscope could not be passed through the stricture. The patient's CDEIS and SES-CD

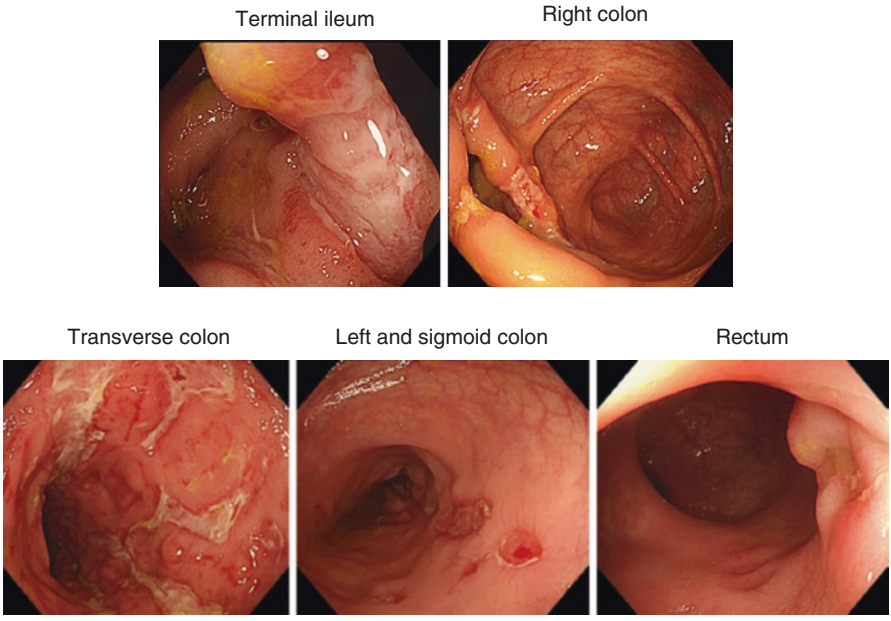


Fig. 17.2 Endoscopic findings at the terminal ileum, right colon, transverse colon, left and sigmoid colon, and rectum in patients with CD prior to use of adalimumab

scores were 19.3 and 28 respectively (Table 17.4a–b). The patient was treated with adalimumab (ADA) and responded to treatment. The CDAI decreased from 275.5 to 134.5 at 14 weeks after administration of ADA. Endoscopic findings at 14 weeks indicated that the severe inflammation with longitudinal ulceration markedly improved, although small ulcerations were still found at the transverse colon and rectum (Fig. 17.3). The CDEIS decreased from 19.3 to 3.5 (Table 17.5a), and the SES-CD decreased from 38 to 7 (Table 17.5b). The CDEIS and SES-CD changes were affected by endoscopic improvement in this patient. Even as clinical and endoscopic improvements were achieved, small ulcerations were still observed. This result is consistent with the observation of endoscopic improvement based on CDEIS (change of CDEIS > 5; 19.3 → 3.5), whereas complete endoscopic remission or mucosal healing was not obtained because the patient had a score of CDEIS >3 with ulceration at 14 weeks after treatment.

17.4 Clinical Utility and Shortcomings of Rutgeerts Postoperative Endoscopic Index

The Rutgeerts score [10] was developed to assess the severity of inflammation at the anastomosis and neoterminal ileum in patients with ileocecal resection.

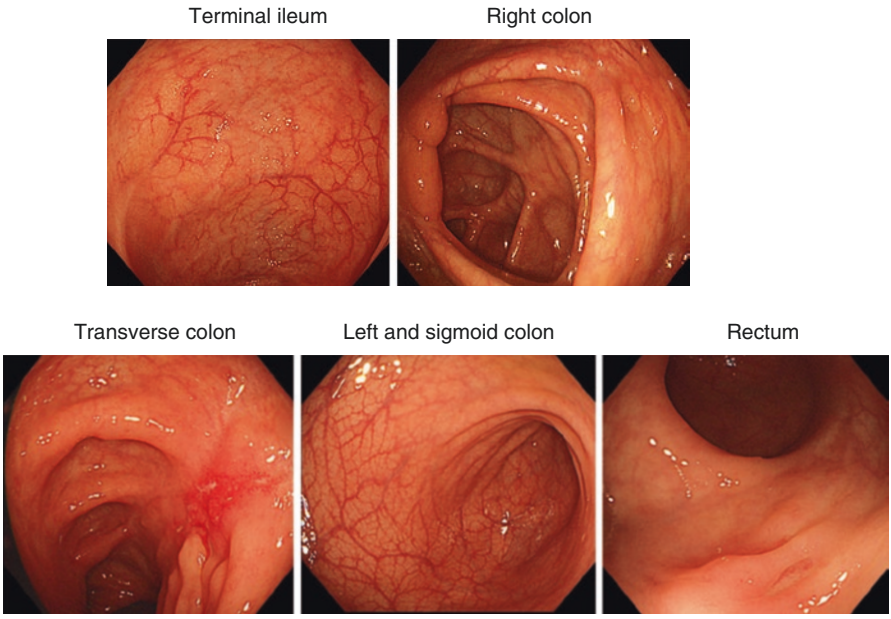


Fig. 17.3 Endoscopic findings at the terminal ileum, right colon, transverse colon, left and sigmoid colon, and rectum in patients with CD after use of adalimumab. Inflammation with deep ulceration is markedly improved

The Rutgeerts score includes rankings of i0, i1, i2, i3, and i4 (Table 17.3, Fig. 17.4). Although it is not validated, the prediction of relapse has been validated using this score. Scores of i0 and i1 indicate a low risk of clinical recurrence, whereas i3 and i4 correspond to a relatively high risk of recurrence. Although this score is useful to assess the severity of inflammation at the anastomosis, it is unclear how this score is determined in patients with any other colonic lesions.

17.5 Recent Advances in Endoscopic Score in CD

The CDEIS and SES-CD were developed and published in 1989 and 2004 respectively. In the past decade, novel endoscopic scores for CD have not been developed

Table 17.3 Rutgeerts score

i0	None of any lesions
i1	≤5 Aphthous ulcers
i2	>5 Aphthous ulcers with normal intervening mucosa, or skip areas of larger lesions or lesions confined to the ileocolic anastomosis (i.e., <1 cm in length)
i3	Diffuse aphthous ulceration with diffusely inflamed mucosa
i4	Diffuse inflammation with large ulcers, nodules, and/or narrowing

Table 17.4 The CDEIS score (a) and SES-CD (b) for assessment of ileocolonic lesions in Crohn's disease

	Ileum	Right colon	Transverse colon	Sigmoid/ left colon	Rectum	
(a) CDEIS						
Deep ulceration (0 if non, 12 point if present)	12	0	12	0	0	24 (Total 1)
Superficial ulceration (0 if non, 6 point if present)	6	6	6	6	6	30 (Total 2)
Surface involved by disease (cm)[a]	3.0	1.5	9.0	3.0	1.5	18 (Total 3)
Surface involved by ulceration (cm)[a]	2.0	0.5	6.5	2.0	0.5	11.5 (Total 4)
Total A = Total 1 + Total 2 + Total 3 + Total 4						83.5
Number (N) of segments exposure (1–5)						5
Total B= Total A/N						16.7
If ulcerated stenosis is present anywhere, add 3 (C)						3
If non-ulcerated stenosis is present anywhere, add 3 (D)						0
CDEIS = Total B + C + D						19.7
(b) SES-CD						
Size of ulcers (0–3)	3	2	3	2	1	11
Ulcerated surface (0–3)	2	1	3	1	1	8
Affected surface (0–3)	1	1	2	1	1	6
Presence of narrowing (0–3)	3	0	0	0	0	3
						28

A patient with deep ulceration at the transverse colon with severe stricture at terminal ileum

[a]Sum of the score for each items (deep ulceration, superficial ulceration, surface involved bydisease, and surface involved by ulceration).

Table 17.5 The CDEIS (a) and SES-CD (b) score for assessment ileocolonic lesions in patients who was treated with adalimumab (ADA)

	Ileum	Right colon	Transverse colon	Sigmoid/ left colon	Rectum	
(a) CDEIS						
Deep ulceration (0 if non, 12 point if present)	0	0	0	0	0	0 (Total 1)
Superficial ulceration (0 if non, 6 point if present)	0	0	6	0	6	12 (Total 2)
Surface involved by disease (cm)	0	0	3.0	0	0.5	3.5 (Total 3)
Surface involved by ulceration (cm)	0	0	1.5	0	0.5	2 (Total 4)
Total A = Total 1 + Total 2 + Total 3 + Total 4						17.5
Number (N) of segments exposure (1–5)						5
Total B = Total A/N						3.5
If ulcerated stenosis is present anywhere, add 3 (C)						0
If non-ulcerated stenosis is present anywhere, add 3 (D)						0
CDEIS = Total B + C + D						3.5
(b) SES-CD						
Size of ulcers (0–3)	0	0	2	0	1	3
Ulcerated surface (0–3)	0	0	1	0	1	2
Affected surface (0–3)	0	0	1	0	1	2
Presence of narrowing (0–3)	0	0	0	0	0	0
						7

Scores were significantly decreased after administration of ADA

because these scores are complex and difficult to score in clinical practice. The development of simpler endoscopic scores for CD is warranted.

Moreover, CDEIS and SES-CD can be evaluated at the terminal ileum and colon. There have been few endoscopic scores to assess the severity of inflammation at the small intestine. Conventional ileocolonoscopy cannot assess inflammation at the mid–small intestine. Recently, novel technologies to enable IBD diagnosis have been developed, such as capsule endoscopy (CE) and balloon-assisted enteroscopy (BAE). CE and BAE have enabled detection in patients of small intestinal lesions with aphthoid lesions, erosions, and small ulcers that had not been detected using

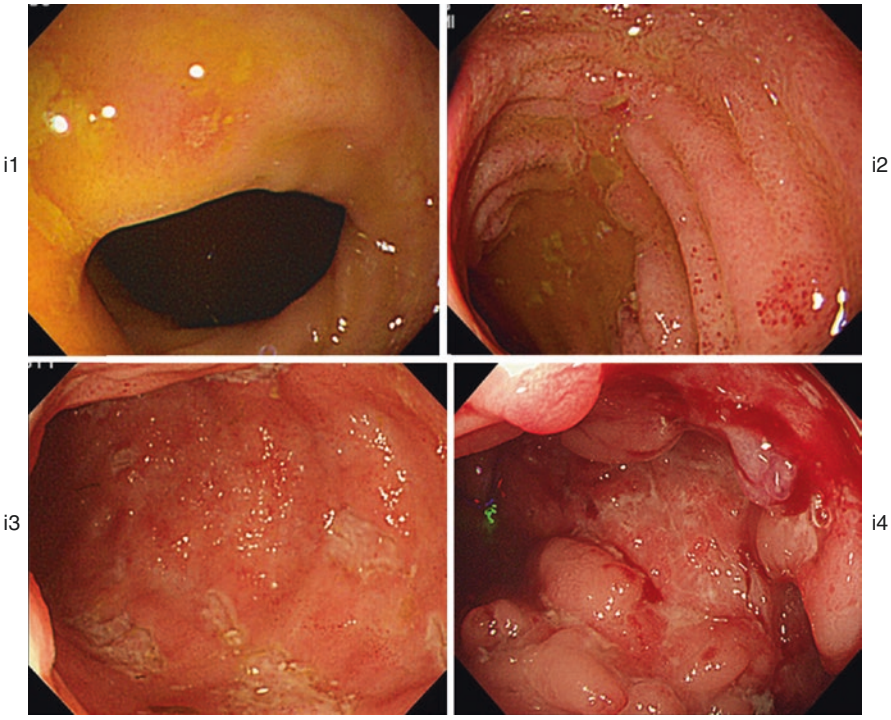


Fig. 17.4 Typical endoscopic findings of Rutgeerts score in a patient with ileocecal colectomy

radiation examination. The Lewis score (LS) and the capsule endoscopy Crohn's disease activity index (CECDAI) have been developed to assess small-bowel inflammation [11, 12]. LS is based on three endoscopic parameters: villous edema, ulcers and stenosis/stricture [11]. CECDAI consists of three parameters/components: an inflammation score, a disease-extent score, and a stricture score [12]. The total score ranges from 0 to 36. For BAE, Takenaka et al. developed a novel endoscopic score that was defined using the modified SES-CD [13]. The total SES-CD score in the small intestine was calculated as the sum of SES-CD in the terminal ileum, proximal ileum, and jejunum. The cutoff value of mucosal lesion and ulcerative lesion was defined as SES-CD $\geq$ 1 and ulcerative lesions SES-CDa $\geq$ 5 respectively, although this criterion should be validated.

Finally, it should be noted that the endoscopic score unquestionably affects the real severity of inflammation in patients with CD, because CD inflammation is transmural in most cases. Although cross-sectional imaging does not easily detect small lesions as described above, it may be useful in assessing transmural inflammation. Popularization of MR enterography and ultrasound sonography is warranted for the diagnosis of CD in the near future.

17.6 Summary

The CDEIS, SES-CD, and Rutgeerts scores have been used in patients with CD. These scores closely correspond to the severity of mucosal inflammation, and changes in the scores are associated with clinical response. However, CDEIS and SES-CD are difficult to score in real clinical practice. The development of a simple score for both small and large intestinal lesions of CD is warranted.

References

1. Naganuma M, Hosoe N, Ogata H. Inflammatory bowel disease and novel endoscopic technologies. Dig Endosc Suppl. 2014;1:20–8.
2. Naganuma M, Hisamatsu T, Kanai T, et al. Magnetic resonance enterography of Crohn's disease. Expert Rev Gastroenterol Hepatol. 2014;3:1–9.
3. Froslie KF, Jahnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133:412–22.
4. Neurath MF, Travis SPL. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61:1619–35.
5. Walsh A, Palmer R, Travis S. Mucosal healing as a target of therapy for colonic inflammatory bowel disease and methods to score disease activity. Gastrointest Endosc Clin N Am. 2014;24:367–78.
6. Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Groupe d'Etudes Therapeutiques des affections Inflammatoires du Tube Digestif (GETAID). Gut. 1989;130:983–9.
7. Mary JY, Lemann M, Colombel J-F, et al. Endoscopic remission and response in Crohn's disease: an objective definition using the CDEIS. Gut. 2006;37(Suppl 1):A55.
8. Hébuterne X, Lémann M, Bouhnik Y, et al. Endoscopic improvement of mucosal lesions in patients with moderate to severe ileocolonic Crohn's disease following treatment with certolizumab pegol. Gut. 2013;62:201–8.
9. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60:505.
10. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the postoperative course of Crohn's disease. Gastroenterology. 1990;99:956–63.
11. Gralnek IM, Defranchis R, Seidman E, et al. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. Aliment Pharmacol Ther. 2008;27:146–54.
12. Gal E, Geller A, Fraser G, et al. Assessment and validation of the new capsule endoscopy Crohn's disease activity index (CECDAI). Dig Dis Sci. 2008;53:1933–7.
13. Takenaka K, Ohtsuka K, Kitazume Y, et al. Comparison of magnetic resonance and balloon enteroscopic examination of deep small intestine in patients with Crohn's disease. Gastroenterology. 2014;47:334–42.

Chapter 18
Mucosal Healing in Ulcerative Colitis

Hiroshi Nakase, Tomoya Iida, Kentaro Kawakami, and Daisuke Hirayama

Abstract Nowadays, the relevance of the endoscopic activity of ulcerative colitis (UC) has been translated into the new concept of "mucosal healing (MH)" as the therapeutic goal to achieve, because considerable scientific evidence indicated the favorable prognostic value of a healed mucosa in clinical outcome of UC. In this regard, MH assessed by endoscopy seems almost like the "gold standard" for evaluating UC activity. On the other hand, we should recognize that there were no prospectively validated endoscopic scoring systems of UC activity in previous clinical trials. In the future, development of new endoscopic scoring systems, which are prospectively validated, will standardize the definition of MH. In addition, recent interest on mucosal healing skews toward not only endoscopic remission but also histological improvement (so-called histological MH). To be precise, histological MH can be an ideal goal for treatment of UC. However, it seems to be more difficult to decide the exact definition of histological MH than that of endoscopic MH. New endoscopic techniques, "confocal endomicroscopy in vivo", might be promising modalities in the assessment of MH. We should await data concerning the real-time evaluation of MH in UC patients by confocal endomicroscopy. There are many issues to be addressed with regard to standardization of MH, therefore, "*The road to justification of MH in the treatment of UC has just started*".

Keyword Ulcerative colitis • Mucosal healing • Clinical outcome • Confocal endomicroscopy

H. Nakase (✉) • T. Iida • K. Kawakami • D. Hirayama
Department of Gastroenterology and Hepatology, Sapporo Medical Univeristy School of Medicine, S-1, W-16, Chuo-Ku, Sapporo, Hokkaido 060-8543, Japan
e-mail: hiropynakase@gmail.com

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_18

18.1 Introduction

In ulcerative colitis (UC), the inflammatory lesions are confined to the mucosa, the most superficial layer of the colon, and the disease almost always involves the distal colon. And the clinical course of UC is characterized by its repeated flare and remission.

The goal for our patients was to induce remission, which is usually defined as resolution of abdominal symptoms, such as restoring continence and absence of rectal bleeding. However, there have not been any data to confirm that symptomatic improvement alters the natural history of UC, nor decreases the lifetime risk for surgery. Where should we go for best management of patients with UC?

To answer this question, the recent concept of "mucosal healing (MH)" has emerged in the field of IBD treatment. The majority of patients with UC who responded clinically to treatment with 5-ASA, corticosteroids, leukocytapheresis, immunosuppressants, anti-TNF alpha antibodies, could achieve MH [1, 2]. How does mucosal healing contribute to management of UC? In this section, we provocatively discuss whether the mucosal healing is optimal as the endpoint of treatment for UC patients.

18.1.1 When Did the Concept of Mucosal Healing Start?

Notably, the concept of MH had already started approximately 50 years ago. In 1966, Wright et al. reported a higher relapse rate in patients who did not achieve MH after oral and rectal steroids when compared with patients who did achieve MH (40% vs 18%). [3] Courtney et al. also reported that flares during a 12-month period following an episode of active colitis were observed in only 4% of the patients with clinical remission and mucosal healing, and in 30% of those whose clinical remission was accompanied by persistent mucosal lesions [4]. In 2001, Bitton et al. reported on clinical, biological, and histologic parameters that would predict time to clinical relapse. Surprisingly, they had already reported that one of the factors related to clinical relapse was basal plasmacytosis on rectal biopsy. The hazard ratio (HR) for predicting clinical relapse was 4.5, and the authors concluded that this factor may help identify patients with inactive UC who will require optimal maintenance therapy [5]. Although MH endpoints have not been focused on in clinical trials, the relevance of the endoscopic activity of UC has been translated into the new concept of "mucosal healing (MH)" as the therapeutic goal to achieve, because considerable scientific evidence indicated the favorable prognostic value of a healed mucosa in the clinical outcome of UC. Thus, MH assessed by endoscopy seems almost like the "gold standard" for evaluating UC activity. However, there are a number of questions to address before granting MH in assessing UC activity. These include: (1) what is the exact definition of MH—is there a uniformly accepted standard? and (2) does MH change the clinical outcome and reduce dysplasia and colorectal cancer in UC patients?

18.1.2 What Is the Exact Definition of MH?: We Know No Validated Definition of MH

Despite no standardized definition of MH, a practical currently accepted definition of MH is "the complete resolution of the visible alterations or lesions, irrespective of their severity and/or type at baseline colonoscopy" [6]. Although there have been 50 years of clinical trials and differently designed endoscopic scoring systems, (Baron score, Mayo score, Sutherland, Powell-Tuck and Rachmilewitz indices, among others) [7–14], the definitions and the scoring methods of these instruments have never been prospectively validated. However, having no validated endoscopic score for UC activity evaluation might reflect the complexity in measuring its disease activity [15].

For example, in recent clinical trials, the Mayo endoscopy subscore has been the most commonly used, defining MH as a score of ≤ 1 (normal mucosa or loss of vascular pattern, but no mucosal friability), when the endoscopy subscore was 2 or 3 at baseline. The Mayo score is not theoretical but might be easily applicable in clinical practice. The main issues on the majority of several indices such as Mayo score include the overlap of mucosal features (such as vascularity, granularity, erythema, friability, bleeding, and ulceration), which could result in inter-observer variation in endoscopic evaluation, and the lack of clear and standardized thresholds for endoscopic remission. In fact, judging from data that a recent RCT on the use of mesalamine in UC patients showed different results after a revision of the endoscopic examination findings by a blinded central reader [16], issues with regard to definition of MH might greatly influence results of clinical trials.

Recently, two new scoring systems have been developed and prospectively validated, the Ulcerative Colitis Endoscopic Index of Severity and the Ulcerative Colitis Colonoscopic Index of Severity [17, 18]. However, data regarding the applicability of these new scoring systems in clinical trials and in clinical practice should be awaited, and accumulation of further clinical trials data with these systems might support the move toward a standardized definition of MH.

18.1.3 Histological Mucosal Healing: Is this an Ideal Therapeutic Goal or Not?

In 2007 the AGA published its "Consensus on Efficacy End Points," stating that "absence of friability, blood, erosions, and ulcers in all visualized segments are the required components of *genuine endoscopic healing*.".

Moreover, regarding microscopic mucosal healing, "the authors do not recommend that histologic remission be used as the primary end point for a therapeutic trial in patients with UC." [19]. Nevertheless, there have been several reports concerning the necessity of histological evaluation in colonic mucosa of UC. Also, it should be noted that the term "mucosal healing" was initially proposed only for the

disappearance of the inflammatory infiltrate in the histological examination [20]. Currently, recent interest on mucosal healing skews toward not only endoscopic remission but also histological improvement. Bessissow et al. reported that the presence of basal plasmacytosis predicts UC clinical relapse in patients with complete mucosal healing, although this was a retrospective study [21]. In addition, Peyrin-Biroulet et al. described that data indicating a prognostically relevant role for histologic activity in the mucosa of UC patients, in addition to the macroscopic activity, have opened the door to the concept of "histological MH", with the complete absence of clinical, laboratory, endoscopic, and histological features of active inflammation [22]. However, questions regarding histological MH should be addressed; [1] how many biopsy specimens should be taken? [2] where should biopsy specimens be taken? and [3] can histological results of rectal biopsy reflect inflammatory condition in the entire colonic mucosa of patients with extensive UC who have endoscopic remission? Possibly, deciding the exact definition of histological MH seems to be more difficult than that of endoscopic MH.

Therefore, I strongly consider that "*The road to justification of histological MH in UC has many turns.*"

18.1.4 Does Mucosal Healing Affect Clinical Outcome in UC?

Do you know the reason why many IBD experts been interested in achievement of MH? Clinical trial data with various IBD treatments might account for this question. During the last decade, anti-TNF alpha antibodies have launched a "*Copernican resolution*" in the clinical approach to IBD patients. These drugs have resulted in rapid and dramatic improvement of clinical symptoms and intestinal mucosal lesions. Since emergence of anti-TNF alpha antibodies in the field of IBD treatment, the relevance of the endoscopic activity of IBD has been definitely stated, and MH has been proposed with increasing strength as a fundamental therapeutic goal of IBD treatment. In this regard, the significance of MH as a treatment goal in IBD is of increasing interest, and has become a common endpoint in clinical trials. For example, in the recent trials of infliximab for moderate to severe UC, assessed by the Mayo score, those patients with documented mucosal healing at week 8 and 30 were more likely to be in remission than those who did not [23]. The ACT1 and ACT2 trials showed that UC patients treated with infliximab who achieved MH at week 8 had a higher rate of clinical remission at week 30 than patients without MH (48.3% vs 9.5%) [23]. Moreover, a post-hoc analysis of the ACT1/ACT2 trials conducted by Colombel et al. demonstrated that a Mayo endoscopy subscore of 0–1 in infliximab-treated patients was related to a lower probability of colectomy than a score of 2–3 through a follow-up period of 54 weeks. [24]. Thus, data in ACT trial suggested that MH could affect clinical outcome of UC. It has been reported that UC patients who achieved clinical remission together with MH after leukocytapheresis had a higher rate of sustained clinical response than those with a clinical response alone (88% vs 41%) [25]. With regard to corticosteroid treatment, it has been reported that the lack of mucosal

healing at 3 months after the first administration of corticosteroid was the only factor associated with negative outcomes at 5 years (use of immunosuppressants, hospitalization, and colectomy) [26]. An observational study of the IBSEN cohort showed that in 513 UC patients, the colectomy rate was lower in patients with MH [defined by a simple endoscopic score of 0–1 (0, normal; 1, light erythema or granularity)] at a 5-year follow-up (2% vs 8%, $P < 0.05$) [27]. Similar results were observed by Solberg et al., who reported a decrease in the colectomy rate in UC patients with MH at 1 year after diagnosis, regardless of the therapy used to achieve it [28].

On the other hand, a meta-analysis of all placebo-controlled trials in UC published in 2007 documented that in four of six trials which included endoscopic remission rates as an endpoint in combination with clinical remission, the endoscopic remission rate was almost the same as the clinical remission rate. This analysis might reflect the viewpoint that the endoscopic assessment of mucosal healing did not yield additional clinical information [29]. Again, we should acknowledge the fact that specific studies showing the superiority of a management based solely on MH over the "traditional" approach are lacking. Taken together, the increasing relevance of the MH achievement in UC has been demonstrated by several data demonstrating the different clinical outcome between UC patients with and without MH, in terms of a reduction of flares as well as reductions in hospitalization and colectomy. However, whether there is a difference in quality of MH among various treatments by which UC patients have achieved MH remains unclear.

18.1.5 Does MH Reduce Dysplasia and Colorectal Cancer in UC?

The increased risk of colorectal cancer incidence in UC patients is a clinically important issue. It is recognized that long-standing UC carries an increased risk for the development of high-grade dysplasia and colorectal carcinoma (CRC), with estimates of risk as high as 20% following 30 years of diagnosis [30]. The mechanism of dysplasia and CRC in UC is strongly associated with sustained mucosal inflammation of colon. In this regard, achievement of MH can contribute to the reduction of CRC risk. Recent data have indicated a possible prognostic role for endoscopic and histologic remission in terms of reductions in not only flares and hospitalization, but also incidence of CRC. Rutter et al. noted that both endoscopic and histological severity of disease impacted cancer risk on univariate analysis; only histological severity continued to show an increased risk for neoplasia following multivariate analysis [31]. An Italian cohort study indicated a lower CRC risk at 17 years of follow-up in azathioprine (AZA)-treated UC patients with MH [32]. Korelitz et al. demonstrated the importance of evaluating histological inflammation in UC patients achieving endoscopic MH to reduce the risk of dysplasia and CRC [33]. It should be noted that several studies have suggested the necessity of histological assessment, even in UC patients with achievement of endoscopic MH, for reduction of risk of colitis-associated cancer.

18.2 Recent Advances in Endoscopy: New Endoscopic Techniques: "Confocal Endomicroscopy in Vivo" in Assessment of MH, Can Endomicroscopy Change the Definition of MH?

Confocal laser microscopy (CLE) was introduced in 2003, which allows in-vivo microscopic imaging of cellular and subcellular structures at approximately 1,000-fold magnification. This intriguing technique has the capability to obtain "real-time" histology such as images of gastrointestinal mucosa. Watanabe et al. investigated the features of CLE in inflamed and non-inflamed rectal mucosa of UC, and compared these results to standard histology. They reported that colonic crypts in non-active ulcerative colitis were small, round, and slightly irregular in arrangement and the crypt lumens of the colonic glands were small and round. Inflammatory cells and capillaries were visible in the lamina propria. On the other hand, the colonic crypts in active ulcerative colitis were large, variously shaped, and irregular in arrangement, and in addition numerous inflammatory cells and capillaries were visible in the lamina propria [34]. Li et al. showed data regarding the significance of CLE in assessing mucosal inflamation of UC. They reported that CLE-assessment of crypt architecture and fluorescein leakage showed good correlation with the corresponding histology results. It should be noted that more than half of the patients with normal mucosa seen on conventional white-light endoscopy revealed acute inflammation on histology [35]. Novel imaging through CLE has the possibility of demonstrating a different dimension of mucosal healing. Moussata et al. reported that CLE could visualize the bacteria translocation in intestinal mucosa in vivo. Their data showed that the translocation of bacteria into the lamina propria was present in 58.8% and 14% of UC patients and normal controls respectively ($P < 0.001$) [36]. This intriguing in-vivo finding supports the possibility that the abnormality of barrier function of intestinal epithelial cells is involved in the pathophysiology of UC. Thus, CLE enables us to understand the interaction between the mucosal layer of UC and intestinal bacteria.

Endocytoscopy (EC; Olympus, Tokyo, Japan) is based on the principle of contact light microscopy. EC systems are either integrated into the distal tip of a standard endoscope (iEC) or probe-based (pEC) [37]. Depending on the system used (iEC or pEC), EC visualizes architectural details, cellular features, and vascular pattern morphology at a magnification of up to 1,390-fold [38]. A recent article demonstrated the correlation of efficacy for assessment of microscopic features in UC patients between endocytoscopy and conventional histopathology [39]. They developed EC findings, a scoring system based on EC findings, that showed a strong correlation with Matts' histological grades. This newly developed EC score showed high reproducibility among investigators, with a κ value of 0.79. Another study determined the reliability of EC for the discrimination of mucosal inflammatory cells and intestinal inflammatory disease activity in patients with IBD [40]. In summary, both CLE and EC hold

significant potential in identifying subtle mucosal inflammation in real-time by identifying single mucosal inflammatory cells in conjunction with architectural changes. However, large prospective multicenter trials evaluating both modalities for prediction of disease course in UC are highly required.

18.3 Summary

Going back to the natural history of UC, more than one-half of UC patients have a benign disease course, while up to one-third are likely to experience frequent flares and potentially dangerous complications. Therefore, what we do is to identify UC patients with higher risk of repeated flares and CRC as much as possible, because the ideal management would imply an aggressive treatment and endoscopic follow-up for the achievement of MH in UC patients with unfavorable courses. In the light of the current evidence regarding MH in UC, we completely agree that the concept of MH is important for UC management. On the contrary, the shift from a symptoms-based to a mucosa-based approach in the management of UC would result in a considerable trend to over-scope and/or over-treat patients for the achievement of MH. Therefore, we always keep in mind that the bottom line of UC management is to focus on a "patient-based" approach, which can overcome the dualism between symptom- and mucosa-targeted approaches.

References

1. Kane S, Lu F, Kornbluth A, et al. Controversies in mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2009;15:796–800.
2. Iacucci M, Ghosh S. Looking beyond symptom relief: evolution of mucosal healing in inflammatory bowel disease. Therap Adv Gastroenterol. 2011;4:129–43.
3. Wright R, Truelove SR. Serial rectal biopsy in ulcerative colitis during the course of a controlled therapeutic trial of various diets. Am J Dig Dis. 1966;11:847–57.
4. Courtney MG, Nunes DP, Bergin CF, et al. Colonoscopic appearance in remission predicts relapse of ulcerative colitis. Gastroenterology. 1991;100:A205.
5. Bitton A, Peppercorn MA, Antonioli DA, et al. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. Gastroenterology. 2001;120:13–20.
6. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61:1619–35.
7. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2:1041–8.
8. Baron JH, Connell AM, Lennard-jones JE. Variation between observers in describing mucosal appearances in proctocolitis. Br Med J. 1964;1:89–92.
9. Powell-Tuck J, Bown RL, Lennard-Jones JE. A comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. Scand J Gastroenterol. 1978;13:833–7.
10. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317:1625–9.

11. Sutherland LR, Martin F, Greer S, et al. 5-aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. Gastroenterology. 1987;92:1894–8.
12. Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ. 1989;298:82–6.
13. Feagan BG, Greenberg GR, Wild G, et al. Treatment of ulcerative colitis with a humanized antibody to the alpha4beta7 integrin. N Engl J Med. 2005;352:2499–507.
14. D'Haens G, Hommes D, Engels L, et al. Once daily MMX mesalazine for the treatment of mild-to-moderate ulcerative colitis: a phase II, dose-ranging study. Aliment Pharmacol Ther. 2006;24:1087–97.
15. Rogler G, Vavricka S, Schoepfer A, et al. Mucosal healing and deep remission: what does it mean? World J Gastroenterol. 2013;19:7552–60.
16. Feagan BG, Sandborn WJ, D'Haens G, et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology. 2013;145:149.e2–57.e2.
17. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013;145:987–95.
18. Samuel S, Bruining DH, Loftus EV, et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. Clin Gastroenterol Hepatol. 2013;11:49.e1–54.e1.
19. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007;132:763–86.
20. Korelitz BI, Sommers SC. Response to drug therapy in Crohn's disease: evaluation by rectal biopsy and mucosal cell counts. J Clin Gastroenterol. 1984;6:123–7.
21. Bessissow T, Lemmens B, Ferrante M, et al. Prognostic value of serologic and histologic markers on clinical relapse in ulcerative colitis patients with mucosal healing. Am J Gastroenterol. 2012;107:1684–92.
22. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clin Gastroenterol Hepatol. 2014;12:929.e2–34.e2.
23. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–76.
24. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141:1194–201.
25. Yamamoto T, Umegae S, Matsumoto K. Mucosal healing in patients with ulcerative colitis during a course of selective leukocytapheresis therapy: a prospective cohort study. Inflamm Bowel Dis. 2010;16:1905–11.
26. Ardizzone S, Cassinotti A, Duca P, et al.. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. Clin Gastroenterol Hepatol. 2011;9:483.e3–9.e3.
27. Frøslie KF, Jahnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133:412–22.
28. Solberg IC, Lygren I, Jahnsen J, et al. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). Scand J Gastroenterol. 2009;44:431–40.
29. Su C, Lewis JD, Goldberg B, et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active ulcerative colitis. Gastroenterology. 2007;32:516–26.
30. Eden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48:526–35.
31. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126:451–9.
32. Actis GC, Pellicano R, David E, et al. Azathioprine, mucosal healing in ulcerative colitis, and the chemoprevention of colitic cancer: a clinical-practice-based forecast. Inflamm Allergy Drug Targets. 2010;9:6–9.

33. Korelitz BL, Sultan K, Kothari M, et al. Histological healing favors lower risks of colon carcinoma in extensive ulcerative colitis. World J Gastroenterol. 2014;20:4980–6.
34. Watanabe O, Ando T, Maeda O, et al. Confocal endomicroscopy in patients with ulcerative colitis. J Gastroenterol Hepatol. 2008;23(Suppl 2):S286–90.
35. Li CQ, Xie XJ, Yu T, et al. Classification of inflammation activity in ulcerative colitis by confocal laser endomicroscopy. Am J Gastroenterol. 2010;105:1391–6.
36. Moussata D, Goetz M, Watson AJ, et al. Confocal laser endomicroscopy for the in vivo identification, localization and quantification of tissue based basteria in patients with different types of colitis. Gastrointest Endosc. 2009;69:131.
37. Neumann H, Fuchs FS, Vieth M, et al. Review article: in vivo imaging by endocytoscopy. Aliment Pharmacol Ther. 2011;33:1183–93.
38. Minami H, Inoue H, Yokoyama A, et al. Recent advancement of observing living cells in the esophagus using CM double staining: endocytoscopic atypia classification. Dis Esophagus. 2012;25:235–41.
39. Bessho R, Kanai T, Hosoe N, et al. Correlation between endocytoscopy and conventional histopathology in microstructural features of ulcerative colitis. J Gastroenterol. 2011;46:1197–202.
40. Neumann H, Vieth M, Neurath MF, et al. Endocytoscopy allows accurate in vivo differentiation of mucosal inflammatory cells in IBD: a pilot study. Inflamm Bowel Dis. 2013;19:356–62.

Chapter 19
The Efficacies and Issues for Endoscopic Assessment of Mucosal Healing in Patients with Crohn's Disease

Kenji Watanabe, Noriko Kamata, Shuhei Hosomi, Takehisa Suekane, Kouji Sano, Tomomi Yukawa, Hirokazu Yamagami, Yasuhiro Fujiwara, Hiroko Nebiki, and Tetsuo Arakawa

Abstract Mucosal healing has been a focus of attention as an emerging ideal treatment goal of Crohn's disease. Endoscopy is the gold standard for evaluating mucosal lesion. Objective precise monitoring, especially for the small bowel, is important for stratifying the treatment strategy. Some limitations and issues for definition of mucosal healing, accessibility of stricture or adhesion, feasible endoscopic score still remain. It is important in clinical practice to identify the appropriate time for intensifying the CD treatment for small ulcerative lesion endoscopically. There are characters for each imaging modality, for instance assessment of intestinal tract wall and extrawall information. The combination with other complementary imaging modalities or biomarkers is useful in optimizing the CD treatment strategy. An appropriate accelerated step-up treatment strategy combined with stratified precise monitoring of the SB should provide optimal prognosis in patients with CD. Endoscopic prediction of long-term prognosis or efficacy of treatment is an important subject for investigation.

Keyword Crohn's disease • Mucosal healing • Endoscopy • Small bowel • Enteroscopy

K. Watanabe (✉)
Department of Intestinal Inflammation Research, Hyogo College of Medicine, 1-1, Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan
e-mail: ke-watanabe@hyo-med.ac.jp

N. Kamata • S. Hosomi • T. Yukawa • H. Yamagami • Y. Fujiwara • T. Arakawa
Department of Gastroenterology, Osaka City University, Osaka, Japan

T. Suekane • K. Sano • H. Nebiki
Department of Gastroenterology, Osaka City General Hospital, 2-13-22 Miyakojima-hondori, Miyakojima-ku, Osaka 534-0021, Japan

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_19

19.1 Introduction

Recent developments for treatment options, especially immunomodulators or biologics, have led to the changing of treatment and monitoring strategies in patients with Crohn's disease (CD). Past treatment targets of CD patients were to avoid hospitalization, and surgical or steroid-free clinical remission. These new treatments can achieve a higher level of remission induction (deep remission: DR) and sustain this DR [1]. And these developments in treatment can provide better long-term prognosis or may provide a changing natural history of CD [2, 3].

We need an appropriate standard to confirm the efficacy of CD treatment or sustain DR. In addition, our clinical practice for CD patients should be performed depending on not only subjective improvements of symptoms but objective monitoring. There are several approaches to the assessment of CD activity: C-reactive protein (CRP), barium contrast X-ray study, endoscopy, ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), fecal calprotectin, and the other biomarkers. Recently, mucosal healing (MH) has been a focus of attention as an emerging ideal treatment goal [4]. Endoscopic examination is the gold standard for assessing MH [5]. Some advantages, efficacies, or issues of endoscopic assessments for MH are described in this chapter.

19.2 Endoscopic Assessments for Mucosal Healing

19.2.1 Advantages and Efficacies

Achieving MH after treatment is a predictor of reduced subsequent disease activity and decreased need for active treatment [6, 7]. Endoscopy is the top imaging modality for evaluating mucosal lesions of the gastrointestinal tract. Endoscopic evaluation is useful for confirming the efficacy of treatments and optimizing treatment strategy [8]. Conventional ileocolonoscopy is used to evaluate mucosal lesions from rectum to terminal ileum. A thin colonoscope is useful for assessing the oral mucosa beyond the stricture in CD patients with stricture [9]. But different approaches are usually used for small bowel (SB).

The SB is the organ most commonly affected by CD. Lesions (e.g., stricture, fistula) responsible for hospitalization or surgery are more frequently located in the SB than in the colon, and the correlation between the presence of an SB lesion and the presence of CD symptoms or elevated CRP is weaker than that for colonic lesions. Therefore, objective imaging assessments are important in detecting CD-related SB lesions; "silent CD" should not be overlooked.

Described as above, there are several complementary imaging modalities for evaluation of SB lesions: SB series, capsule endoscopy (CE), balloon-assisted enteroscopy (BAE), magnetic resonance enterography (MRE), CT enterography (CTE), and US (Fig. 19.1). CE generally has the most superior diagnostic yield for SB mucosal lesions, and is helpful in determining the insertion route of BAE

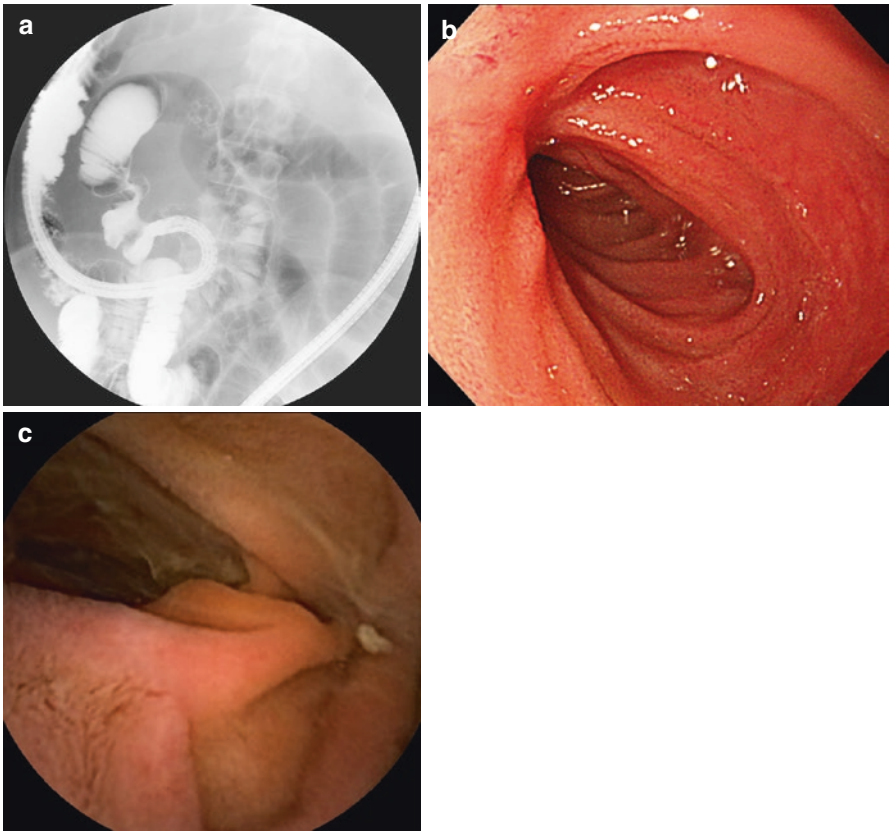


Fig. 19.1 The comparison of three complementary imaging modalities, selective small-bowel series under endoscopic examination (**a**), balloon-assisted enteroscopy (**b**: single-balloon enteroscopy) and capsule endoscopy (**c**). The small-bowel series is useful and feasible to understand the whole image for distribution or shape of lesion. In contrast, endoscopy is superior for visualizing the mucosal lesion

(Fig. 19.2). BAE can take a biopsy specimen and perform selective contrast study or balloon dilation therapy to the stricture [10]. But using CE risks capsule retention, and using BAE risks perforation or difficulties in deep insertion, resulting from stricture or adhesion. Recently, MRE has become a popular way to examine SB in patients with CD, because it is also able to assess abnormalities on or outside the wall without requiring radiation [11]. But if MRI (MRE or MR enterocolonography: MREC) is enough to assess the mucosal lesion of gastrointestinal tract, ileocolonoscopy should not be needed. The best possible use should be made of the complementary characteristics of various SB imaging modalities.

Endoscopic monitoring is useful for identifying the proper time to change the treatment; even in the absence of clinical symptoms, the treatment may need to be intensified if endoscopic findings worsen. It is known that pharmacokinetic approaches with biologics are helpful stratified treatment strategies in CD patients.

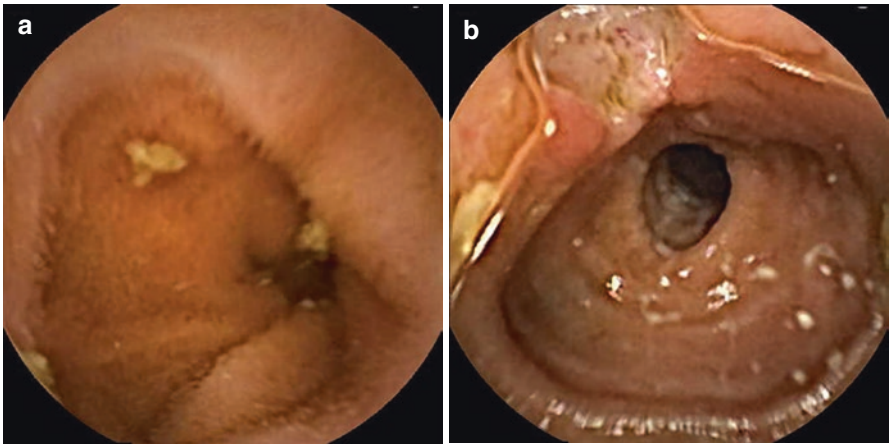


Fig. 19.2 Endoscopic monitoring is useful to identify the time for intensifying treatment of Crohn's disease. This patient was treated with immunomodulator, and continued clinical remission. Capsule endoscopy visualized erosion in the middle of ileum (**a**). After 1 year, capsule endoscopy revealed ulcer as worsening trend in the middle of the ileum (**b**). The physician decided to administrate anti-TNFα agent

However, regardless of the pharmacokinetic data, confirmation of the SB lesion activity is often needed in clinical practice. Further examinations involving fecal calprotectin measurement will also be needed to assess SB lesion status.

19.2.2 Definition of Mucosal Healing

To identify when treatment should be intensified, we must define MH, including partial MH. Of course, complete MH with scarring is acceptable as MH. But structuring occurs as the result of MH after effective remission induction therapy. How can we categorize that condition in MH (Fig. 19.3)? And the definition of partial MH should be discussed depending on the results of further several investigations. When small active lesions remain endoscopically after remission induction therapy, what is the standard of endoscopic findings for confirming the efficacy of the remission induction therapy as (partial) MH? The greater difficulty is; what is the standard of endoscopic findings to intensify the treatment during remission maintenance therapy? If we find the erosion or small ulcer, do we need to intensify the treatment? What we can do now is to continue precise objective monitoring and recognize the improving or worsening tendency of endoscopic findings.

There are some endoscopic scores for CD. CDEIS (Crohn's disease endoscopic index of severity) or SES-CD (Simple Endoscopic Score for Crohn's disease) are available for evaluating the endoscopic activity of ileum and colorectum. Some investigations have used a score lower than 3 for CDEIS or a score lower than 5 for

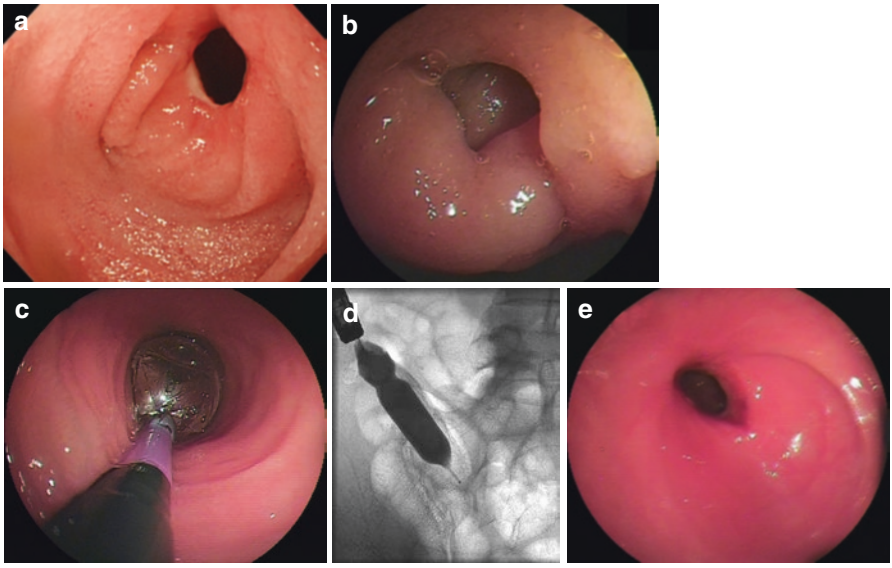


Fig. 19.3 This Crohn's disease patient suffered abdominal fullness and pain. Single balloon enteroscopy revealed a stricture in the lower part of ileum, but there was a risk of perforation in performing endoscopic balloon dilatation because of existence of ulcer in the stricture (**a**). After additional treatment of anti-TNFα agent, complete mucosal healing was achieved (**b**). Therefore, we performed endoscopic balloon dilatation (**c**, **d**), and then the symptoms were improved (**e**)

SES-CD as the definition of MH [12] However, they are inconvenient to use in clinical practice because of complex calculation. And they were produced before CE or BAE. They account for four parts of colorectum but only one part of SB. In addition, SB is assessed only for the ileum. This is an imbalance. The Rutgeerts score is simple and feasible in clinical practice, but it is limited to use for neoterminal ileum in case of CD after ileocecal resection. For CE, there are two scores, Lewis score and CECDAI (capsule endoscopy Crohn's disease activity index). But the Lewis score is not specialized for CD, and neither is yet validated for MH.

Transmural inflammation is a characteristic pathological finding of CD. There is still debate whether MH is a sufficient treatment goal of CD. The initial lesion of CD is an aphthoid lesion in the mucosa of the GI tract. This means that MH is at least a necessary condition. Histological healing or transmural healing may become better ideal treatment goalS in the future [13].

19.2.3 Remaining Issues

As mentioned above, further investigations are needed to stratify a CD objective monitoring strategy which depends on endoscopy and the other imaging modalities, especially for SB. Although endoscopy is situated as one of the objective

examinations, it is well-known that inter- or intra-observer variations exist for the evaluation of endoscopic findings. Therefore, endoscopic assessment is objective monitoring in one sense, but subjective in another sense. In this sense, the development of a more feasible, invariable, and validated endoscopic score is required. There are difficult tasks to be undertaken for the development of a novel endoscopic score for CD, complementary assessment for mucosa, GI tract wall and extrawall information, and different aspects of ulcerative lesion and deformity.

There are some risks associated with the difficulty of deep insertion by BAE in CD cases involving severe active lesion or adhesion. The patency capsule is useful to confirm functional patency of the GI tract as pretest of CE. However, there are a few reports of adverse events relating to the patency capsule, the occurrence of obstructive symptoms or CE retention after confirming functional patency by using patency capsule [14, 15]. Medical cost is also important. The cost of CE examination is more expensive than other imaging modality examinations in Western countries [16].

19.3 Recent Advances for the Assessment of Mucosal Healing

The combination of precise monitoring with not only the other imaging modalities is important in stratifying the treatment strategy for CD. Identifying the rationale for discontinuation of biologics is also an important issue for CD clinical management, because of expensive treatment. If the endoscopy confirmed the complete MH and the serum concentration of biologics was not detectable, the biologics can be withdrawn.

Even in a single CD patient, coexistence of healed lesion and non-healed lesion is often observed endoscopically. The basic science approach should investigate the local pathogenesis for these differences. This may provide the development of CD treatment.

Endoscopic prediction of long-term prognosis or efficacy of treatment is an important subject for investigation. In particular, molecular imaging by endoscopy is a technique not requiring a high level of skill and useful for estimating the efficacy of CD treatment [17].

19.4 Summary

In summary, endoscopy is the gold standard for assessing mucosal CD lesions. And MH is an ideal treatment goal as a necessary condition. However, there are several limitations and issues to resolve. The combination with other complimentary imaging modalities or biomarkers is useful in optimizing CD treatment strategy. An appropriate accelerated step-up treatment strategy combined with stratified precise monitoring of the SB should provide optimal prognosis in patients with CD.

References

1. Hall B, Holleran G, Chin JL, et al. A prospective 52 week mucosal healing assessment of small bowel Crohn's disease as detected by capsule endoscopy. J Crohns Colitis. 2014;8:1601–9.
2. Mandel MD, Miheller P, Müllner K, et al. Have biologics changed the natural history of Crohn's disease? Dig Dis. 2014;32:351–9.
3. Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lémann score. Inflamm Bowel Dis. 2011;17:1415–22.
4. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61:1619–35.
5. D'Incà R, Caccaro R. Measuring disease activity in Crohn's disease: what is currently available to the clinician. Clin Exp Gastroenterol. 2014;20:151–61.
6. Beppu T, Ono Y, Matsui T, et al. Mucosal healing of ileal lesions is associated with long-term clinical remission after infliximab maintenance treatment in patients with Crohn's disease. Dig Endosc. 2015;27:73–81.
7. Frøslie KF, Jahnsen J, Moum BA, et al. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133:412–22.
8. Bouguen G, Levesque BG, Pola S, et al. Endoscopic assessment and treating to target increase the likelihood of mucosal healing in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12:978–85.
9. Morimoto K, Watanabe K, Noguchi A, et al. Clinical impact of ultrathin colonoscopy for Crohn's disease patients with strictures. J Gastroenterol Hepatol. 2015;30(Suppl 1):66–70.
10. Yamagami H, Watanabe K, Kamata N, et al. Small bowel endoscopy in inflammatory bowel disease. Clin Endocrinol. 2013;46:321–6.
11. Takenaka K, Ohtsuka K, Kitazume Y, et al. Comparison of magnetic resonance and balloon enteroscopic examination of the small intestine in patients with Crohn's disease. Gastroenterology. 2014;147:334–42.
12. Annese V, Daperno M, Rutter MD, et al. European evidence-based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7:982–1018.
13. Bryant RV, Winer S, Travis SP, et al. Systematic review: histological remission in inflammatory bowel disease. Is 'complete' remission the new treatment paradigm? An IOIBD initiative. J Crohns Colitis. 2014;8:1582–97.
14. Cohen SA, Ephrath H, Lewis JD, et al. Pediatric capsule endoscopy: review of the small bowel and patency capsules. J Pediatr Gastroenterol Nutr. 2012:54409–13.
15. Herrerias JM, Leighton JA, Costamagna G. Agile patency system eliminates risk of capsule retention in patients with known intestinal strictures who undergo capsule endoscopy. Gastrointest Endosc. 2008;67:902–9.
16. Maconi G, Bolzoni E, Giussani A, et al. Accuracy and cost of diagnostic strategies for patients with suspected Crohn's disease. J Crohns Colitis. 2014;8:1684–92.
17. Atreya R, Neumann H, Neufert C, et al. In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease. Nat Med. 2014;20:313–8.

Chapter 20
Endoscopic Intervention in Inflammatory Bowel Disease

Fumihito Hirai and Toshiyuki Matsui

Abstract Today, since we have balloon-assisted enteroscope (BAE) for small intestine, it is possible to perform endoscopic treatment for various small-bowel disorders. In this chapter, we describe endoscopic interventions for small-bowel disorders, particularly inflammatory bowel diseases.

Patients with Crohn's disease sometimes have massive bleeding that requires transfusion or surgery. In cases where the bleeding point can be detected endoscopically, which is relatively rare, endoscopic small-bowel hemostasis is performed using BAE.

BAE enables endoscopic balloon dilation (EBD) to be performed even for deeply situated strictures of the small intestine. EBD is indicated for small-bowel tumors and inflammatory diseases such as Crohn's disease (CD), NSAID-induced enteropathy, intestinal tuberculosis, and chronic non-specific multiple ulcers of small intestine to avoid surgery. EBD for small-bowel disorders seems to be quite effective according to short-term analysis of many reports.

A well-designed prospective study is necessary to confirm the long-term efficacy and safety of EBD.

Keywords Balloon-assisted enteroscopy • Endoscopic interventions • Endoscopic hemostasis • Endoscopic mucosal resection • Endoscopic balloon dilation

F. Hirai (✉) • T. Matsui
Department of Gastroenterology, Fukuoka University Chikushi Hospital,
1-1-1 Zokumyoin, Chikusino, Fukuoka 818-8502, Japan
e-mail: fuhirai@cis.fukuoka-u.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_20

20.1 Endoscopic Interventions for Small-Bowel Disorders

Balloon-assisted enteroscopy (BAE) enables gastroenterologists and endoscopists not only to observe the entire small intestine, but also to perform biopsies and endoscopic interventions. It is a major breakthrough in terms of the diagnosis and treatment of small-bowel disorders. In particular, almost all endoscopic interventions such as hemostasis, endoscopic mucosal resection, endoscopic balloon dilation, and placement of metallic stents can be performed for small-bowel lesions, even those located in the deeper portion of the small intestine. Today, there are two BAE systems that can be used to observe the entire small intestine. One is a double-balloon enteroscope (Fujifilm Medical Co., Tokyo, Japan), which Dr. Yamamoto developed and is the most frequently used in Japan [1]. The other one is a single-balloon enteroscope (Olympus Co., Tokyo, Japan) [2]. These are quite useful for the correct diagnosis of small-bowel disorders, especially small-bowel tumors, vascular lesions, and inflammatory diseases, and they allow biopsies and various endoscopic interventions to be performed immediately after observation. However, it is sometimes not easy to perform the endoscopic treatments using BAE compared to gastroduodenoscopy or colonoscopy, because there are situations in which it is difficult to maintain a good visual field due to the narrow space, no straightening with insertion, and peristalsis. BAE also has some disadvantages, which are its invasiveness, need for preparation, and the technical difficulty of insertion. We have to select these modalities for small-bowel examination according to the patient's status, indication, purpose, and suspected disease. In this chapter, we describe endoscopic interventions for small-bowel disorders, particularly inflammatory bowel diseases (IBDs).

20.2 Endoscopic Interventions

20.2.1 Hemostasis

We usually perform gastroduodenoscopy and colonoscopy for cases with gastrointestinal bleeding. Capsule endoscopy and BAE are then performed in cases of obscure gastrointestinal bleeding (OGIB). There are several strategies for OGIB using CE, BAE, and other modalities (Fig. 20.1) [3, 4]. If the causative lesions can be detected, hemostasis can be performed by BAE. Basically, all of the devices used for hemostasis in colonoscopy are available for use with BAE. We can use clipping, argon plasma coagulation (APC), electronic coagulation including biceps and hypertonic saline–epinephrine (HSE) injection, and so on. Endoscopists should select the method of hemostasis according to the hemorrhagic lesion.

For vascular lesions, an endoscopic classification of small intestinal vascular lesions (Yano–Yamamoto classification, Table 20.1) [4] is useful for selecting the hemostatic procedure. In general, the coagulation method is adopted for types Ia, Ib, and IIa. Clipping is indicated for types Iia, Iib, and III. Some type III cases, which

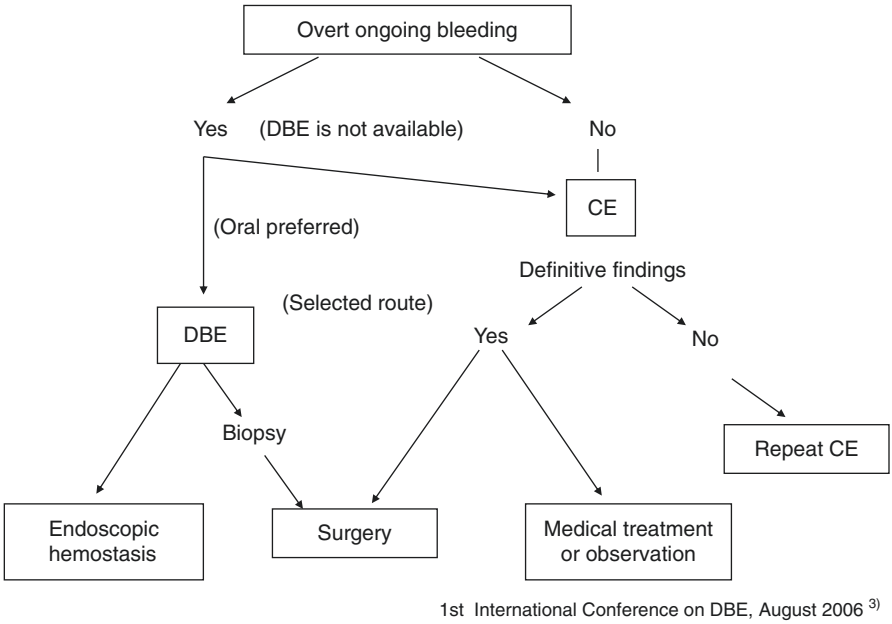


Fig. 20.1 Algorithm for small-bowel examination for OGIB

Table 20.1 Endoscopic classification of small intestinal vascular lesions (Yano-Yamamoto classification) [5]

Type	Lesion
Type 1a	Punctuate erythema (less than 1 mm) with or without oozing
Type 1b	Patchy erythema (a few mm) with or without oozing
Type 2a	Punctuate erythema (less than 1 mm) with pulsatile bleeding
Type 2b	Pulsatile red protrusion without surrounding venous dilatation
Type 3	Pulsatile red protrusion with surrounding venous dilatation
Type 4	Other lesions not classified into any of the above categories

are relatively large pulsating protrusions, require angiography or surgery. For type IV, which are large hemangiomas and other vascular lesions that are difficult to treat with endoscopic hemostasis, endoscopic tattooing, or clipping would be effective for creating landmarks for surgical treatment. As for small-bowel tumors, gastrointestinal stromal tumor (GIST) is often observed as the source of bleeding. In most cases, a GIST has ulceration and bleeding that is caused from a vascular lesion within the ulceration. APC or electronic coagulation is useful for temporary hemostasis. However, considering its potential for malignancy, surgical resection is needed for small bowel GIST to prevent re-bleeding, increase in size, and metastasis. Other tumors, such as adenomas, adenocarcinomas, malignant lymphomas, and carcinoid tumors, have the potential risk of bleeding. However, active bleeding from these lesions is not frequently seen when performing DBE.

In IBDs, small-bowel ulcerative lesions are most commonly observed endoscopically, and they have a potential risk of bleeding (Fig. 20.2). However, massive bleeding is infrequent in patients with IBDs. Patients with Crohn's disease sometimes have massive bleeding that requires transfusion. However, we usually cannot detect the bleeding point because of the widespread small-bowel lesions, even with BAE or CE. Therefore, angiography or surgery is required in such cases [5]. Thus, endoscopic small-bowel hemostasis is performed for the few cases in which the bleeding point can be detected with BAE (Fig. 20.3).

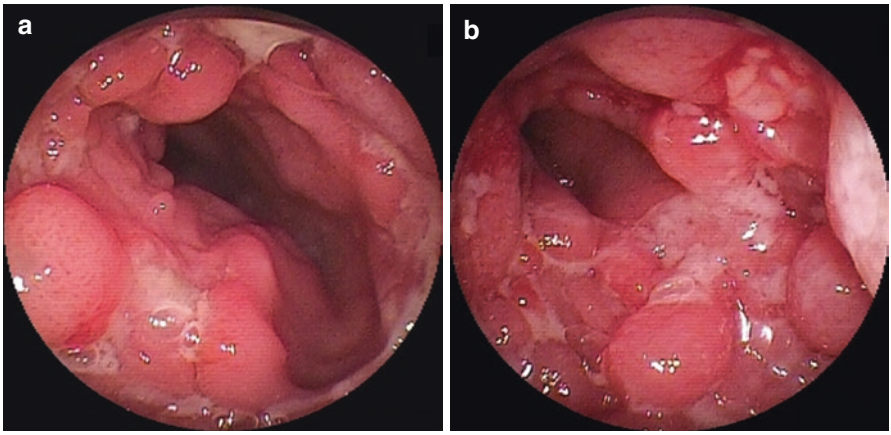


Fig. 20.2 Endoscopic findings of DBE show multiple open ulcers in the ileum (**a**, **b**)

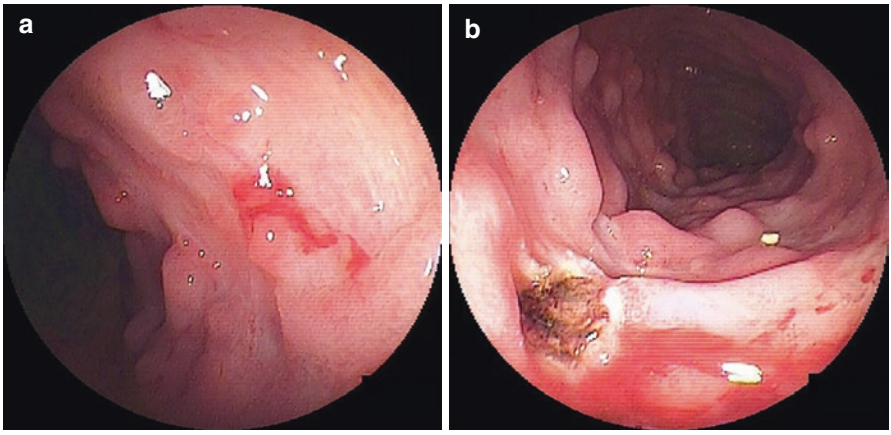


Fig. 20.3 A vessel with active bleeding is seen in the ileal longitudinal ulcer (**a**). Hemostasis using a heater probe is performed to the vessel (**b**). **a**, **b** Reprinted with permission from Hirai F, et al. Small-bowel bleeding in Crohn's disease (in Japanese). Stomach and Intestine 2010; 45: 379–387. Copyright 2009 by IGAKU-SHOIN Ltd

20.2.2 Endoscopic Mucosal Resection

Endoscopic mucosal resection (EMR) is indicated for small-bowel tumors, such as early cancers, adenomas, and other benign tumors. However, early cancers and adenomas are quite rare in the small bowel compared to the esophagus, stomach, and colon. In benign tumors, Peutz-Jeghers syndrome (PJS) usually shows multiple sessile polyps in the small intestine. These sessile polyps often cause small-bowel intussusception and require surgical intervention. When considering the benefit of preventing surgery, EMR is useful for the small-bowel polyps of PJS. Therefore, these polyps, which are large in some cases, are a good indication for EMR [6]. Since almost all small-bowel tumors of PJS are pedunculated polyps, EMR is not very difficult. However, careful snaring and cutting are important to avoid perforation because of the narrow working space in the small intestine.

In patients with IBDs, there are relatively rare cases that need EMR. Although IBD patients often have inflammatory polyps, EMR is indicated for lesions with obvious bleeding.

20.2.3 Endoscopic Balloon Dilation

Strictures of the gastrointestinal tract occur for various reasons, including inflammation, malignant tumors, and adhesions. They often cause obstructive symptoms or ileus. EBD for strictures of the esophagus, stomach, duodenum, and large intestine has been established as an effective and safe procedure [7–11]. However, EBD for strictures of the small intestine has been used only in those locations where colonoscopy or push enteroscopy can be inserted. BAE, which was recently used for small-bowel disorders, enables EBD to be performed even for deeply situated strictures of the small intestine. Endoscopic balloon dilation is indicated for small bowel tumors and inflammatory diseases such as Crohn's disease (CD), NSAID-induced enteropathy (Fig. 20.4), intestinal tuberculosis, and chronic nonspecific multiple ulcers of small intestine (Fig. 20.5). As for patients with IBDs, we consider that this procedure is a therapeutic modality that should be attempted before surgical therapy. In particular, small-bowel strictures of CD are a good indication for EBD because severe strictures of the small intestine are the major cause of surgery. When considering the relapsing nature of this disease, it is important to avoid frequent surgical therapy and short-bowel syndrome. The indication for EBD is symptomatic small-bowel stricture or a severe stricture through which an endoscope cannot be passed [7]. Basically, this endoscopic intervention is not indicated for small-bowel strictures with a deep ulcer, fistula, abscess, or severe deformity [7, 11].

We usually perform EBD using a DBE (EN-450 T5/W or EN-580 T, FUJI FILM Medical Co., Tokyo, Japan) and a 12–18 mm through-the-scope (TTS) balloon catheter (CRETM balloon catheter, Boston Scientific Co., Natick, MA, USA) under

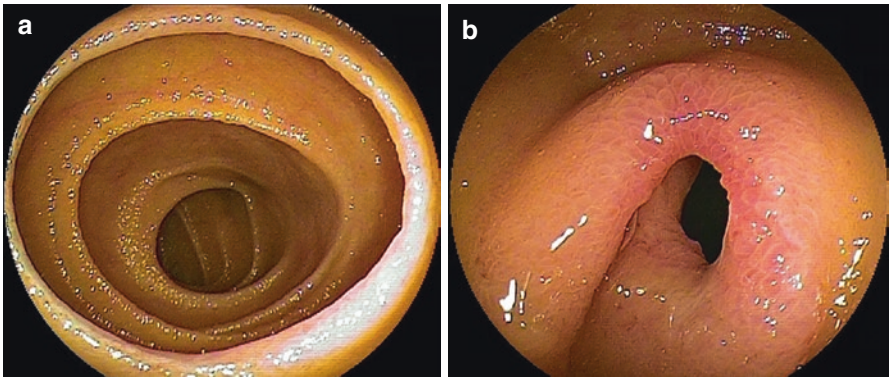


Fig. 20.4 Multiple circumferential ulcer scars along with Kerckring's fold are seen in the jejunum (**a**), and a jejunal stricture is observed (**b**)

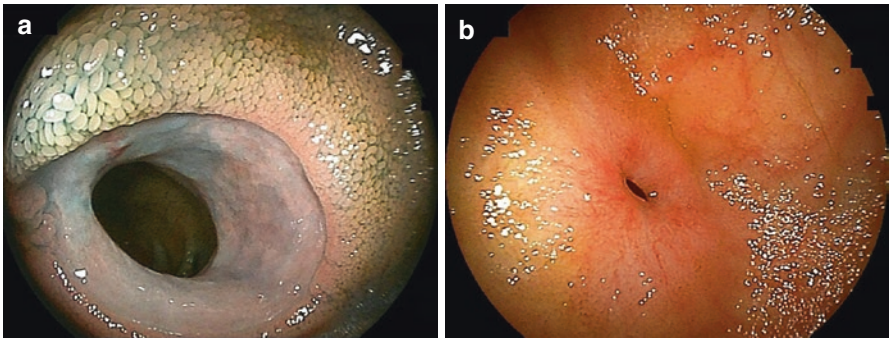


Fig. 20.5 This is a typical case with chronic non-specific multiple ulcers of the small intestine. A completely circumferential ulcer is seen in the upper ileum (**a**). It has developed to a severe stricture after total parenteral nutrition therapy (**b**)

X-ray observation. The inflating balloon pressure of 35–45 pounds per inch is maintained for 1–2 min. After EBD, we check the stricture site to determine whether there is any severe bleeding or perforation (Fig. 20.6).

Although there are not many reports regarding this procedure for patients with CD, the short-term success rates have been relatively high (80–100%, Table 20.2) [7–11]. Long-term outcomes have not been sufficiently analyzed, but one cohort study reported a high surgery-free rate [11]. However, the re-EBD rate was high in this report. EBD using BAE has the potential to improve the clinical course and quality of life (QOL) of CD patients with small intestinal strictures. It is necessary to prospectively observe a larger number of patients for a longer period to confirm the efficacy and safety of EBD. Currently, a nationwide, prospective, multi-center study of EBD for CD patients having small-bowel strictures is ongoing as the framework of a study project undertaken by the Study Group on Intractable Diseases, using Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan.

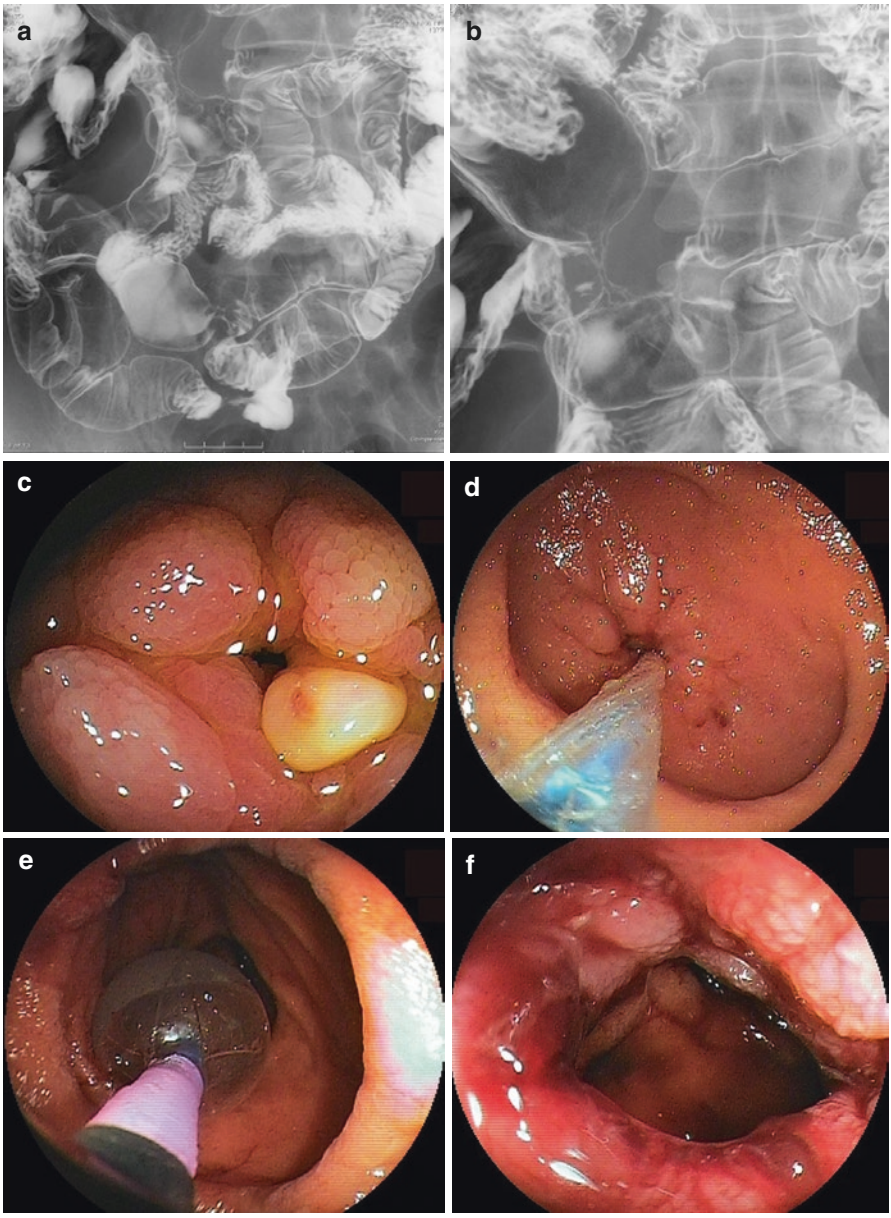


Fig. 20.6 X-ray findings show multiple ileal strictures (**a**). One of the strictures is severe with oral dilatation. (**b**). The scope cannot be passed through the severe ileal stricture that is seen on X-ray. (**c**). The balloon dilation catheter is inserted (**d**) and inflated (**e**) at the stricture site. The scope can be passed through the stricture after endoscopic balloon dilation (**f**)

Table 20.2 Efficacy and safety of endoscopic balloon dilation for small bowel strictures

Author, year, Ref.	Number	Technically successful (%)	Clinical efficacy (%)	Adverse events (%)	Observation time (months)
Fukumoto, et al., 2007 [7]	31 (23)[a]	N/A	74	0 (0)[b]	12
Ohymiya, et al., 2009 [8]	22 (16)	96	N/A	N/A	N/A
Despott, et al., 2009 [9]	11 (11)	73	73	9	21
Hirai, et al., 2010 [10]	25 (25)	72	72	8 (0)	11
Hirai, et al., 2014 [11]	65 (65)	80	80	9 (1.5)	42

[a]Number of patients with CD
[b]Percentage with perforation
N/A Not applicable

References

1. Yamamoto H, Kita H, Sunada K, Hayashi Y, Sato H, Yano T, Iwamoto M, Sekine Y, Miyata T, Kuno A, Ajibe H, Ido K, Sugano K. Clinical outcomes of double-balloon endoscopy for the diagnosis and treatment of small-intestinal diseases. Clin Gastroenterol Hepatol. 2004;2:1010–6.
2. Bourreille A, Ignjatovic A, Aabakken L, Loftus EV, Eliakim R, Pennazio M, Bouhnik Y, Seidman E, Keuchel M, Albert JG, et al. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. Endoscopy. 2009;41:618–37.
3. Sugano K, Marcon N. The first international workshop on double balloon endoscopy: a consensus meeting report. Gastrointest Endosc. 2007;66(Suppl):S7–S11.
4. Raju GS, Gerson L, Das A, et al. American Gastroenterological Association (AGA) institute technical review on obscure gastrointestinal bleeding. Gastroenterology. 2007;133:1697–717.
5. Yano T, Yamamoto H, Sunada K, et al. Endoscopic classification of vascular lesions of the small intestine (with videos). Gastrointest Endosc. 2008;67:169–72.
6. Ohmiya N, Nakamura M, Takenaka H, et al. Management of small-bowel polyps in Peutz-Jeghers syndrome by using enteroclysis, double-balloon enteroscopy, and videocapsule endoscopy. Gastrointest Endosc. 2010;72:1209–16.
7. Fukumoto A, Tanaka S, Yamamoto H, et al. Diagnosis and treatment of small-bowel stricture by double-balloon endoscopy. Gastrointest Endosc. 2007;66:S108–12.
8. Ohmiya N, Arakawa D, Nakamura M, et al. Small-bowel obstruction: diagnostic comparison between double-balloon endoscopy and fluoroscopic enteroclysis, and the outcome of enteroscopic treatment. Gastrointest Endosc. 2009;69:84–93.
9. Despott EJ, et al. Effective dilation of small-bowel strictures by double-balloon enteroscopy in patients with symptomatic Crohn's disease (with video). Gastrointest Endosc. 2009;70:1030–6.
10. Hirai F, Beppu T, Sou S, et al. Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. Dig Endosc. 2010;22:200–4.
11. Hirai F, Beppu T, Takatsu N, et al. Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease. Dig Endosc. 2014;26:545–51.

Chapter 21
Surveillance Colonoscopy

Katsuyoshi Matsuoka, Yasushi Iwao, and Takanori Kanai

Abstract Patients with long-standing ulcerative colitis (UC) have an increased risk of developing colorectal cancer (CRC). The risk of CRC is associated with disease duration and extent, and histological and endoscopic severity of inflammation. UC-associated CRC is often accompanied by dysplasia, which is a neoplastic lesion itself and is assumed to be pre-cancerous lesions. Patients with long-standing UC are recommended to undergo regular surveillance colonoscopy, which utilizes dysplasia as a marker of synchronous or metachronous development of CRC. Chromoendoscopy can increase the detection rate of dysplasia in surveillance colonoscopy, and is replacing the traditional step-biopsy method. Dysplasia is histologically categorized as high-grade (HGD) or low-grade dysplasia (LGD) and is endoscopically classified to visible or invisible lesions. Visible dysplasia with distinct border can be resected endoscopically, followed by close surveillance. In case of invisible dysplasia (detected by step biopsy), colectomy is recommended for patients with HGD. The management of invisible LGD is controversial.

Keywords Ulcerative colitis • Dysplasia • Surveillance • Colorectal cancer

K. Matsuoka (✉)
Department of Gastroenterology and Hepatology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan

Department of Gastroenterology and Hepatology, Tokyo Medical and Dental University, Tokyo, Japan
e-mail: matsuoka@fk2.so-net.ne.jp

Y. Iwao
Center for Preventive Medicine, Keio University School of Medicine, Tokyo, Japan

T. Kanai
Department of Gastroenterology and Hepatology, Keio University School of Medicine,, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_21

21.1 Ulcerative Colitis-Associated Colorectal Cancer

21.1.1 Risk of Developing Colorectal Cancer in Ulcerative Colitis

It is widely accepted that patients with long-standing ulcerative colitis (UC) have an increased risk of developing colorectal cancer (CRC). The risk of CRC in UC patients is influenced by the duration and extent of the disease. A meta-analysis showed that the cumulative incidence of CRC or dysplasia in UC patients is 2% at 10 years, 8% at 20 years, and 18% at 30 years after the onset of the disease [1]. The data from the St. Mark's Hospital surveillance program observed a similar trend; the cumulative incidence of CRC is 2.5% at 20 years, 7.6% at 30 years, and 10.8% at 40 years [2]. Patients with extensive disease have a higher risk of CRC than those with left-sided colitis. Patients with only proctitis have no increased risk of CRC.

Additional risk factors include severe histological inflammation [3], concomitant primary sclerosing cholangitis (PSC), and a family history of CRC. Endoscopic appearance is also associated with an increased risk of developing CRC or dysplasia. Rutter et al. showed that the presence of inflammatory polyps or stricture increases the risk [4].

The risk of colorectal neoplasms seems to be decreased over time, possibly due to the recent advance of the treatment of UC. A national cohort study from Denmark showed the overall relative risk for CRC in patients with UC decreased from 1.34 in the 1980s to 0.57 in the 2000s [5].

21.1.2 Dysplasia

Dysplasia, defined as unequivocal neoplastic epithelium, is often accompanied with UC-associated CRC. Dysplasia is considered as a pre-cancerous lesion, and UC-associated CRC is assumed to arise from it. Dysplasia is histologically categorized as low-grade dysplasia (LGD) or high-grade (HGD) [6]. In addition to its malignant potential, dysplasia is regarded as a marker of concomitant or future development of CRC. Dysplasia-associated lesion or mass (DALM), where dysplasia forms an endoscopically raised lesion, has a higher risk of CRC [7].

21.2 Surveillance

21.2.1 Surveillance Program

Surveillance for CRC is recommended for patients with long-standing UC in order to detect neoplasms at an early stage. Surveillance also aims to detect dysplasia, as dysplasia is a neoplastic lesion itself and also a marker for synchronous or

metachronous development of CRC. Most guidelines recommend UC patients to undergo surveillance colonoscopy every 1–2 years beginning 7–10 years after the onset of disease symptoms. Surveillance colonoscopy should be performed when the disease is in remission if possible.

The optimal surveillance intervals have not yet been determined. The guidelines of the British Society of Gastroenterology recommend determining the surveillance intervals considering the risk factors of each patient such as disease extent, severity of endoscopic/histological inflammation, presence of post-inflammatory polyps or stricture, family history of CRC, and concomitant PSC [8]. It is important to stratify the risks to increase the cost-effectiveness of surveillance.

Although the effect of surveillance colonoscopy on mortality has not yet been proven by randomized controlled studies, retrospective cohort studies showed that CRC can be found at an earlier stage in patients who undergo surveillance [9, 10], leading to reduced mortality from CRC in UC patients.

21.2.2 Endoscopic Features of Dysplasia

For successful surveillance, it is important to understand the endoscopic features of dysplasia. It is endoscopically classified to visible or invisible lesions (Table 21.1). Visible dysplasia is further categorized into polypoid or nonpolypoid lesions (Fig. 21.1). The advancement of endoscopic technology has enabled dysplastic lesions to be more clearly recognizable, with a distinct border, and the term "DALM" has recently become less used.

21.2.3 Step Biopsy

Dysplastic lesions may be overlooked because those in UC patients are often flat. To find such flat dysplasia, step biopsy is applied to surveillance colonoscopy. A general procedure for step biopsy is that four biopsy specimens are taken in every 10 cm from the cecum to the rectum, requiring at least 32 biopsy specimens in one

Table 21.1 Endoscopic classification of dysplasia [11]

Visible dysplasia
Polypoid
Pedunculated
Sessile
Nonpolypoid
Superficial elevated
Flat
Depressed
Invisible dysplasia

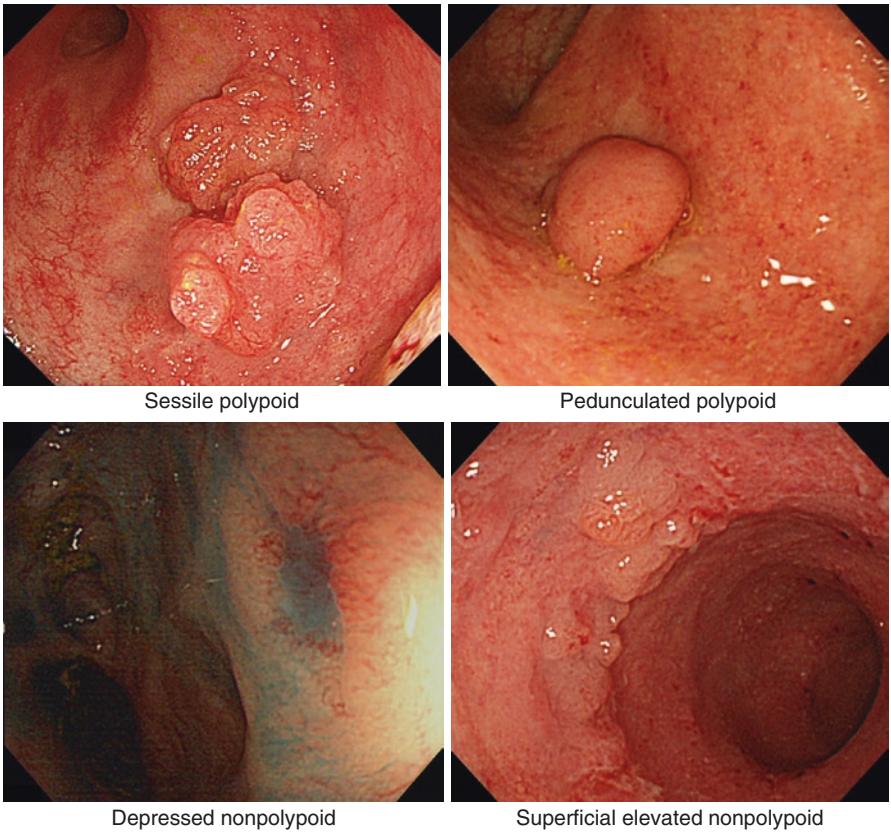


Fig. 21.1 Endoscopic features of dysplasia

surveillance colonoscopy. Despite this time-consuming procedure, the detection rate of neoplastic lesions is very low [12]. A recent randomized controlled study demonstrated the detection rates of neoplasia are comparable between the step biopsy and targeted biopsy methods [13]. Although step biopsy is still recommended in most of the guidelines for surveillance in patients with UC, as discussed below, target biopsy will replace step biopsy, along with the advancement of new endoscopic technology such as high-definition endoscopy and chromoendoscopy.

21.2.4 Chromoendoscopy

Chromoendoscopy with dyes such as methylene blue or indigo carmine can increase the detection rate of dysplasia in surveillance compared with conventional white-light colonoscopy. Kiesslich et al. demonstrated that chromoendoscopy with methylene blue detected three times more dysplastic lesions than conventional white-light colonoscopy

[14]. A meta-analysis of seven studies comparing chromoendoscopy with white-light colonoscopy reported that the relative risk of detection of dysplasia with chromoendoscopy is 1.8 [95% CI, 1.2–2.6] compared with white-light colonoscopy, and chromoendoscopy increases the absolute risk by 6% [95% CI, 3–9%] [11]. Surveillance with chromoendoscopy has an advantage in terms of cost, because it needs fewer biopsy specimens than white-light colonoscopy. Thus, chromoendoscopy with target biopsy becomes the recommended procedure for surveillance in recent guidelines [11]. Step biopsy is recommended only if chromoendoscopy is not available.

The usefulness of narrow-band imaging in the detection of UC-associated CRC/dysplasia is controversial [15]. Other new imaging techniques such as endomicroscopy and confocal endoscopy were also examined but have not yet been implemented in clinical practice.

21.2.5 Magnifying Endoscopy

Pit pattern diagnosis with magnifying endoscopy is implemented in the diagnosis of sporadic CRC/adenoma. This diagnostic method is useful to differentiate neoplastic lesions from non-neoplastic lesions; Types I and II are non-neoplastic lesions and Types III, IV, and V are neoplastic lesions. Data on the usefulness of pit pattern diagnosis in the diagnosis of UC-associated dysplasia is limited. Kiesslich et al. reported that, in UC patients, 30 out of 32 dysplastic lesions (93.8%) showed Types III or IV and 82 (95.3%) out of 86 inflammatory hyperplastic lesions showed Type I or II [14]. In contrast, a Japanese group reported that specificity of the pit pattern diagnosis in UC-associated dysplasia was 100%; however, neoplastic patterns (Type III-V) were also observed in non-dysplastic areas, because inflamed mucosa could show various surface patterns [16], resulting in a low sensitivity of 57%. The diagnostic value of pit pattern diagnosis in UC-associated neoplastic lesions remains undetermined.

21.2.6 Management of Dysplasia

The management of dysplasia differs based on whether the lesion is endoscopically visible or not. If the dysplastic lesion is visible with a distinct border, and no dysplasia is found in other areas in colitic mucosa, it can be removed endoscopically. A recent meta-analysis of ten studies involving 376 patients in whom polypoid dysplasia was resected reported that the incidence of CRC was 5.3 cases/1,000 patient-years [95% CI, 2.7–10.1] during follow-up [17]. This risk of CRC can be acceptable for both patients and physicians, considering the risks of colectomy. After confirming complete resection of the lesion, the patient should be on close surveillance.

Detecting HGD in flat mucosa in surveillance colonoscopy, total colectomy must be considered, because the rate of concurrent CRC ranges from 47 to 67% in patients with flat HGD [11]. Colectomy may be considered in patients with flat LGD. It has

been reported that advanced neoplasia was found in 18 patients (16%) out of 113 patients with flat LGD after a median follow-up of 48 months [18]. A meta-analysis involving 477 patients with flat LGD showed the rate concurrent CRC was 22% and that of progression to any advanced lesion was 14.6% [19]. When colectomy is avoided, frequent surveillance at the interval of 3–6 months is recommended for patients with flat LGD.

21.3 Sporadic Adenoma in Patients with Ulcerative Colitis

Sporadic adenoma may coincidentally develop in patients with UC. The diagnosis is challenging if the lesion is inside colitic areas, because it is difficult to distinguish UC-associated dysplastic polypoid lesions from sporadic adenoma. UC-associated dysplastic polypoid lesions that resemble endoscopically and histologically sporadic adenoma are referred as adenoma-like DALM. Engelsgjerd et al. followed 24 UC patients with endoscopically resected adenoma-like DALM. Fourteen patients (58%) developed further adenoma-like DALM, but only one patient (4%) developed LGD during the mean observational period of 42.4 months, suggesting a benign clinical course of adenoma-like DALM [20].

21.4 Case Presentation

21.4.1 Case 1. Low-Grade Dysplasia in Flat Mucosa

This patient was a 38-year-old female with extensive colitis who had a 15-year history of UC. Surveillance colonoscopy revealed a reddish area in the rectum (Fig. 21.2a). Indigo carmine dye spray showed a superficial elevated lesion with a distinct border line (Fig. 21.2b). A histological examination of biopsy specimens taken from this lesion demonstrated LGD with positive p53 staining (Fig. 21.2c, d).

21.4.2 Case 2. Dysplasia-Associated Lesion or Mass

This patient was a 51-year-old female with extensive colitis who had a 19-year history of UC. Surveillance colonoscopy revealed a polypoid lesion with villous mucosa in the rectum (Fig. 21.3a). The lesion could be more clearly observed with indigo carmine dye spray (Fig. 21.3b). Magnifying endoscopy showed the surface pattern of villous Type IV (Fig. 21.3c). Histological examination of biopsy specimens taken from this lesion demonstrated HGD (Fig. 21.3d).

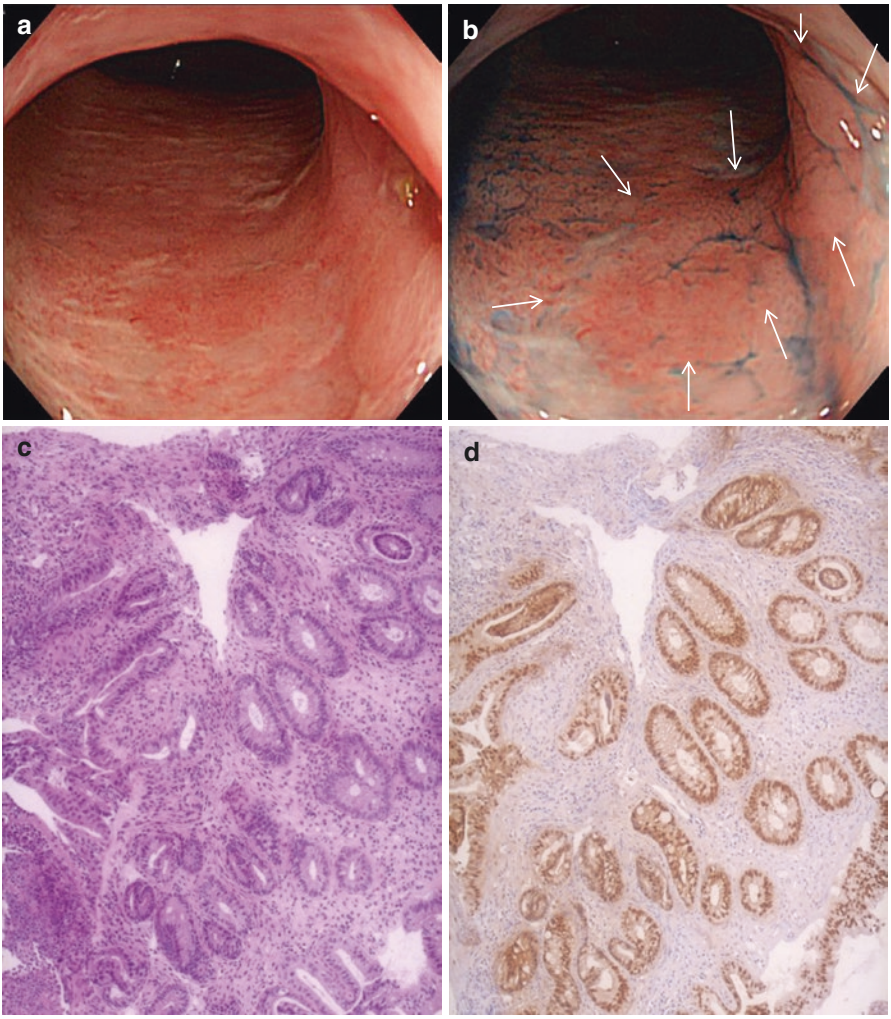


Fig. 21.2 Low-grade dysplasia in flat mucosa. (**a**) Colonoscopy revealed a reddish area in the rectum. (**b**) Indigo carmine dye spray showed a superficial elevated lesion with a distinct border line (*white arrows*). (**c**) Hematoxylin & eosin staining of biopsy specimens revealed low-grade dysplasia. (**d**) Immunohistochemical staining of p53 was diffusely positive

21.4.3 Case 3 Multiple Dysplasia

This patient was a 40-year-old male with left-sided colitis who had an 18-year history of UC. Multiple lesions were detected on surveillance colonoscopy: a pedunculated lesion and a surface elevated lesion were in the sigmoid colon (Fig. 21.4a), a tiny surface elevated lesion also in the sigmoid colon (Fig. 21.4b), and a villous lesion (Fig. 21.4c) and a superficially elevated lesion (Fig. 21.4d) were in the rectum. The first three lesions showed HGD, and the last two lesions showed LGD.

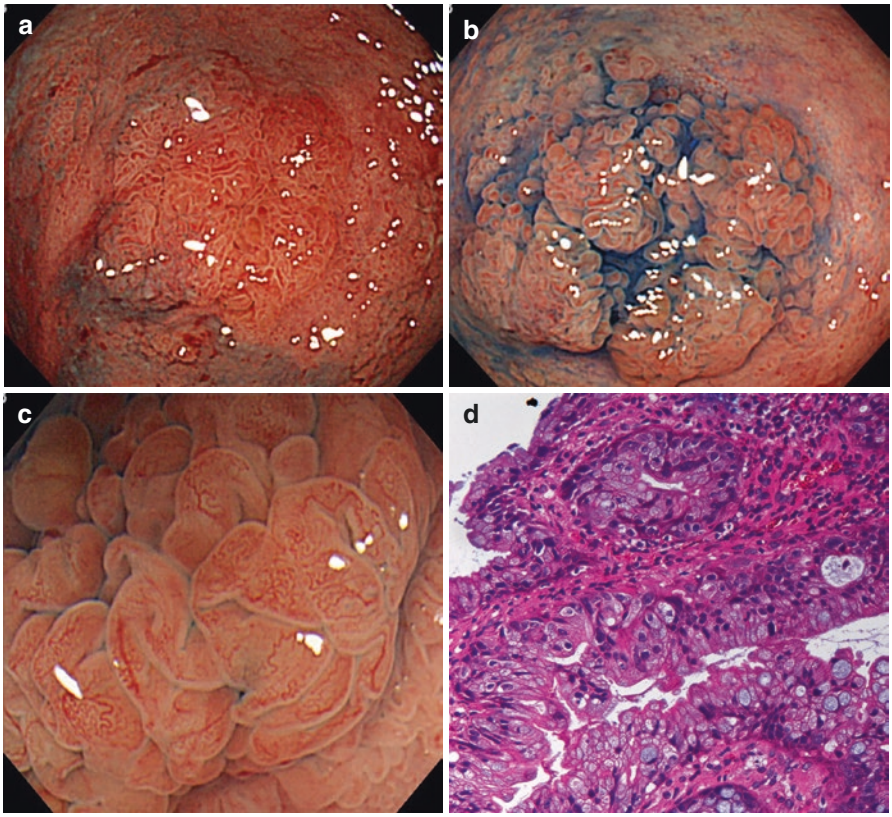


Fig. 21.3 Dysplasia associated lesion or mass. (**a**) Colonoscopy revealed a polypoid lesion with villous mucosa in the rectum. (**b**) Indigo carmine dye spray showed a villous tumor. (**c**) Magnifying endoscopy showed the surface pattern of villous Type IV. (**d**) Histological examination of biopsy specimens demonstrated high-grade dysplasia

21.4.4 Case 4 Sporadic Adenoma

This patient was a 64-year-old male, who had been diagnosed as extensive UC a decade earlier. He had been well with mesalamine. He underwent surveillance colonoscopy, which revealed a flat elevated lesion in the ascending colon (Fig. 21.5a, b). The lesion was well demarcated from the surrounding mucosa. A biopsy specimen taken from the lesion revealed a typical feature of tubular adenoma with severe atypia (Fig. 21.5c). Biopsy specimens taken from either surrounding mucosa or other parts of the colon showed no dysplasia. This lesion was, therefore, diagnosed as a sporadic adenoma and removed with endoscopic submucosal dissection (Fig. 21.5d). The resected specimen revealed no dysplastic change in the surrounding mucosa, confirming the diagnosis of sporadic adenoma.

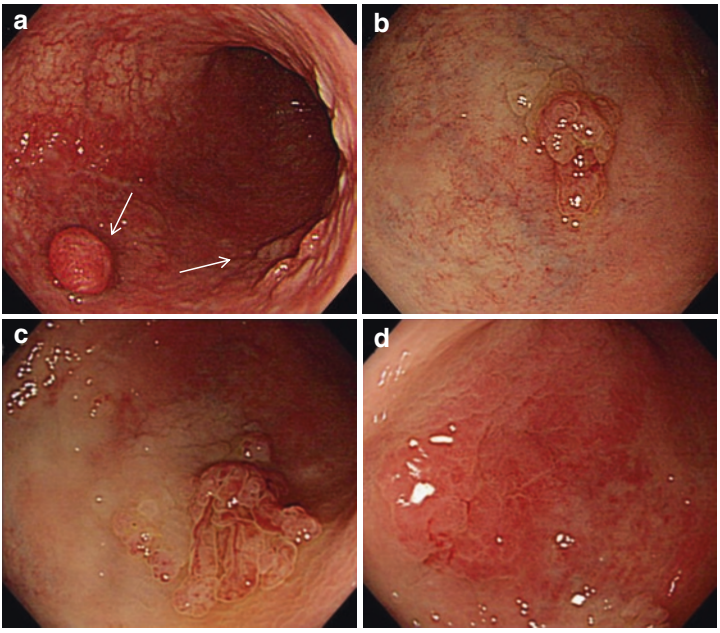


Fig. 21.4 Multiple dysplasia. (**a**) Two lesions were detected on colonoscopy (*white arrows*). (**b**) A tiny surface-elevated lesion was found in the sigmoid colon. (**c**) A villous lesion was found in the rectum. (**d**) A superficially elevated lesion was found in the rectum

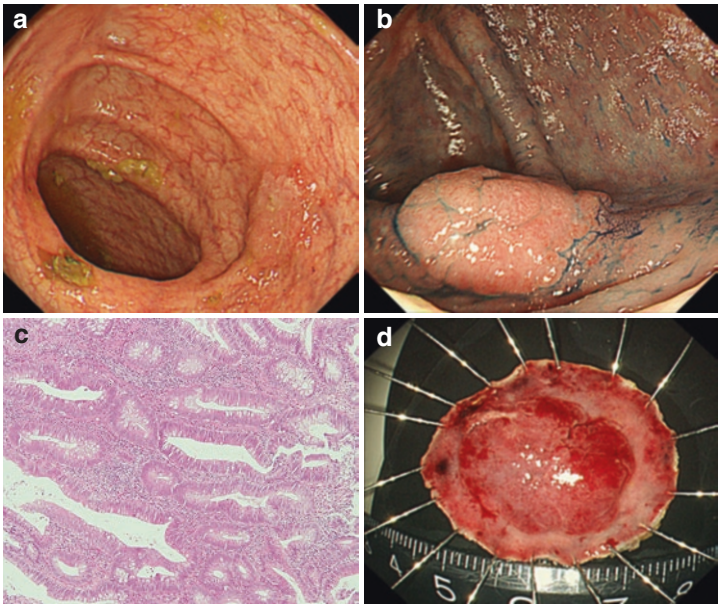


Fig. 21.5 Sporadic adenoma in a patient with ulcerative colitis. (**a**) Colonoscopy revealed a flat elevated lesion in the ascending colon. (**b**) Indigo carmine dye spray revealed a lateral-spreading tumor. (**c**) Histological examination of biopsy specimens demonstrated a typical feature of tubular adenoma with severe atypia. (**d**) The lesion was completely removed with endoscopic submucosal dissection

References

1. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48(4):526–35.
2. Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology. 2006;130(4):1030–8. doi:10.1053/j.gastro.2005.12.035.
3. Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, Williams C, Price A, Talbot I, Forbes A. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126(2):451–9.
4. Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Cancer surveillance in longstanding ulcerative colitis: endoscopic appearances help predict cancer risk. Gut. 2004;53(12):1813–6. doi:10.1136/gut.2003.038505.
5. Jess T, Simonsen J, Jorgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology. 2012;143(2):375–381.e371. quiz e313–e374 doi:10.1053/j.gastro.2012.04.016.
6. Riddell RH, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, Ahren C, Correa P, Hamilton SR, Morson BC, et al. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. Hum Pathol. 1983;14(11):931–68.
7. Blackstone MO, Riddell RH, Rogers BH, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. Gastroenterology. 1981;80(2):366–74.
8. Cairns SR, Scholefield JH, Steele RJ, Dunlop MG, Thomas HJ, Evans GD, Eaden JA, Rutter MD, Atkin WP, Saunders BP, Lucassen A, Jenkins P, Fairclough PD, Woodhouse CR. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010;59(5):666–89. doi:10.1136/gut.2009.179804.
9. Choi CH, Rutter MD, Askari A, Lee GH, Warusavitarne J, Moorghen M, Thomas-Gibson S, Saunders BP, Graham TA, Hart AL. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: an updated overview. Am J Gastroenterol. 2015;110(7):1022–34. doi:10.1038/ajg.2015.65.
10. Choi PM, Nugent FW, Schoetz Jr DJ, Silverman ML, Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. Gastroenterology. 1993;105(2):418–24.
11. Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology. 2015;148(3):639–51. e628 doi:10.1053/j.gastro.2015.01.031.
12. van den Broek FJ, Stokkers PC, Reitsma JB, Boltjes RP, Ponsioen CY, Fockens P, Dekker E. Random biopsies taken during colonoscopic surveillance of patients with longstanding ulcerative colitis: low yield and absence of clinical consequences. Am J Gastroenterol. 2014;109(5):715–22. doi:10.1038/ajg.2011.93.
13. Watanabe T, Ajioka Y, Mitsuyama K, Watanabe K, Hanai H, Nakase H, Kunisaki R, Matsuda K, Iwakiri R, Hida N, Tanaka S, Takeuchi Y, Ohtsuka K, Murakami K, Kobayashi K, Iwao Y, Nagahori M, Iizuka B, Hata K, Igarashi M, Hirata I, Kudo SE, Matsumoto T, Ueno F, Watanabe G, Ikegami M, Ito Y, Oba K, Inoue E, Tomotsugu N, Takebayashi T, Sugihara K, Suzuki Y, Watanabe M, Hibi T. Comparison of targeted vs random biopsies for surveillance of ulcerative colitis-associated colorectal cancer. Gastroenterology 2016;151(6):1122–1130. doi: 10.1053/j.gastro.2016.08.002.
14. Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial

neoplasia and colon cancer in ulcerative colitis. Gastroenterology. 2003;124(4):880–8. doi:10.1053/gast.2003.50146.
15. Dekker E, van den Broek FJ, Reitsma JB, Hardwick JC, Offerhaus GJ, van Deventer SJ, Hommes DW, Fockens P. Narrow-band imaging compared with conventional colonoscopy for the detection of dysplasia in patients with longstanding ulcerative colitis. Endoscopy 2007;39(3):216–21. doi:10.1055/s-2007- 966214.
16. Hata K, Watanabe T, Motoi T, Nagawa H. Pitfalls of pit pattern diagnosis in ulcerative colitis-associated dysplasia. Gastroenterology. 2004;126(1):374–6.
17. Wanders LK, Dekker E, Pullens B, Bassett P, Travis SP, East JE. Cancer risk after resection of polypoid dysplasia in patients with longstanding ulcerative colitis: a meta-analysis. Clin Gastroenterol Hepatol. 2014;12(5):756–64. doi:10.1016/j.cgh.2013.07.024.
18. van Schaik FD, ten Kate FJ, Offerhaus GJ, Schipper ME, Vleggaar FP, van der Woude CJ, Stokkers PC, de Jong DJ, Hommes DW, van Bodegraven AA, Siersema PD, Oldenburg B. Misclassification of dysplasia in patients with inflammatory bowel disease: consequences for progression rates to advanced neoplasia. Inflamm Bowel Dis. 2011;17(5):1108–16. doi:10.1002/ibd.21467.
19. Thomas T, Abrams KA, Robinson RJ, Mayberry JF. Meta-analysis: cancer risk of low-grade dysplasia in chronic ulcerative colitis. Aliment Pharmacol Ther. 2007;25(6):657–68. doi:10.1111/j.1365-2036.2007.03241.x.
20. Engelsgjerd M, Farraye FA, Odze RD. Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis. Gastroenterology. 1999;117(6):1288–94. discussion 1488–1291

Chapter 22
Surveillance Colonoscopy (Cases of Small Intestinal Cancers in Crohn's Disease, Cases of Anal Cancers in Crohn's Disease)

Motoi Uchino and Hiroki Ikeuchi

Abstract It has recently been recognized that long-standing Crohn's disease (CD) is associated with an increased risk of carcinogenesis. Three types of gastrointestinal carcinomas occur more frequently in patients with CD than in the general population: cancers arising from small-bowel lesions, from colorectal lesions, and from peri-anal lesions, which include both stricturing and fistulizing lesions. However, cancer surveillance for CD has not yet been established, especially for small-bowel and peri-anal lesions. The difficulties of cancer diagnosis are illustrated by two case presentations. Case 1 involved a 16-year ileal stricture in a patient with CD who was admitted for bowel obstruction. He was diagnosed postoperatively as having poorly differentiated adenocarcinoma with peritoneal dissemination. Case 2 involved a 33-year history of an anal lesion with stricture in a CD patient who was diagnosed as having advanced as well as differentiated adenocarcinoma at the anal canal. Prior examinations every 3 months within 6 months could not detect the cancer. Cancer associated with Crohn's lesions seems to be difficult to diagnose early. Although the diagnostic strategy remains unclear, carcinogenesis needs to be considered.

Keywords Crohn's disease • Colitis-associated cancer • Small intestinal cancer • Peri-anal cancer

22.1 Introduction

It has recently been recognized that long-standing Crohn's disease (CD) lesions are associated with an increased risk of carcinogenesis, similar to ulcerative colitis [1, 2]. Three types of gastrointestinal carcinomas occur more frequently in patients with CD

M. Uchino (✉) • H. Ikeuchi
Department of Inflammatory Bowel Disease, Hyogo College of Medicine,
1-1 Mukogawa-Cho, Nishinomiya, Hyogo 663-8501, Japan
e-mail: uchino2s@hyo-med.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_22

than in the general population: cancer arising from small-bowel lesions, from colorectal lesions, and from peri-anal lesions, which include both stricturing and fistulizing lesions [2–6]. However, the locations of cancers differ geographically. When considering geographic variations, the risk of colorectal cancer (CRC) associated with CD is significantly higher in North America and the United Kingdom than in Scandinavian countries [6]. Stahl et al. found in their series that only 17% ($n = 4$) of cancers in CD patients were located in the rectum, which was much lower than in sporadic cancer (38%) [7]. Furthermore, 59% ($n = 14$) were located in the ascending and transverse colon in CD patients, which was significantly higher than in sporadic cancer (28%). On the other hand, Mizushima et al. reported that 34 of 44 CRCs (77.3%) in Japanese patients with CD arose in the sigmoid colon, rectum, and anal canal/fistula [8]. There may be genetic and environmental factors associated with developing CRC in patients with CD.

Although small-bowel cancer (SBC) occurring in combination with CD is not as common as CRC, a strong association between CD and SBC has been suggested. In the recent large, prospective, cohort study for SBC in CD [9], five SBCs were found in 8222 patients with small-bowel CD during a median 35 months of follow-up. The incidence rates of SBC were 0.235 per 1000 patient-years (95% confidence interval [95%CI], 0.076–0.547) among patients with small-bowel CD and 0.464 per 1000 patient-years (95% CI, 0.127–1.190) among those with small-bowel CD for 8 years. This accounted for approximately 30% of the risk of CRC in patients with CD of the colon.

22.2 Diagnosis

In the diagnosis of cancer with CD regardless of location, it is generally difficult to detect the disease at an early stage. Most long-standing CD lesions are complicated with strictures or penetrating lesions. Contrast examinations with X-ray images are similar between CD lesions and cancer. Moreover, endoscopic examinations with biopsy are generally difficult due to intestinal or anal strictures. In addition, whether diagnostic biopsy from all existing CD lesions should be performed to detect cancer should be performed at each examination remains unclear. In fact, cancer surveillance programs and proper predictive factors for cancer in patients with CD still remain unclear.

Making an early definitive diagnosis of combined cancer was difficult before surgery, especially in SBC and peri-anal cancer (PAC), and the definitive diagnosis was often obtained based on an intraoperative or postoperative pathological diagnosis. Palascak-Juif et al. reported that SBC was difficult to diagnose and was diagnosed preoperatively in only one of 20 patients who had CD, as compared with 22 of 40 patients who had sporadic adenocarcinoma [10]. In SBC, it is hard to reach small intestinal lesions, except those at the terminal ileum, by endoscopic examination.

With respect to PAC, severe chronic complicated perianal disease in CD patients seems to be associated with an increased risk of cancer in the lower rectum and anal

canal. In most cases, it concerns a colloid carcinoma [11]. It is probable that chronic irritation at either end of a fistula can trigger the degeneration of scar tissue into cancer. The diagnosis is also difficult, due to lack of specificity of symptoms and signs to distinguish cancer from other anal lesions, and the diagnosis is often delayed, resulting in a poor prognosis.

22.3 Case Presentation 1

22.3.1 Small-Bowel Cancer in Crohn's Disease

A male developed diarrhea at the age of 18 years and was diagnosed with stricturing CD at the ileum. He had been treated with oral 5-ASA and an elemental diet. At the age of 34 years, he was admitted due to bowel obstruction. Figure 22.1 shows the findings of an examination with contrast material via a long tube. There were multiple severe strictures at the short segment near the terminal ileum with the shell sign. Abdominal CT examination showed wall thickening of the ileum at the same location (Fig. 22.1) with obvious lymph node swelling in the mesentery, but no ascites, abscess, fistula, or lesion suspicious of malignancy was found (Fig. 22.2). The findings of the ileum distal to the obstruction via total colonoscopy are shown in Fig. 22.3. A severe stricture at the ileum through which the scope could not pass

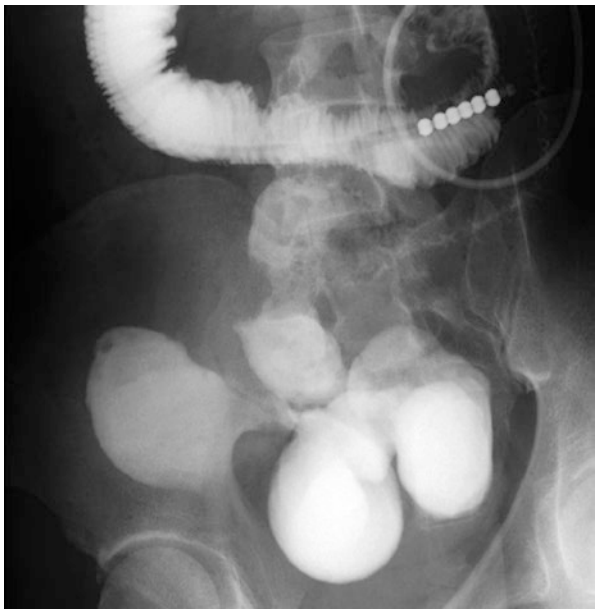


Fig. 22.1 Preoperative small intestinal examination with contrast material via a long tube. Multiple strictures with intestinal dilation as shell signs are found at the ileum

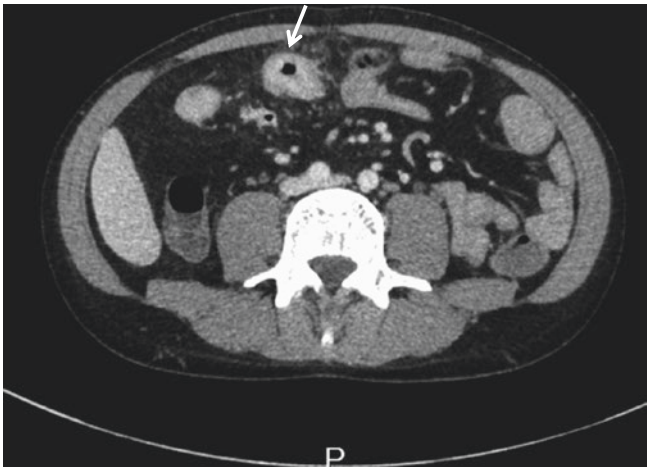


Fig. 22.2 Findings of preoperative enhanced-abdominal CT scan. The *white arrow* indicates the wall thickening of the ileum with lymph node swelling at the mesentery. Ascites, an abscess, or a fistula is not detected. No evidence of suspected malignancy is seen

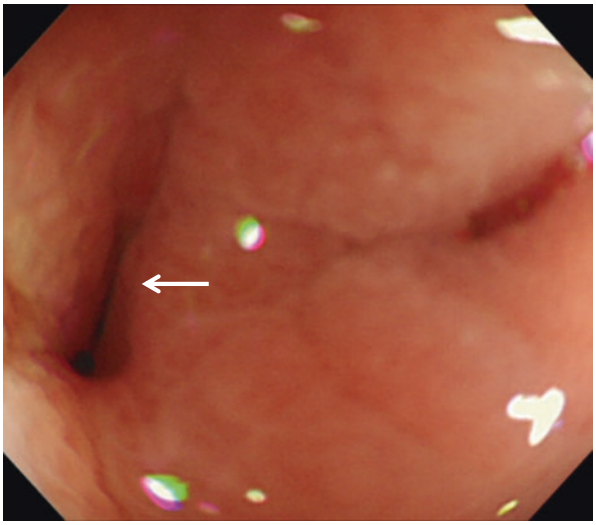


Fig. 22.3 Preoperative endoscopic findings at the ileum distal from the obstruction via total colonoscopy. A severe stricture through which the colonoscope cannot pass is found at the ileum. Colonoscopy could not reach the proximal CD lesions. The *white arrow* shows the orifice of the small intestinal lumen

was detected. Histological findings of the biopsy specimen taken at colonoscopy at the end of the stricture showed no evidence or suspicion of malignancy. Surgery was performed to remove the stricturing segment. During the laparotomy, multiple nodes were found in the peritoneal cavity, which led to a diagnosis of peritoneal dissemination of a poorly differentiated adenocarcinoma. In the resected specimen,

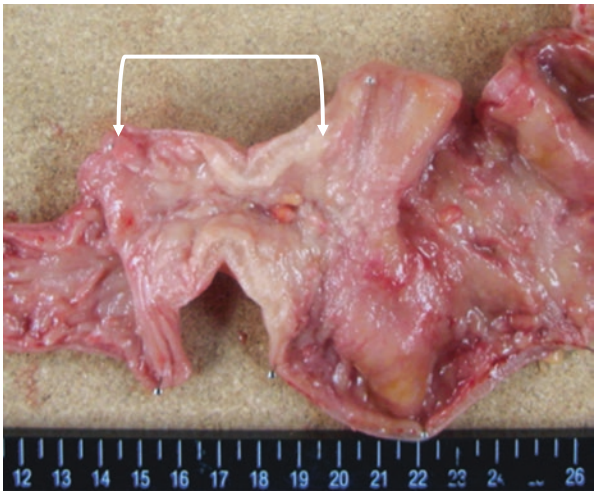


Fig. 22.4 Resected specimen of small-bowel cancer in a patient with CD. Thickened wall and ulceration with scar formation are found at the ileum. There are no findings causing suspicion of cancer. Cancer cells could be detected in most of this stricture lesion on histological examination, although that was invisible grossly, and no distinct border was evident. The *white bracket with arrows* shows the cancer lesion

cancer invasion was observed over the external serosa, although the cancer lesions could not be recognized clearly because they were similar to inflamed and thick-walled CD lesions (Fig. 22.4). The patient died of cancer cachexia 4 months after surgery, although chemotherapy was performed.

22.4 Case Presentation-2

22.4.1 Peri-Anal Cancer in Crohn's Disease

A male developed diarrhea at the age of 22 years and was diagnosed with stricturing CD with ileo-colic behavior. He was surgically treated once at the age of 22 years during his history of CD, which included ileo-cecal resection. He had an anal stricture without a fistula from the initial onset of CD. He had been treated with an elemental diet and oral 5-ASA administration. During outpatient observation, carcinoembryonic antigen (CEA) levels increased gradually above the normal limit (CEA 7.8 ng/ml, normal range <5 ng/ml) at the age of 55 years. Surveillance colonoscopy could not detect any lesions that were malignant or suspicious of malignancy. Subsequently, repeated examinations with colonoscopy were performed in every quarter, because CEA values continued to increase continuously. The initial findings on colonoscopy of the anal canal are shown in Fig. 22.5 (CEA 9.3 ng/ml). Findings of repeated colonoscopies after 6 months are shown in Fig. 22.6 (CEA 12.2 ng/ml). Adenocarcinoma was detected by histological examinations in biopsy

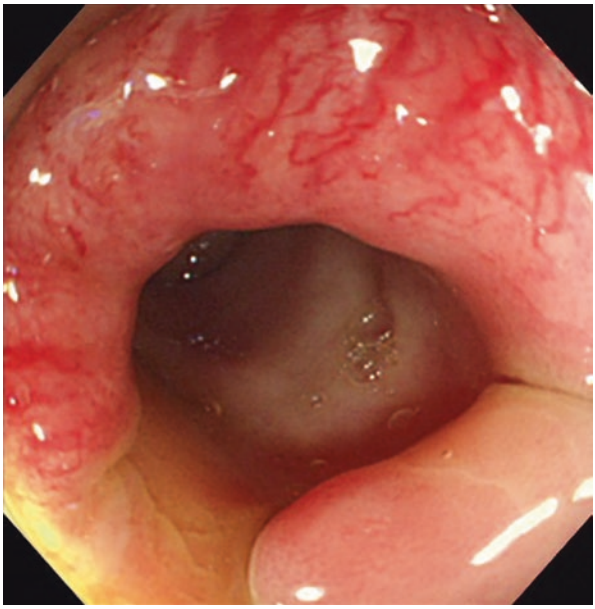


Fig. 22.5 Findings of colonoscopy at the anal canal stricture 6 months prior to the diagnosis of cancer. Although there is slightly irregularity at the transitional zone, no findings causing suspicion of cancer or ulceration of Crohn's disease are seen

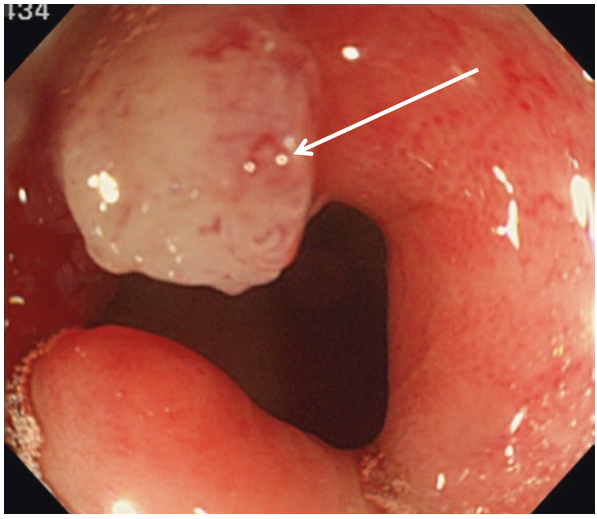


Fig. 22.6 Findings of colonoscopy at the anal canal stricture at the time of diagnosis of cancer. A white elevated cancer lesion with a distinct vascular pattern and irregularity is seen (*arrow*)

specimens only at the last examination. During these follow-up periods, neither pelvic magnetic resonance imaging (MRI) nor positron emission tomography (PET) could detect this PAC. He was surgically treated with abdominoperineal resection and was diagnosed with well-differentiated adenocarcinoma with a mucinous component invading the muscularis propria. He needed additional chemoradiotherapy for local recurrence over 25 months after surgery.

22.5 Recent Advances in Diagnostic Examinations

Unfortunately, there is no useful tool that diagnoses or predicts cancer in CD patients at present. Therefore, diagnosis can only be done with a combination of imaging modalities. The presence of a complex fistula, an associated stricture, and perineal pain prevent a thorough examination of the anus and perineal areas, thus making diagnosis of a concomitant carcinoma difficult. Devon et al. reported that 14 patients with cancer of the anus all had multiple imaging studies, including MRI, CT, and endorectal ultrasound, but none of these studies was diagnostic of carcinoma [12]. The diagnosis of cancer was made preoperatively in ten of 14 patients, usually after multiple biopsies. In four patients, despite multiple tissue biopsies, the diagnosis was made intra-operatively ($n = 2$) or postoperatively ($n = 2$) [12].

There are no formal guidelines for screening and surveillance of cancers associated with CD in the lower rectum and perianal regions. Friedman reported that if the endoscopist is unable to pass the stricture and perform surveillance with a standard pediatric endoscope, a barium enema or CT colonography should be considered to evaluate the proximal colon, with possible referral to an expert center [13].

For anorectal cancer, pelvic MRI is the best method for examining cancer localization and invasion, as well as its positional relationship with surrounding organs. Since an anal fistula carcinoma related to mucinous cancer frequently forms mucus retention, multilocular cyst-like findings are frequently observed on T2-weighted MRI images. However, early detection of cancer is usually difficult in most cases.

Some recent reports have indicated the potential of PET to assess CD activity [14]. On the other hand, there is no report of the potential of PET to assess CD-associated malignant tumors. In our study, we performed PET in four patients prior to surgery; two were positive and two were negative. Based on our limited experience, the accuracy rate of PET is not high, possibly because of the high rate of mucinous cell type carcinoma in CD-associated cancer. In addition, Whiteford et al. reported that the sensitivity of PET for detecting mucinous carcinoma was lower than that for non-mucinous cancer [15].

Severe chronic complicated perianal disease in CD patients seems to be associated with an increased risk for cancer in the lower rectum and anal canal. Laurent et al. noted that a high degree of suspicion for carcinoma must be considered during a rectal examination under anesthesia, with biopsy, curettage, or brushing of the fistulous tract recommended [16].

In conclusion, proper, early diagnosis of cancer in CD is difficult, especially in SBC and PAC. Cancer risk is high in CD; although the incidence may not be very high today, it will increase in the future. Although a proper evaluation and surveillance strategy needs to be established in the future, we should always consider carcinogenesis associated with CD lesions, even in patients with no complaints during conservative treatment.

References

1. Ullman TA. Dysplasia and colorectal cancer in Crohn's disease. J Clin Gastroenterol. 2003;36:75–8.
2. Sjödahl RI, Myrelid P, Söderholm JD. Anal and rectal cancer in Crohn's disease. Color Dis. 2003;5:490–5.
3. Jess T, Gamborg M, Matzen P, et al. Increased risk of intestinal cancer in Crohn's disease: a meta-analysis of population-based cohort studies. Am J Gastroenterol. 2005;100:2724–9.
4. Ky A, Sohn N, Weinstein MA, et al. Carcinoma arising anorectal fistulas of Crohn's disease. Dis Colon Rectum. 1998;41:992–6.
5. Connel WR, Sheffield JP, Kamm MA, et al. Lower gastrointestinal malignancy in Crohn's disease. Gut. 1994;35:347–52.
6. Canavan C, Abrams KR, Mayberry J. Meta-analysis colorectal and small bowel cancer risk in patients with Crohn's disease. Aliment Pharmacol. 2006;23:1097–104.
7. Stahl TJ, Schoetz DJ, Roberts PL, et al. Crohn's disease and carcinoma: increasing justification for surveillance? Dis Colon Rectum. 1992;35:850–6.
8. Mizushima T, Ohno Y, Nakajima K, et al. Malignancy in Crohn's disease and clinical characteristics in Japan. Digestion. 2010;81:265–70.
9. Elriz K, Carrat F, Carbonnel F, et al. Incidence, presentation, and prognosis of small bowel adenocarcinoma in patients with small bowel Crohn's disease: a prospective observational study. Inflamm Bowel Dis. 2013;19:1823–6.
10. Palascak-Juif V, Bouvier AM, Cosnes J, et al. Small bowel adenocarcinoma in patients with Crohn's disease compared with small bowel adenocarcinoma de novo. Inflamm Bowel Dis. 2005;11:828–32.
11. Devroe H, Coene L, Mortelmans JM, et al. Colloid carcinoma arising in an anorectal fistula in Crohn's disease: a case report. Acta Chir Belg. 2005;105:110–1.
12. Devon KM, Brown CJ, Burnstein M, et al. Cancer of the anus complicating perianal Crohn's disease. Dis Colon Rectum. 2009;52:211–6.
13. Freidman S. Cancer in Crohn's disease. Gastroenterol Clin N Am. 2006;35:621–39.
14. Neurath MF, Vehling D, Schunk K, et al. Noninvasive assessment of Crohn's disease activity: a comparison of 18F-fluorodeoxyglucose positron emission tomography, hydromagnetic resonance imaging, and granulocyte scintigraphy with labeled antibodies. Am J Gastroenterol. 2002;97:1978–85.
15. Whiteford MH, Whiteford HM, Yee LF, et al. Usefulness of FDG-PET scan in the assessment suspected metastatic or recurrent adenocarcinoma of the colon and rectum. Dis Colon Rectum. 2000;43:759–67.
16. Laurent S, Barbeaux A, Detroz B, et al. Development of adenocarcinoma in chronic fistula in Crohn's disease. Acta Gastroenterol Belg. 2005;68:98–100.

Part IV
Endoscopy in IBD: International Differences

Chapter 23
Endoscopy in Inflammatory Bowel Disease: Asian Perspectives with Respect to Japan

Mamoru Watanabe

Abstract Endoscopy has an important role in the management of gastrointestinal tract disease in Japan. Mucosal healing is a new goal of the management of inflammatory bowel disease (IBD). This has expanded the use of endoscopy. This chapter presents a review of the use of endoscopy for IBD in Japan. Surveillance colonoscopy with target biopsy for long-standing ulcerative colitis (UC) is advocated. A consensus statement has been developed for the diagnosis and management of intestinal Behçet's disease (BD) in Japan, and adalimumab has been approved to treat BD based on the findings of a Japanese multicenter study. A patency capsule that does not have a radioactive tag has been developed for capsule endoscopy (CE). CE can also be used as an alternative to traditional endoscopy to identify small intestinal lesions in patients with UC. Balloon-assisted endoscopy (BAE) is the gold standard for small intestinal lesions, and is more sensitive than magnetic resonance (MR) imaging for detecting intestinal damage. Endoscopic balloon dilation for the removal of foreign bodies, including retained capsule endoscope, is also important. Endocytoscopy is a developing technology to assess inflammation, and endocytoscopic narrow band imaging is useful for evaluating the severity of UC.

Keywords Ileocolonoscopy • Capsule endoscopy • Balloon-assisted endoscopy • Endocytoscopy • Narrow band imaging

M. Watanabe
Department of Gastroenterology and Hepatology, Advanced Clinical Center for Inflammatory Bowel Disease, Tokyo Medical and Dental University,
1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan
e-mail: mamoru.gast@tmd.ac.jp

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_23

23.1 Introduction

Endoscopy is the most widely used procedure used to manage gastrointestinal tract disease in Japan. Gastroenterologists are also endoscopists, and endoscopic findings are directly incorporated into the therapeutic strategy.

In Japan, Crohn's disease (CD) is diagnosed according to a single, well-established set of diagnostic criteria first established in 1976 and updated in 1995 [1]. These criteria consist of combinations of specific morphological findings. The diagnosis of CD is confirmed based on the presence of longitudinal ulcers, or a cobblestone-like appearance on colonoscopy or enteroscopy. Endoscopy is indispensable.

Recently, mucosal healing has been advocated as a new goal of inflammatory bowel disease (IBD) treatment [2]. Mucosal healing is identified on endoscopy, and as such, is endoscopic healing. Because most doctors involved in the management of IBD in Japan are also endoscopists, this new paradigm is familiar, and this paradigm shift has led to expanded roles of endoscopy in IBD. Advances in enteroscopy, particularly the advent of balloon-assisted endoscopy (BAE) developed by Yamamoto [3] and capsule endoscopy (CE) [4], have made possible a detailed investigation of the small intestine, the part of the bowel most affected in CD.

Here, recent reports from Japan are reviewed, and the application of endoscopy in daily practice is discussed.

23.2 Ileocolonoscopy (ICS)

Most cases of CD are diagnosed by ICS, and ICS is widely used to assess inflammation in ulcerative colitis (UC). In Japan, ICS is the most important endoscopy for the management of IBD.

Long-standing UC is associated with an increased risk of colorectal cancer. Surveillance colonoscopy is important for the early detection of UC-associated tumors. Biopsy is an important procedure to detect dysplasia as a sign of early-stage carcinoma. In the past, step biopsies at an interval of 10 cm were recommended for surveillance [5]. However, in many cases, more than 30 biopsies were required. Therefore, the procedure was expensive. Recent advances in high-resolution endoscopy have enabled a detailed observation of the mucosa. Biopsy specimens represent only a small part of mucosal lesions, and the lesions could be overlooked with conventional endoscopy. With the advent of high-resolution endoscopy, collecting tissue from selected areas of the mucosa (so-called target biopsy) has been proposed. This approach has advantages over step biopsy, not only with respect to cost but also for more effective early detection of tumors.

However, early stage UC-associated tumors can be cryptic and may be missed. Therefore, it is important to understand the typical endoscopic findings of early neoplastic changes. The Research Group for Intractable Inflammatory Bowel

Disease of the Ministry of Health, Labour, and Welfare of Japan reviewed the typical endoscopic findings on conventional endoscopy and chromoendoscopy [6]. The group also conducted a randomized, controlled study to compare step biopsy and target biopsy, and showed that target biopsy detects dysplasia at a similar rate as step biopsy [7]. Therefore, surveillance endoscopy is changing from blind step biopsy to intentional target biopsy.

Another important target for ICS is Behçet's disease (BD). In 2007, the Japan consensus statement for the diagnosis and management of intestinal BD was developed. Recently, renewed consensus-based practice guidelines for the diagnosis and treatment of intestinal BD have been released. These updated guidelines state that the diagnosis of intestinal BD can be made if there is a typical oval-shaped large ulcer in the terminal ileum, or ulceration or inflammation in the small or large intestine [8].

ICS is also used to monitor the treatment of gastrointestinal disease. In 2014, adalimumab was approved for the treatment of BD in Japan. This acceptance was based on a multicenter, open-label, uncontrolled study to evaluate the efficacy and safety of adalimumab in patients with intestinal BD who were refractory to corticosteroid and/or immunomodulatory therapies. In that study, a composite efficacy index including endoscopic assessments was developed, and this index was combined with gastrointestinal symptoms to evaluate efficacy. Previously, there was no widely accepted clinical index for assessing intestinal BD activity. In that study, endoscopy had an important role in the objective evaluation of intestinal BD because patient-reported symptoms may be influenced by the knowledge of the treatment allocation in unblinded trials [9].

23.3 Capsule Endoscopy (CE)

The advent of CE represents a major advance in endoscopy of the small bowel. Previously, enteroscopy could only effectively target the terminal ileum or proximal jejunum. CE enables the visualization of the whole gut, and is very sensitive for detecting mucosal lesions. The small intestine is the most commonly affected part of the bowel in CD. Therefore, CE is recommended in the World Organization of Digestive Endoscopy and the European Crohn's and Colitis Organization (OMED–ECCO) consensus guidelines for use in patients with unexplained symptoms when other examinations have been negative [10].

However, there are some complications associated with CE, including capsule retention. Retention is defined as a capsule endoscope remaining in the digestive tract for more than 2 weeks [11]. In patients with CD, stenosis of the bowel lumen is not uncommon, and one study has reported capsule retention in 13% of patients with established CD [12]. Therefore, CE can be problematic in CD patients. To address the problem of capsule retention, the revised patency capsule was developed in 2011 [13]. This patency capsule does not have a radioactive tag and is therefore safer than the original patency capsule. Patency is established when the complete

patency capsule is evacuated or is located in the colon within 30 h of administration. Since approval of the patency capsule, the indications for CE have expanded, and the use of the method has increased. However, sometimes it is difficult to judge whether the patency capsule has reached the colon or is still in the small intestine, particularly when the capsule is located in the pelvic area on plain X-ray.

UC is not only a disease of the colon but also is a systemic disease. Recent studies have reported small intestinal lesions detected by CE in patients with UC [14, 15]. Of the 20 UC patients in the first study, eight (40%) had small bowel lesions [14]. Of the 23 UC patients in the second study, 13 (57%) had small bowel lesions and eight (35%) had erosions [15]. Therefore, small-bowel lesions in UC are not as rare as once thought.

The use of CE is not only indicated for the investigation of the small intestine but also for the colon. Recently, the applicability of CE of the colon in patients with UC was reported [16]. Typically, a large volume of cleansing liquid is necessary as preparation before colonic CE. However, that study showed that smaller volumes of polyethylene glycol solution (2 l) with prokinetics were useful for CE to assess UC [16]. The completion rate was only 69% in 8 h, but the colonic CE score and the conventional ICS score showed a strong correlation. Optimal preparation is required, but colonic CE may become a viable alternative approach for assessing UC.

23.4 Balloon-Assisted Endoscopy (BAE)

BAE was developed by Yamamoto [3]. With this method, the entire gastrointestinal tract can be investigated in daily clinical practice. This approach was rapidly adopted for the investigation of IBD, and BAE has become the gold standard to assess mucosal lesions of the small intestine. In Western countries, magnetic resonance (MR) enterography is still preferred over BAE. However, we have shown that MR imaging is less sensitive for detecting intestinal damage such as stenosis, although it is useful for detecting active lesions in the small intestine [17]. Some patients have significant stenoses that can only be detected on endoscopy.

The most important benefit of BAE is ready access to lesions. Many procedures can be performed with BAE, including direct observation, selected contrast radiography, and biopsy. Therefore, BAE is not only useful for diagnosis and assessment but also for treatment. In particular, stenosis can be effectively treated using endoscopic balloon dilation (EBD) [18]. The long-term efficacy of EBD has been reported, although the high redilation rate remains a clinical problem of this procedure [19]. A national study to evaluate EBD is ongoing.

BAE is also used for the removal of foreign bodies, including retained endoscopy capsules. It is also useful in young patients with CD. In a study of 17 procedures in 12 children and adolescents with established or suspected CD, accurate diagnosis was achieved in 7/8 cases (88%) of suspected CD [20]. The procedure was well tolerated and no serious complications were reported. Although operators must be highly skilled, BAE is a safe and effective procedure for the management of CD.

23.5 Future Technologies

Endocytoscopy (ECS) is a new method for disease assessment. It provides real-time ultra-magnifying microscopic imaging in vivo and is useful to assess inflammation. An ECS score has been proposed, i.e., the sum of indices for shape (0–3), the distance between crypts (0–2), and the visibility of superficial microvessels (0–1) [21].

With narrow band imaging (NBI), further assessment is possible. Recently, the efficacy of endocytoscopic narrow band imaging (EC-NBI) to evaluate the severity of inflammation in UC was reported [22]. The authors concluded that the EC-NBI finding of capillaries in the rectal mucosa was strongly correlated with histological inflammation, and aided in the differential diagnosis between active and inactive UC.

23.6 Summary

Endoscopy has many important roles in the management of IBD. Familiarity with the use of endoscopy is essential for better clinical practice in gastroenterology.

References

1. Hisabe T, Hirai F, Matsui T, et al. Evaluation of diagnostic criteria for Crohn's disease in Japan. J Gastroenterol. 2014;49(1):93–9. doi:10.1007/s00535-013-0798-x.
2. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut. 2012;61:1619–35.
3. Yamamoto H, Sekine Y, Sato Y, et al. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc. 2001;53:216–20.
4. Iddan G, Meron G, Glukhovsky A, et al. Wireless capsule endoscopy. Nature. 2000;405:417.
5. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale—update based on new evidence. Gastroenterology. 2003;124:544–60.
6. Matsumoto T, Iwao Y, Igarashi M, et al. Endoscopic and chromoendoscopic atlas featuring dysplastic lesions in surveillance colonoscopy for patients with long-standing ulcerative colitis. Inflamm Bowel Dis. 2008;14:259–64.
7. Watanabe T, Ajioka Y, Matsumoto T, et al. Target biopsy or step biopsy? Optimal surveillance for ulcerative colitis: a Japanese nationwide randomized controlled trial. J Gastroenterol. 2011;46(Suppl 1):11–6.
8. Hisamatsu T, Ueno F, Matsumoto T, et al. The 2nd edition of consensus statements for the diagnosis and management of intestinal Behçet's disease: indication of anti-TNFα monoclonal antibodies. J Gastroenterol. 2014;49:156–62.
9. Tanida S, Inoue N, Kobayashi K, et al. Adalimumab for the treatment of Japanese patients with intestinal Behçet's disease. Clin Gastroenterol Hepatol. 2015;13:940–8.
10. Bourreille A, Ignjatovic A, Aabakken L, et al. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED–ECCO consensus. Endoscopy. 2009;41:618–37.
11. Cave D, Legnani P, de Ranchis R, et al. ICCE consensus for capsule retention. Endoscopy. 2005;37:1065–7.

12. Cheifetz AS, Kornbluth AA, Legnani P, et al. The risk of retention of the capsule endoscope in patients with known or suspected Crohn's disease. Am J Gastroenterol. 2006;101:2218–22.
13. Nakamura M, Hirooka Y, Yamamura T, et al. Clinical usefulness of novel tag-less agile patency capsule prior to capsule endoscopy for patients with suspected small bowel stenosis. Dig Endosc. 2015;27:61–6.
14. Hisabe T, Ninomiya K, Matsui T, et al. Small bowel lesions detected with wireless capsule endoscopy in patients with active ulcerative colitis and with post-proctocolectomy. Dig Endosc. 2011;23:302–9.
15. Higurashi T, Endo H, Yoneda M, et al. Capsule–endoscopic findings of ulcerative colitis patients. Digestion. 2011;84:306–14.
16. Hosoe N, Matsuoka K, Naganuma M, et al. Applicability of second generation colon capsule endoscope to ulcerative colitis: a clinical feasibility study. J Gastroenterol Hepatol. 2013;28:1174–9.
17. Takenaka K, Ohtsuka K, Kitazume Y, et al. Comparison of magnetic resonance and balloon enteroscopic examination of the small intestine in patients with Crohn's disease. Gastroenterology. 2014;147:334–42.
18. Hirai F, Beppu T, Sou S, et al. Endoscopic balloon dilatation using double-balloon endoscopy is a useful and safe treatment for small intestinal strictures in Crohn's disease. Dig Endosc. 2010;22:200–4.
19. Hirai F, Beppu T, Takatsu N, et al. Long-term outcome of endoscopic balloon dilation for small bowel strictures in patients with Crohn's disease. Dig Endosc. 2014;26:545–51.
20. Uchida K, Yoshiyama S, Inoue M, et al. Double balloon enteroscopy for pediatric inflammatory bowel disease. Pediatr Int. 2012;54:806–9.
21. Bessho R, Kanai T, Hosoe N, et al. Correlation between endocytoscopy and conventional histopathology in microstructural features of ulcerative colitis. J Gastroenterol. 2011;46:1197–202.
22. Maeda Y, Ohtsuka K, Kudo S, et al. Endocytoscopic narrow-band imaging efficiency for evaluation of inflammatory activity in ulcerative colitis. World J Gastroenterol. 2015;21:2108–15.

Chapter 24
Endoscopy in Inflammatory Bowel Disease: Asian Perspective—Korea

Byong Duk Ye and Suk-Kyun Yang

Abstract With the increasing incidence of inflammatory bowel disease (IBD) over the past few decades, the proper diagnosis and treatment of IBD are being emphasized in Korea. Recently, several Korean studies have addressed the role of endoscopy in the management of IBD. In contrast to traditional conceptions, the atypical distribution of inflammation is not infrequently observed in patients with ulcerative colitis (UC). Appendiceal skip inflammation is common in patients with UC and may precede typical features of UC development, but it does not seem to be related to the clinical course. Intestinal tuberculosis (ITB) is still prevalent in Korea, and must be differentiated from Crohn's disease (CD). In a colonoscopy, anorectal lesions, longitudinal ulcers, aphthous ulcers, and a cobblestone appearance are more commonly observed in CD, whereas the involvement of fewer than four segments, a patulous ileocecal valve, transverse ulcers, and scars or pseudopolyps suggest ITB rather than CD. In up to 90% of cases, it was possible to correctly diagnose CD and ITB using a simple scoring system with the above eight parameters. A mycobacterial culture assay with colonoscopic biopsy specimens must be performed to aid the diagnosis of ITB in suspected cases. Isolated terminal ileal ulcerations not diagnosed with CD, ITB, or nonsteroidal anti-inflammatory agent-associated enteropathy remain an area of uncertainty. However, their prognosis appears favorable without progression to a significant condition in most cases; thus, over-diagnosis and/or over-treatment should be avoided.

Keywords Ulcerative colitis • Crohn's disease • Intestinal tuberculosis • Isolated terminal ileal ulcerations

B.D. Ye • S.-K. Yang (✉)
Department of Gastroenterology and Inflammatory Bowel Disease Center, University of Ulsan College of Medicine, Asan Medical Center,
88 Olympic-Ro, 43-Gil, Songpa-Gu, Seoul 05505, South Korea
e-mail: sky@amc.seoul.kr

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_24

24.1 Introduction

In the past, inflammatory bowel disease (IBD) was considered very rare in Korea. However, during recent decades, a population-based epidemiologic study shows steadily increasing incidence rates of both ulcerative colitis (UC) and Crohn's disease (CD) in Korea, although they are still lower than those in Western countries [1, 2]. Korean patients with IBD were reported to have different clinical characteristics compared with Western patients, such as a male predominance, a lower proportion of isolated colonic disease, and a higher incidence of perianal fistula in CD [1–3], and a lower colectomy rate in UC [4]. In addition, Korea has a high prevalence of tuberculosis (TB), resulting in more frequent encounters of intestinal tuberculosis (ITB) cases mimicking CD. When considering this situation, endoscopy could play a unique role in managing IBD in Korea. In this chapter, the clinical application of endoscopy in the management of UC, CD, and ITB will be discussed, with a focus on recent Korean studies.

24.2 Clinical Application of Endoscopy for Inflammatory Bowel Diseases

24.2.1 Can Colonoscopy Tell More About the Extent of Ulcerative Colitis?

UC was traditionally regarded as showing endoscopically continuous inflammation with invariable involvement of the rectum. The exception to this concept is UC associated with primary sclerosing cholangitis (PSC), which has often shown rectal sparing in previous Western reports [5, 6]. In a Korean study, consistent with Western studies, macroscopic or microscopic rectal sparing was more commonly observed in patients with UC associated with PSC than those with UC alone [7]. However, an atypical distribution of inflammation is not rarely observed in untreated UC patients, even in those with UC, but without PSC. In a recent Korean study, of 240 patients with newly diagnosed UC, 46 patients (19.2%) showed an atypical distribution of lesions upon initial colonoscopy: eight (3.3%) showed rectal sparing, and 38 (15.8%) showed patchy/segmental skip lesions other than appendiceal skip inflammation (Fig. 24.1) [8]. However, the clinical course of patients with atypical distributions was similar to that of patients with a typical distribution in terms of remission, relapse, disease extension, colectomy, and mortality [8]. Appendiceal skip inflammation, often referred to as appendiceal orifice inflammation (AOI), is also a lesion separated from the main inflammation (Fig. 24.2) [9]. According to a Korean study, AOI is observed in about half of patients (48/94, 51.1%) with newly diagnosed distal UC [10]. In a colonoscopic follow-up study of 19 patients with AOI, but without concomitant typical features of UC, typical UC developed in five

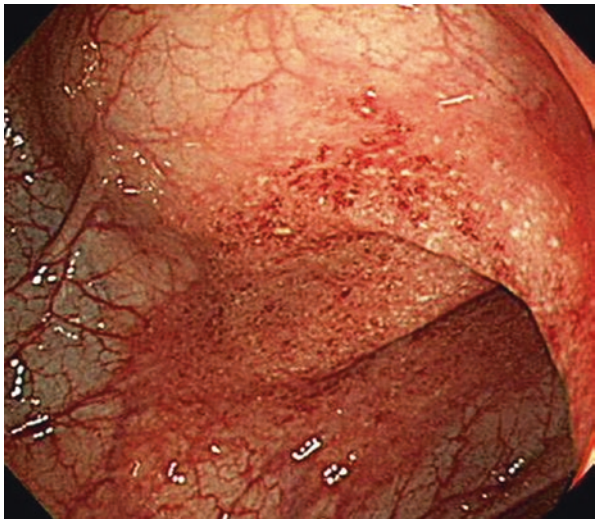


Fig. 24.1 Patchy inflammation in distal ascending colon

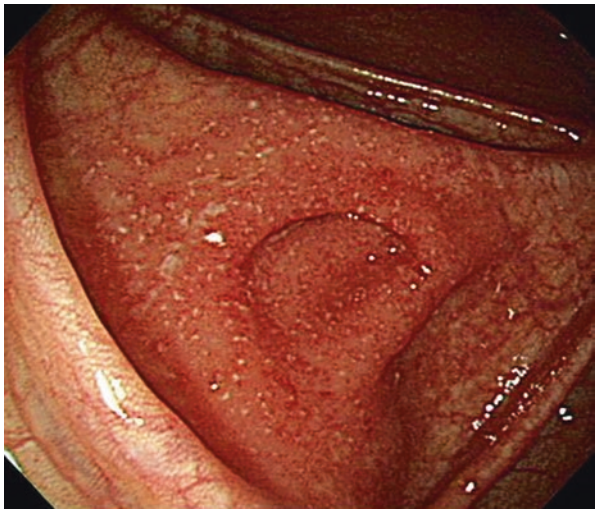


Fig. 24.2 Appendiceal skip inflammation showing typical inflammatory lesion of ulcerative colitis surrounding the orifice of the appendix

patients (26.3%), suggesting AOI precedes development of UC at least in some cases [11]. However, in comparing AOI-positive and -negative distal UC patients, there were no differences in terms of clinical remission, relapse, or proximal disease extension [10].

24.2.2 Colonoscopic Differential Diagnosis Between Crohn's Disease and Intestinal Tuberculosis

Tuberculosis (TB) is still a prevalent disease in Korea, although its incidence has been gradually decreasing [12, 13]. Intestinal involvement of TB, that is ITB, shares clinical features with CD, such as abdominal pain, diarrhea, weight loss, and fever. It is often challenging to differentiate between CD and ITB during colonoscopic evaluations. A Korean study proposed a simple colonoscopic scoring system for differentiation between CD and ITB [14]. In that study, anorectal lesions, longitudinal ulcers, aphthous ulcers, and a cobblestone appearance were more commonly observed in CD (Fig. 24.3), whereas the involvement of fewer than four segments, a patulous ileocecal valve, transverse ulcers, and scars or pseudopolyps suggested ITB rather than CD (Fig. 24.4) [14]. A score of +1 was assigned to the four parameters that were suggesting CD, and −1 to the other four parameters, which were indicative of ITB [14]. The colonoscopic diagnosis was considered to be CD when the sum of the scores for the above eight parameters was greater than zero, and the diagnosis to be ITB when that sum was less than zero; the diagnosis was regarded as indeterminate when the sum was zero [14]. Using the above scoring system, 87.5% of patients (77/88) were able to be correctly diagnosed with either CD or ITB [14]. Meanwhile, through a culture assay using both solid and liquid media for colonoscopic biopsy tissue, the sensitivity of a culture for *Mycobacterium tuberculosis* in diagnosing ITB could be increased up to 44.1%, suggesting the importance of culture assay for suspected ITB cases [15].

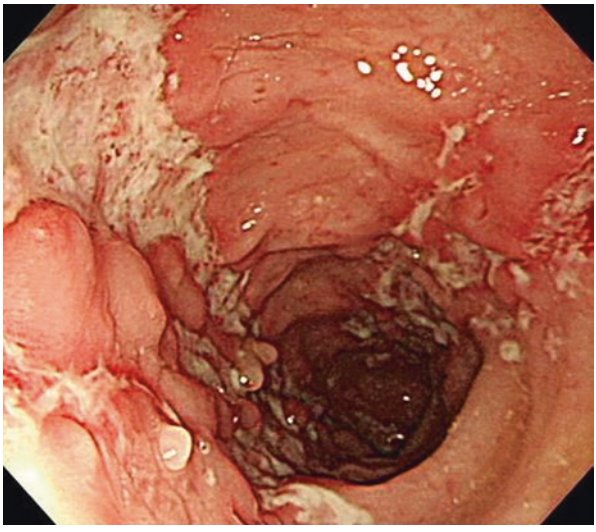


Fig. 24.3 Typical colonoscopic feature of Crohn's disease showing longitudinal discrete ulcers

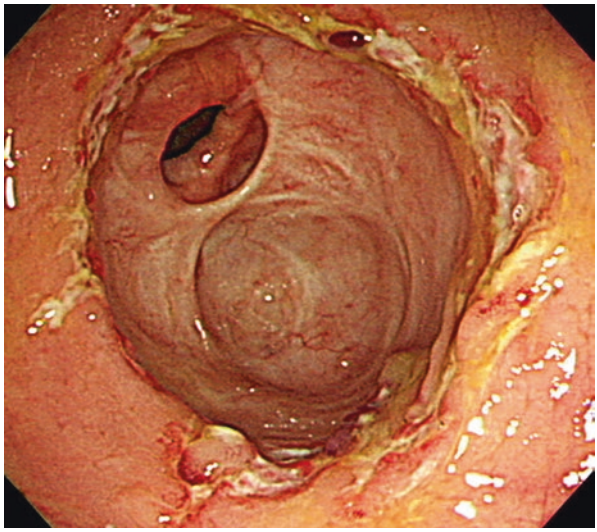


Fig. 24.4 Typical colonoscopic feature of intestinal tuberculosis showing a circular ulcer, a patulous ileocecal valve, and scars

24.2.3 What is the Clinical Implication of Isolated Terminal Ileal Ulcers?

During a screening colonoscopy, aphthous or small ulcerations confined to the terminal ileum unaccompanied by coincidental ulcerations in the ileocecal valve or colon (isolated terminal ileal ulcers [ITIUs]) may be observed sometimes [16]. However, their natural course and prognosis have remained unclear. In a recent Korean study, 93 cases with ITIUs without colorectal symptoms, a history of nonsteroidal anti-inflammatory drug consumption, a history of colorectal surgery, or oral or genital ulcerations were followed for a mean duration of 30 months [16]. Of the 93 patients, ITIUs resolved without any treatment in 60 patients (64.5%) and continued in 30 patients (32.3%) without any progression [16]. Of the remaining three patients, two patients (2.2%) were diagnosed with ITB and one patient (1.1%) was diagnosed with CD [16]. These results suggest a favorable prognosis of ITIU, but larger-scaled, long-term follow-up studies in other ethnic groups are needed for a more proper characterization of ITIUs.

24.3 Summary

In areas with distinctive epidemiologic characteristics of chronic inflammatory disorders of the gastrointestinal tract, such as Korea, endoscopy may play a unique role. Recent Korean studies suggest the essential role of colonoscopy in the correct differential diagnosis of IBD as well as in predicting the clinical course of IBD. By

acquiring knowledge of the endoscopic features of various inflammatory disorders and by applying this knowledge appropriately depending on the clinical situation, the quality of IBD care can be improved.

References

1. Yang SK, Yun S, Kim JH, Park JY, Kim HY, Kim YH, Chang DK, Kim JS, Song IS, Park JB, Park ER, Kim KJ, Moon G, Yang SH. Epidemiology of inflammatory bowel disease in the Songpa-Kangdong district, Seoul, Korea, 1986–2005: a KASID study. Inflamm Bowel Dis. 2008;14(4):542–9. doi:10.1002/ibd.20310.
2. Thia KT, Loftus Jr EV, Sandborn WJ, Yang SK. An update on the epidemiology of inflammatory bowel disease in Asia. Am J Gastroenterol. 2008;103(12):3167–82. doi:10.1111/j.1572-0241.2008.02158.x.
3. Park SH, Yang SK, Park SK, Kim JW, Yang DH, Jung KW, Kim KJ, Ye BD, Byeon JS, Myung SJ, Yoon YS, Yu CS, Kim JH. Long-term prognosis of Crohn's disease and its temporal change between 1981 and 2012: a hospital-based cohort study from Korea. Inflamm Bowel Dis. 2014;20(3):488–94. doi:10.1097/01.MIB.0000441203.56196.46.
4. Lee HS, Park SH, Yang SK, Lee J, Soh JS, Lee S, Bae JH, Lee HJ, Yang DH, Kim KJ, Ye BD, Byeon JS, Myung SJ, Yoon YS, Yu CS, Kim JH. Long-term prognosis of ulcerative colitis and its temporal change between 1977 and 2013: a hospital-based cohort study from Korea. J Crohns Colitis. 2014; doi:10.1093/ecco-jcc/jju017.
5. Loftus Jr EV, Harewood GC, Loftus CG, Tremaine WJ, Harmsen WS, Zinsmeister AR, Jewell DA, Sandborn WJ. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. Gut. 2005;54(1):91–6. doi:10.1136/gut.2004.046615.
6. Jorgensen KK, Grzyb K, Lundin KE, Clausen OP, Aamodt G, Schrumpf E, Vatn MH, Boberg KM. Inflammatory bowel disease in patients with primary sclerosing cholangitis: clinical characterization in liver transplanted and nontransplanted patients. Inflamm Bowel Dis. 2012;18(3):536–45. doi:10.1002/ibd.21699.
7. Ye BD, Yang SK, Boo SJ, Cho YK, Yang DH, Yoon SM, Kim KJ, Byeon JS, Myung SJ, Yu CS, Yun SC, Kim JH. Clinical characteristics of ulcerative colitis associated with primary sclerosing cholangitis in Korea. Inflamm Bowel Dis. 2011;17(9):1901–6. doi:10.1002/ibd.21569.
8. Park SH, Yang SK, Park SK, Kim JW, Yang DH, Jung KW, Kim KJ, Ye BD, Byeon JS, Myung SJ, Kim JH. Atypical distribution of inflammation in newly diagnosed ulcerative colitis is not rare. Can J Gastroenterol Hepatol. 2014;28(3):125–30.
9. Yang SK, Jung HY, Kang GH, Kim YM, Myung SJ, Shim KN, Hong WS, Min YI. Appendiceal orifice inflammation as a skip lesion in ulcerative colitis: an analysis in relation to medical therapy and disease extent. Gastrointest Endosc. 1999;49(6):743–7.
10. Byeon JS, Yang SK, Myung SJ, Pyo SI, Park HJ, Kim YM, Lee YJ, Hong SS, Kim KJ, Lee GH, Jung HY, Hong WS, Kim JH, Min YI. Clinical course of distal ulcerative colitis in relation to appendiceal orifice inflammation status. Inflamm Bowel Dis. 2005;11(4):366–71.
11. Park SH, Yang SK, Kim MJ, Yang DH, Jung KW, Kim KJ, Ye BD, Byeon JS, Myung SJ, Kim JH. Long term follow-up of appendiceal and distal right-sided colonic inflammation. Endoscopy. 2012;44(1):95–8. doi:10.1055/s-0031-1291443.
12. Kim HJ. Current status of tuberculosis in Korea. Korean J Med. 2012;82(3):257–62. doi:10.3904/kjm.2012.82.3.257.
13. World Health Organization. WHO Global tuberculosis report 2013. http://www.who.int/tb/publications/global_report/en/. Accessed 23 Sept 2014.
14. Lee YJ, Yang SK, Byeon JS, Myung SJ, Chang HS, Hong SS, Kim KJ, Lee GH, Jung HY, Hong WS, Kim JH, Min YI, Chang SJ, Yu CS. Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. Endoscopy. 2006;38(6):592–7. doi:10.1055/s-2006-924996.

15. Ye BD, Yang SK, Kim D, Shim TS, Kim SH, Kim MN, Lee YJ, Na HK, Park SH, Yang DH, Kim KJ, Byeon JS, Myung SJ, Kim JH. Diagnostic sensitivity of culture and drug resistance patterns in Korean patients with intestinal tuberculosis. Int J Tuberc Lung Dis. 2012;16(6):799–804. doi:10.5588/ijtld.11.0252.
16. Chang HS, Lee D, Kim JC, Song HK, Lee HJ, Chung EJ, Kim TH, Park HW, Byeon JS, Yang SK, Choe JW. Isolated terminal ileal ulcerations in asymptomatic individuals: natural course and clinical significance. Gastrointest Endosc. 2010;72(6):1226–32. doi:10.1016/j.gie.2010.08.029.

Chapter 25
Endoscopy in Chinese Inflammatory Bowel Disease Patients: Similarities and Differences to the Western World

Jiaming Qian and Dong Wu

Abstract Inflammatory bowel disease (IBD) comprising Crohn's disease (CD) and ulcerative colitis (UC) is prevalent in developed countries, and has been thought of as a "Western disease". However, recent years have witnessed an explosive growth of IBD patients in China. China differs with Western countries in differential diagnoses of IBD. Intestinal tuberculosis, infectious colitis, and Behçet's disease are common in China, and resemble CD and UC both clinically and endoscopically. A combination of colonoscopy, radiography, and serologic studies aid in making the distinction. Advanced endoscopic imaging such as chromoendoscopy and digital mucosal enhancement is rapidly spreading in China, allowing better surveillance and screening for precancerous lesions in IBD patients.

Keywords Inflammatory bowel disease • Ulcerative colitis • Crhon's disease, • Infectious colitis • Intestinal tuberculosis • Behçet's disease • Differential diagnosis • Endoscopy

25.1 Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), results from an inappropriate immune response to normal intraluminal microbiota in a genetically susceptible host [1]. The diagnosis of IBD depends on clinical presentation, image studies, and pathological investigation. Endoscopy aids in the differential diagnosis of IBD, the assessment of disease extent and activity, and screening and surveillance for dysplasia and cancer. Furthermore, in patients with IBD complications, endoscopy offers therapeutic benefit including bleeding control and stricture dilation [2].

J. Qian (✉) • D. Wu
Department of Gastroenterology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, No.1 Shuaifuyuan Wangfujing Dongcheng District, Beijing 100730, China
e-mail: qianjiaming1957@126.com

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_25

IBD is characterized by frequent episodes of relapse, disruptive nature of intestinal tissue, and disabling complications, and thus constructs striking challenges to gastroenterologists and endoscopists worldwide. In China, IBD was previously thought to be rare, but is now increasing rapidly in parallel with a booming economy and fast westernization of life style. In this article we summarize clinical applications of endoscopy in IBD based on our experience and understanding in Chinese IBD patients.

25.2 IBD in China: Past, Present, and Prospect

IBD was recognized as a chronic intestinal disorder in western countries back in the eighteenth century. For example, Ludwig Van Beethoven (1770–1827), the world-acclaimed musician, had very likely suffered from UC since his adolescence [3]. It was not until two centuries later, however, that physicians in China started to look into this idiopathic and often refractory disease. To the best of our knowledge, the first Chinese patient with UC was described in detail by Wen from Peking Union Medical College Hospital in 1956 [4]. The first Chinese consensus of UC diagnostic criteria, including endoscopic features, was proposed during the first National Conference of Digestive Disease in 1978. Because of the high prevalence of tuberculosis in China, the clinical distinction between CD and intestinal tuberculosis has been the bottleneck for most of the time [4, 5]. The British pathologist and IBD expert B. C. Morson first confirmed the existence of CD in China. During his visit to China in 1978, he agreed with his Chinese colleagues about the diagnoses of CD after thorough examination of the pathological samples provided by Peking Union Medical College Hospital [4]. Based on these findings, Liu and Pan first established the diagnostic criteria of CD in China, and emphasized the importance of exclusion of enterocolonic tuberculosis [5].

Population-based epidemiological surveys of IBD in China revealed an incidence of UC varying from 1.45 to 2.05 per 100,000 person-years, and CD from 0.13 to 1.09 per 100,000 person-years [6, 7, 8]. Similar to that of Japan and Korea, the prevalence of IBD has been rapidly increasing in China in recent years. It has been estimated that the total number of Chinese IBD patients had increased by 2.5-fold over the previous decade, in particular a 15.7-fold increase in patients with CD [9]. It is clear that China is following the same path of fast-growing IBD seen in the developed world during mid-twentieth century. Given the prolonged course and refractory nature of the disease, we can reasonably expect that IBD will become one of the most common digestive diseases in China in the near future.

25.3 Intestinal Tuberculosis and CD: Endoscopic Pitfalls

Mycobacterium tuberculosis can involve any part of the gastrointestinal tract, most commonly affecting the colon and terminal ileum. The rectum is often spared. Intestinal tuberculosis (ITB) and CD have overlapping clinical and endoscopic presentations but involve very different therapeutic options, thus making the distinction between these

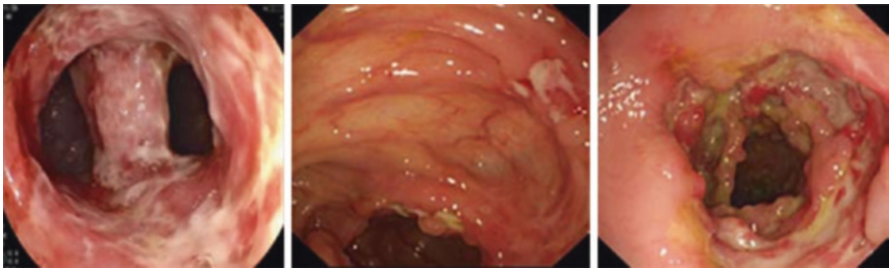


Fig. 25.1 Typical endoscopic features of ITB (from *left* to *right*): deformity and constant opening of the ileocecal valve; irregular transverse ulcers; localized involvement of the ascending colon with transverse ulcers with rolled edges

two entities a necessity [4, 5]. However, distinguishing CD from ITB is often difficult, if not impossible, based on endoscopic findings alone, and the entire clinical picture should be taken into account. Endoscopic appearances favoring the diagnosis of ITB include sparing of the rectum, deformity of the ileocecal valve, transverse ulcers, and involvement of fewer than four segments (Fig. 25.1). In contrast, anorectal lesions, longitudinal ulcers, aphthous ulcers, and cobblestone or nodular appearance are significantly more common in patients with CD than in patients with ITB [5, 10, 11]. Despite rapid advances in image technique, colonoscopic differentiation between ITB and CD is far from satisfactory in ITB endemic areas such as China. Therefore, other modalities have been investigated to aid the distinction. For instance, in-vitro interferon γ-release assay has a sensitivity of 84.2% and a specificity of 75.4% for the diagnosis of ITB, and thus helps in distinguishing ITB from CD in China [12]. In addition, Mao et al. reported that computed tomographic enterography (CTE) added information to colonoscopy and increased the diagnostic accuracy of either CD or ITB from 66.7% (70/105) to 95.2% (100/105). On CTE findings, segmental small-bowel involvement and comb sign are independent predictors for CD, whereas mesenteric lymph node changes (calcification or central necrosis) and focal ileocecal lesions were more common in ITB [13].

On the other hand, if patients with ITB are misdiagnosed with CD and erroneously given corticosteroid and immunosuppressant medications, tuberculosis may easily disseminate and cause severe complications or even death. Therefore, anti-tuberculosis treatment with close monitoring is routinely recommended when clinical distinction of ITB and CD is not possible [14]. According to the updated consensus by Chinese IBD experts in 2012, ITB often responds to antibiotic treatment in 2–4 weeks. A repeated colonoscopy after 8–12 weeks of therapy helps to confirm the diagnosis of ITB if remarkable improvement and healing of original lesions are recorded [14].

25.4 Distinguish IBD from Other Infectious Colitis

After exclusion of ITB, the initial diagnosis of IBD remains challenging because many other diseases have similar clinical and endoscopic presentations. Unlike Western countries where intestinal infectious diseases are uncommon, these entities

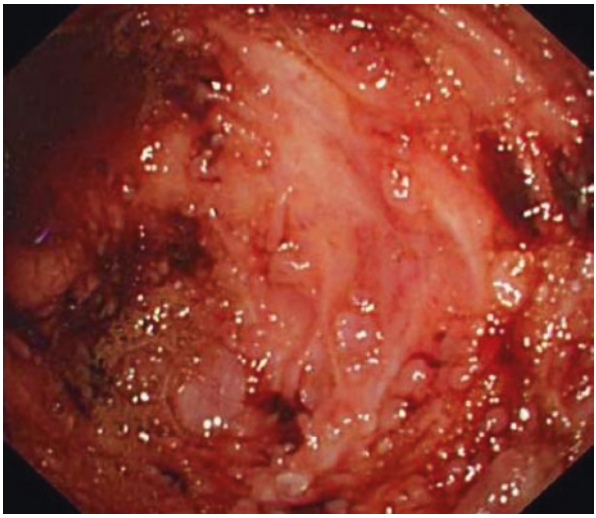


Fig. 25.2 Amebic colitis presents with a large ulcer and inflamed mucosa

remain strong competing diagnoses against IBD in China. Approximately 38% of patients with mucoid bloody diarrhea and suspected IBD turned out to have an infectious etiology [15]. Endoscopy is the most sensitive method for evaluating mucosal abnormalities, and is the only method to obtain biopsy for histologic and microbiological studies. The following are some infectious colitides relatively common in China that should be excluded before making a diagnosis of IBD.

Amebic colitis (*Entamoeba histolytica*) is a protozoan infection that most commonly affects the cecum and right colon. Colonoscopy typically reveals friable and erythematous mucosa with discrete large ulcers covered by mucopurulent exudates (Fig. 25.2). Biopsy specimens of the ulcer margins provide a sensitivity of 60–90% for trophozoites to make the diagnosis [16].

Schistosomiasis (*Schistosoma japonicum*) is predominantly endemic in the lake and marshland areas in central and east China. The parasite infects 5.1% of regional people, and causes significant morbidity [17]. Endoscopic features include free pus, intense mucosal reddening, and yellowish exudates in the mucosal surface (Fig. 25.3). In some cases, schistosomiasis presents skipping lesions that mimic CD.

Shigella dysenteriae is a gram-negative bacterium that causes dysentery. The organism invades the large intestine and produces fever, cramps, bloody diarrhea, and tenesmus. The endoscopic appearance often resembles UC. A thorough history, positive stool culture, and response to antibiotic therapy help to establish the diagnosis.

Patients who present with IBD are prone to opportunistic infections including cytomegalovirus (CMV) and *Clostridium difficile (C. difficile)*. In a cohort of IBD patients from central China, the prevalence, risk factors, and clinical presentation of CMV infection are comparable to those in Western IBD patients [18]. The characteristic colonoscopic finding of *C. difficile* colitis is pseudomembrane formation comprising yellow-white plaques. But in IBD patients superinfected by *C. difficile*, endoscopy findings may be relatively unspecific [19] (Fig. 25.4). Fecal assay of *C. difficile* toxin A and B confirms the diagnosis.

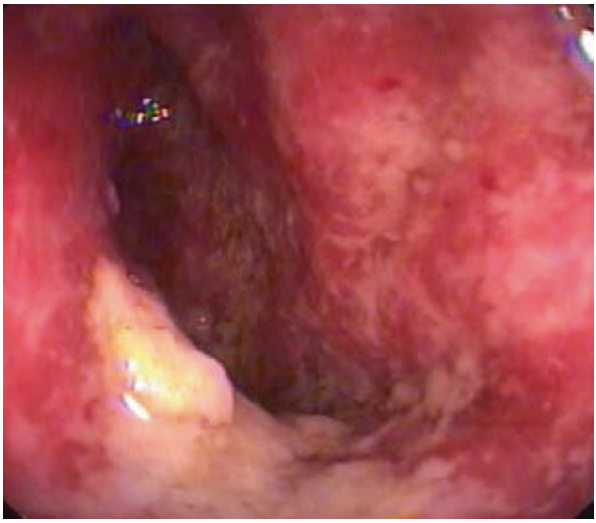


Fig. 25.3 Schistosomiasis causes an ulcer with edema and yellow exudates

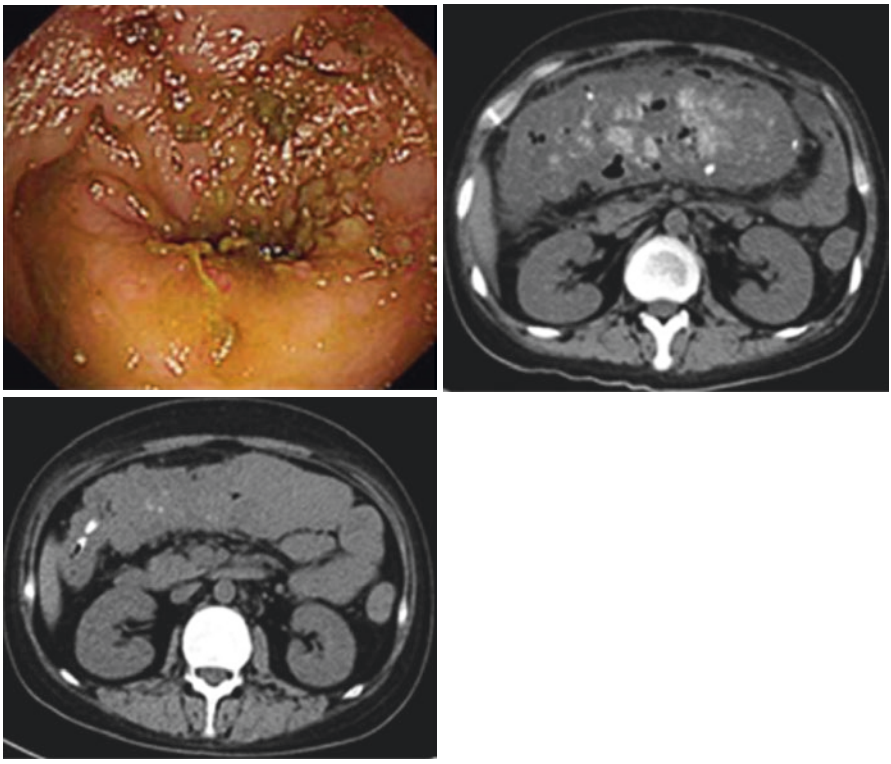


Fig. 25.4 A 25-year old man with UC was superinfected by Clostridium difficile and presented with edematous colon mucosa (*left*). He developed toxic megacolon (*middle*) and responded to oral vancomycin (*right*)

Similarly to Japan and Korea, noninfectious diseases such as intestinal Behçet's disease (BD), ischemic colitis, and radiation colitis are also common in the Chinese population. These disorders should be taken into consideration before making a diagnosis of IBD. Among these entities BD resembles CD in many aspects, and often creates a diagnostic dilemma. Both diseases commonly have a young age of onset, nonspecific gastrointestinal symptoms, similar extraintestinal manifestations, and chronic, waxing and waning course. A comparative study conducted in our institute revealed some valuable strategies for the distinction of BD and CD. In terms of colonoscopic findings, the study showed that focal involvement, ileocecal valve deformity, solitary ulcers, large ulcers (>2 cm), and circumferential ulcers were more common in intestinal BD patients, whereas segmental involvement, longitudinal ulcers, a cobblestone appearance, and pseudopolyps were more common in CD (Figs. 25.5 and 25.6) [20].

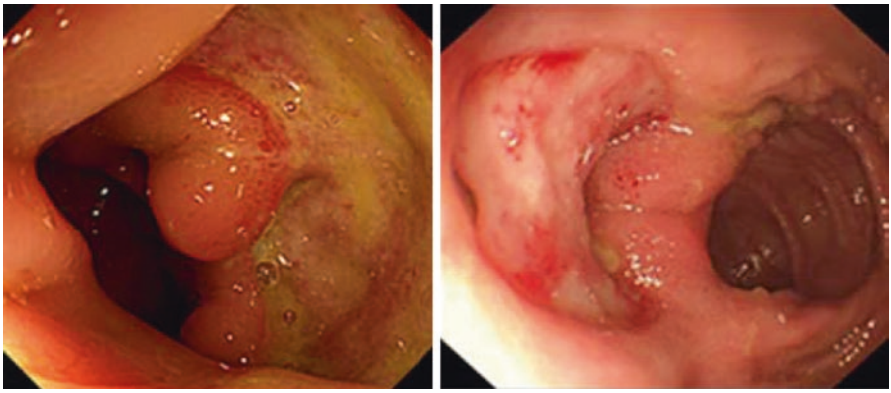


Fig. 25.5 Single large ulcer in the right colon of BD patients

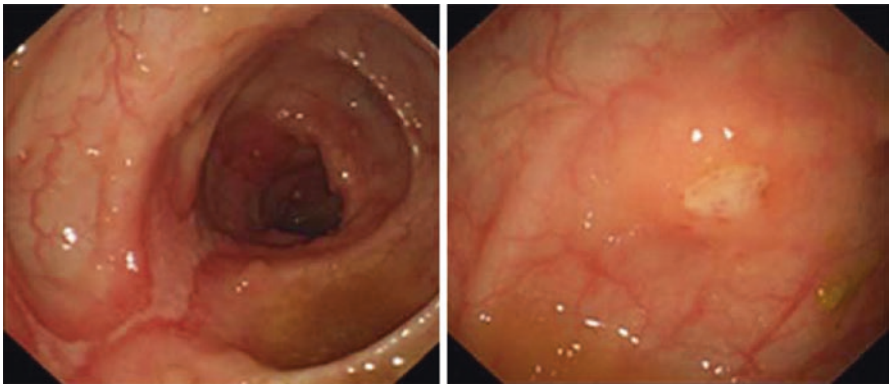


Fig. 25.6 Longitudinal and aphthous ulcers in CD patients

25.5 Surveillance Colonoscopy in China

Patients with long-standing UC and CD are associated with an increased risk of developing precancerous dysplasia lesions and colorectal cancer. Chinese IBD consensus endorsed a screening and surveillance strategy based on risk stratification [15]. The majority of colonic dysplastic lesions are macroscopically detectable, although the endoscopic appearance can be subtle, varied, and mimics post-inflammatory alterations. To date, chromoendoscopy is the only technique that has consistently yielded positive results in large, well-designed clinical studies [21]. Chinese IBD consensus recommends chromoendoscopy as a preferred dysplasia-detection tool [14]. Narrow-band imaging (Fig. 25.7), I-SCAN (Fig. 25.8), Fuji intelligent chromoendoscopy (FICE), and confocal laser endomicroscopy have yielded conflicting results, but have potential value to detect and diagnose dysplasia in selected patients.

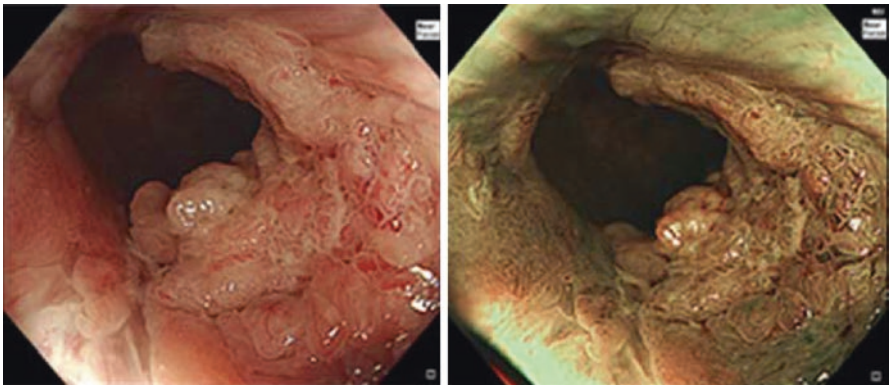


Fig. 25.7 A rectal lesion of high-grade intraepithelial neoplasia that involves the anus in a patient with 18 years' history of UC (*left*: white light; *right*: NBI)

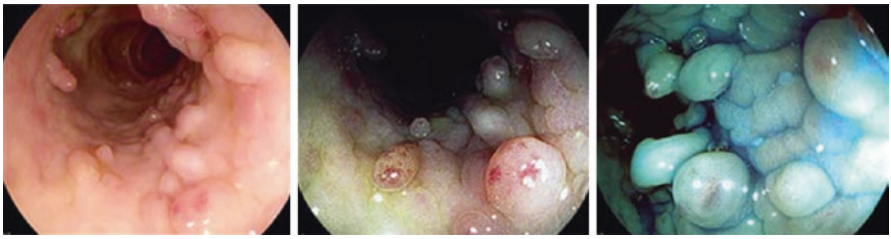


Fig. 25.8 A flat lesion of adenoma with low-grade intraepithelial neoplasia (*black arrow*) surrounded by inflammatory polyps in a patient with 15 years' history of UC (from *left* to *right*: white light, I-SCAN, indigocarmine spray)

25.6 Challenges and Opportunities

Experts around China have established a national IBD collaboration network, and great advances have been made on the epidemiology, basic biology, and clinical management of IBD since the first decade of this century. The huge population and vast area of China provide great opportunities for basic and clinical studies in IBD. Aware of the gap that presently exists in IBD research between China and the Western world, we aim to develop our own evidence-based guidelines and multidisciplinary approach strategies that fulfill the ever-growing healthcare need of Chinese IBD patients.

References

1. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009;361(21):2066–78.
2. Chen M, Shen B. Endoscopic therapy for Kock pouch inflammatory bowel disease. Gastrointest Endosc. 2014;80(2):353–9.
3. Larkin E. Beethoven's illness: a likely diagnosis. Proc R Soc Med. 1971;64(5):493–6.
4. Pan GZ. To narrow the gap with the international, to strengthen the study of inflammatory bowel disease. In: Research progress of inflammatory bowel disease. Cheng Du: Sichuan Science and Technology Press; 2000. pp. 41–43.
5. Liu TH, Pan GZ, Chen MZ. Crohn's disease. Clinicopathologic manifestations and differential diagnosis from enterocolonic tuberculosis. Chin Med J. 1981;94(7):431–40.
6. Yang H, Li YM, Wu W, et al. The incidence of inflammatory bowel disease in northern China: a prospective population-based study. PLoS One. 2014;9:e101296.
7. Zeng ZR, Zhu ZH, Yang YY, et al. Incidence and clinical characteristics of inflammatory bowel disease in a developed region of Guangdong province, China: a prospective population-based study. J Gastroenterol Hepatol. 2013;28(7):1148–53.
8. Zhao J, Ng SC, Lei Y, et al. First prospective, population-based inflammatory bowel disease incidence study in mainland of China: the emergence of "Western disease". Inflamm Bowel Dis. 2013;19(9):1839–45.
9. Ouyang Q, Xue LY. Inflammatory bowel disease in the 21st century in China: turning challenges into opportunities. J Dig Dis. 2012;13(4):195–9.
10. Lee YJ, Yang SK, Byeon JS, et al. Analysis of colonoscopic findings in the differential diagnosis between intestinal tuberculosis and Crohn's disease. Endoscopy. 2006;38(6):592–607.
11. Zhou ZY, Luo HS. Differential diagnosis between Crohn's disease and intestinal tuberculosis in China. Int J Clin Pract. 2006;60(2):212–4.
12. Li Y, Zhang LF, Liu XQ, et al. The role of in vitro interferon γ-release assay in differentiating intestinal tuberculosisfrom Crohn's disease in China. J Crohns Colitis. 2012;6(3):317–23.
13. Mao R, Liao WD, He Y, et al. Computed tomographic enterography adds value to colonoscopy in differentiating Crohn's disease from intestinal tuberculosis: a potential diagnostic algorithm. Endoscopy. 2015;47(4):322–9.
14. Cooperative Group of Inflammatory Bowel Diseases of Digestive Disease of Chinese Medical Association: Chinese consensus on standard management of inflammatory bowel diseases. CJD. 2012; 32:796–813.
15. Tedesco FJ, Hardin RD, Harper RN. Infectious colitis endoscopically simulating inflammatory bowel disease: a prospective evaluation. Gastrointest Endosc. 1983;29(3):195–7.
16. Li E, Stanley Jr SL. Protozoa. Amebiasis. Gastroenterol Clin N Am. 1996;25(3):471–92.

17. Wang LD, Chen HG, Guo JG, et al. A strategy to control transmission of *Schistosoma japonicum* in China. N Engl J Med. 2009;360(2):121–8.
18. Yi F, Zhao J, Luckheeram RV, et al. The prevalence and risk factors of cytomegalovirus infection in inflammatory bowel disease in Wuhan. Central China Virol J. 2013;10:43.
19. Landsman MJ, Sultan M, Stevens M, et al. Diagnosis and management of common gastrointestinal tract infectious diseases in ulcerative colitis and Crohn's disease patients. Inflamm Bowel Dis. 2014;20(12):2503–10.
20. Li J, Li P, Bai J, et al. Discriminating potential of extraintestinal systemic manifestations and colonoscopic features in Chinese patients with intestinal Behçet's disease and Crohn's disease. Chin Med J. 2015;128(2):233–8.
21. Naymagon S, Marion JF. Surveillance in inflammatory bowel disease: chromoendoscopy and digital mucosal enhancement. Gastrointest Endosc Clin N Am. 2013;23(3):679–94.

Chapter 26
Endoscopy in Inflammatory Bowel Disease: A South Asian Perspective from India

Amarender Singh Puri

Abstract Inflammatory bowel disease is an emerging problem in India with a relatively high prevalence rate, especially in the northern parts of the country. In line with other Asian data, ulcerative colitis is far more prevalent than Crohn's disease in India. Endoscopy services in India are still restricted to metropolitan areas and larger cities, with very limited availability in the smaller cities. Availability of colonoscopy has been one of the major factors responsible for the paradigm shift in the recognition of IBD and its differentiation from intestinal tuberculosis in India. Therapeutic endoscopy as a non-surgical treatment modality for IBD is restricted to a few centers in the country. Colorectal carcinoma occurs at a much lower rate in patients with or without IBD possibly due to the low consumption of red meat in India. For this reason, guidelines for surveillance colonoscopy in patients with ulcerative colitis are not practiced routinely in most centers. Procedures such as chromoendoscopy and endoscopic submucosal dissection are still in their infancy in India. With greater numbers of IBD patients expected in the future, there is a dire need to improve the existing status of endoscopic and colonoscopic services in the country.

Keywords Inflammatory bowel disease • Intestinal tuberculosis • Ulcerative colitis • Crohn's disease

A.S. Puri
Department of Gastroenterology, GB Pant Institute of Medical Education and Research, 1, Jawaharlal Nehru Marg, New Delhi 110002, India
e-mail: amarender.puri@gmail.com

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_26

Inflammatory bowel disease (IBD) is a relatively new entrant in the Indian subcontinent, as bacterial, mycobacterial, or protozoal infections accounted for the vast majority of enteric and colonic diseases in the past. Over the last six decades there has been a paradigm shift in the nature of intestinal diseases in India, which can be directly attributed to the improvement in socio-economic status since India achieved its independence in 1947. The other major factor for the increased recognition of IBD in India has been the development of super-specialty centers which over the years have trained a large number of gastroenterologists, who have created an awareness of IBD in the Indian subcontinent. Currently there are at least 21 centers in India which offer a post-doctoral degree in the super-specialty of gastroenterology in India. Although this appears to be a large number, it is woefully short of covering the needs of a nation which has a population exceeding 1.2 billion. To cover the severe deficiency of specialists in various fields due to the limited availability of seats at the post-doctoral level, the Indian government started diploma courses in almost all super-specialties in the 1990s under an autonomous body called the National Board of Examinations [1]. Needless to say, this innovative idea has become a huge success and has gone a long way in reducing the shortfall of trained specialists in many parts of India.

Similarly, endoscopy was first introduced in India in the mid-1980s at a few select centers; however over the next three decades endoscopy services have become available not only in the metro cities but also in the smaller cities all over the country. India does, however, have the dubious distinction that no Board certification is required by a physician for offering this service in the public domain. This has resulted in several physicians and surgeons performing endoscopic procedures even though they have received no formal training in endoscopy. This is the prime reason for the wide disparity in the competence of endoscopists in India. The disparity is much more marked in colonoscopic procedures as compared to upper GI endoscopic procedures.

The first report of ulcerative colitis (UC) in India came in the 1930s. It remained an esoteric disease till Khosla et al. showed a relatively high prevalence rate of 44 per 100 K in the northern part of the country [2]. At about the same time, it was recognized that there was a high prevalence of IBD in Indian migrants to the UK that was at par or even higher than the native Caucasian population [3]. Sood et al. undertook another study in the Indian state of Punjab and confirmed two findings: first, that the prevalence of the disease was nearly identical to the earlier study by Khosla et al. and second, that the ethnic group of Punjabis were more prone to develop IBD, as shown by the migrant studies from the UK [4]. More recently, the Indian Society of Gastroenterology constituted a task force to evaluate the epidemiology and clinical spectrum of IBD [5, 6]. Since the task force data was derived from a questionnaire filled by practicing gastroenterologists, the information derived from it cannot be as authentic as actual field surveys and epidemiological studies.

Crohn's disease (CD) was considered to be rare in India but of late, several studies have cleared this misconception and the disease is now being recognized in different parts of the country [5]. As was the case with UC, it was data from the UK

which brought to light the fact that CD occurs with the same frequency in the Asian immigrants as the indigenous Caucasian population [7]. The effect is more marked in the second generation of immigrants who were born in their adopted country. Unlike many Asian or European countries, the ethnic population of India is not homogenous as it is a mixture of Caucasian population in the northern region, Mongoloid in the eastern region and Dravidian in the southern part of the country. The southern part of the country has reportedly a higher incidence of CD than the northern region. The reverse trend supposedly exists for UC; however, there is no published data on the epidemiology from most parts of the country. All published data on the prevalence of UC has come only from the northern regions of the country, and more data is needed to substantiate these observations. Similarly, there are no published data to support the claim that Crohn's colitis (L 2 disease on Montreal Classification) occurs more commonly than small-bowel Crohn's or Crohn's ileocolitis.

The recognition of CD in India has certainly added to the diagnostic confusion, as both CD disease and TB have a predilection for the ileo-cecal region. Additionally, transmural involvement with granulomas is the histopathologic hallmark of both the diseases. Despite all the advances in the recent past, the clinical differentiation between the two diseases remains a major diagnostic dilemma in regions of the world where both the diseases occur. Empirical ATT for a period of 6–8 weeks is still a common practice followed by many gastroenterologists when definitive evidence (AFB or caseating granuloma) of tuberculosis is lacking.

The introduction of endoscopy in clinical practice in India resulted in a paradigm shift from radiologically-based diagnosis to histologic diagnosis for several diseases. In the pre-endoscopic era, the diagnosis of intestinal TB was largely based on a combination of clinical experience supported by barium studies. After the introduction of colonoscopy, characteristic features of tubercular involvement of the colon were recognized and more importantly, acid fast bacilli could be demonstrated in the biopsy specimens along with granulomas to give a definite diagnosis [8]. Subsequently, gross differentiating features at colonoscopy between CD and intestinal TB were also recognized, and this is one of the major factors which has led to the increased recognition of CD in India.

Therapeutic endoscopy for IBD in India is limited to a few advanced centers only. Single- or double-balloon enteroscopy is the domain of a select teaching hospitals or large set-ups in the private sector. This is largely due to the fact that the ratio of UC to CD is skewed heavily in favour of the former. Our own unpublished data suggests a ratio of 20:1 in favour of UC. The limited availability of fluoroscopy units in many private and government sector hospitals is a major limiting factor for therapeutic work in this field in India. Only a small fraction of small-bowel strictures attributed to CD or intestinal TB are managed by small-bowel therapeutic endoscopy. The average physician when faced with the problem of luminal obstruction in the setting of CD or intestinal TB is more likely to send the patient to the surgeon due to the above-mentioned constraints. A surgical option is perceived as a single-time therapy, whereas endoscopy is considered as repetitive procedure and therefore associated with a higher financial burden.

We have recently published our experience documenting that a combination therapy of endoscopic balloon dilatation under fluoroscopic guidance and anti-tubercular therapy should be the initial therapy for tubercular strictures of the pyloro-duodenal region, and that surgery should be reserved only for those who fail medical therapy [7]. Until there is wider availability of centers offering endotherapy for small-bowel diseases at a reasonable cost, the situation is unlikely to change in the immediate future.

There are significant differences between UC in the West or developed nations versus south Asian countries (India). One of the major differences pertains to the much lower incidence of colonic malignancy in the Indian patients with UC versus from the West. It is a well known fact that the incidence and prevalence of colorectal carcinoma (CRC) unrelated to UC in India is one of the lowest in the world. This has been attributed to the low consumption of red meat in India vis a vis the West. Hence, it is not surprising that the occurrence of CRC in patients with UC is also much lower than the figures from the West. Venkatraman et al. reported that in patients with a disease duration of 10–20 years the incidence density of CRC was 2.3/1,000 person years for all patients with UC and 4.5/1,000 for patients with pancolitis. The high incidence of CRC in both UC and non-IBD related CRC in the West is largely responsible for the innovations to detect early cancer through screening programmes and chromoendoscopy. The direct fallout of this has been the development of new endoscopy-based techniques such as endoscopic submucosal dissection (ESD) for excision of localized tumors. Routine screening after the age of 50 years for CRC is not advocated in India as it is not cost-effective. Similarly, despite the available guidelines, only a small proportion of patients with UC undergo surveillance colonoscopies. Chromoendoscopy for screening of CRC in UC patients is hardly being done, even at large centers. The technique of ESD is very much in its infancy in India, and there are less than five centers in India which have an adequate experience in ESD.

In summary, despite the increasing recognition of IBD in India, endoscopy services are largely limited to the metropolitan areas and the larger cities. The differentiation of TB from Crohn's disease remains an unsolved problem in the Indian context. As compared to the West or even some developed Asian countries, therapeutic small- and large-bowel endoscopic procedures are available at a few select centres only. With greater numbers of IBD patients expected in the future, there is a dire need to improve the existing status of endoscopic and colonoscopic services in the country.

References

1. Mulder CJ, Puri AS, Reddy DN. Gastroenterology training in private hospitals: India versus South Africa. World J Gastroenterol. 2010;16(8):948–52.
2. Khosla SN, Girdhar NK, Lal S, Mishra DS. Epidemiology of ulcerative colitis in hospital and select general population of northern India. J Assoc Phys India. 1986;34:405–7.

3. Probert CS, Jayanthi V, Pinder D, Wicks AC, Mayberry JF. Epidemiological studies of ulcerative proctocolitis in Indian migrants and the indigenous population of Leicestershire. Gut. 1992;33:687–93.
4. Sood A, Midha V, Sood N, Bhatia AS, Avasthi G. Incidence and prevalence of ulcerative colitis in Punjab, North India. Gut. 2003;52:1587–5900.
5. Makhariya GK, Ramakrishna BS, Abraham P, et al. Indian Society of Gastroenterology task force on inflammatory bowel disease. Survey of inflammatory bowel diseases in India. Indian J Gastroenterol. 2012;31:299–306.
6. Ramakrishna BS, Makhariya GK, Abraham P, et al. Indian Society of Gastroenterology Task force on inflammatory bowel disease. Indian Society of Gastroenterology consensus on ulcerative colitis. Indian J Gastroenterol. 2012;31:307–23.
7. Fellows IW, Freeman JG, Holmes GK. Crohn's disease in the city of Derby, 1951–1985. Gut. 1990;31:1262–5.
8. Pullimood AB, Ramakrishna BS, Kurian G, et al. Endoscopic mucosal biopsies are useful to distinguish granulomatous colitis due to Crohn's disease from tuberculosis. Gut. 1999;45: 537–41.
9. Puri AS, Sachdeva S, Mittal VV, et al. Endoscopic diagnosis, management and outcome of gastroduodenal tuberculosis. Indian J Gastroenterol. 2012;31(3):125–9.

Chapter 27
Endoscopy in Inflammatory Bowel Disease: Asian Perspective—Singapore

Webber Pak Wo Chan, Choon Jin Ooi, and Roy Soetikno

Abstract The incidence and prevalence of inflammatory bowel disease is rising in Asia. The diagnosis of IBD remains challenging, given the high incidence of infectious colitis and TB in this region. Endoscopy serves a number of functions in the management of IBD. In this chapter, we will review the current care of patients with IBD, with a focus in the utility of endoscopy in Singapore. Endoscopy is essential in the diagnosis of IBD, exclusion of other differential diagnosis and for colorectal cancer surveillance.

Keywords IBD, epidemiology • Tuberculosis • High-definition endoscopy • Chromoendoscopy • Colorectal cancer

27.1 Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic immune-mediated diseases of unknown etiology with both intestinal and extraintestinal manifestations. The incidence and prevalence of IBD have been reported to be lower in Asia as compared to the Americas and Europe. Recently, the Asia–Pacific Crohn's and Colitis Epidemiology (ACCESS) study [1] group showed that there is a rising prevalence and incidence trend in the last two decades. The crude annual overall incidence values per 100,000 individuals were 1.37 for IBD in Asia in 2011. In Singapore, the crude annual incidence of IBD was

W.P.W. Chan • R. Soetikno
Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore, Singapore

C.J. Ooi (✉)
Gleneagles Medical Centre, 6A Napier Road, 258500 Singapore, Singapore
e-mail: oseejay@gmail.com

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_27

1.06 per 100,000 persons in 2011–2012, with UC occurring more than CD (0.61 versus 0.4 per 100,000 persons). The ratios of UC to CD were 2.0 in Asia and 0.5 in Australia. Note that complicated CD (stricturing, penetrating, or perianal disease) was more common in Asia than Australia (52% vs 24%; $P < 0.001$), and that a family history of IBD was less common in Asia (3% vs 17%; $P < 0.001$) [1].

Endoscopy serves a number of functions in the management of IBD including diagnosis, monitoring of treatment response, surveillance, and treatment of complications. This chapter provides a snapshot of the current care of patients with IBD, with a focus on the utility of endoscopy in Singapore.

27.2 Colonoscopy with Ileoscopy: Diagnosis

The prevalence of tuberculosis (TB) is high in Singapore, similar to many other Asian countries. Therefore, differentiating IBD from intestinal tuberculosis is critical in the management of IBD. This is in concert with the Asia Pacific Consensus Statements on Crohn's Disease [2]. According to the World Health Organization (WHO), there were an estimated nine million people who developed TB in 2013, of whom more than half (56%) were in the South-East Asia and Western Pacific Regions [3]. India and China alone accounted for 24% and 11% of total cases respectively. In Singapore, the incidence rate of TB was 37.6 per 100,000 population in 2013 [4], showing a slight decrease compared with the incidence rate between 2009 and 2012, which stagnated at 38.6–40.9 per 100,000 population. There were a total of 2,962 cases of TB notified in 2013. This comprised 1420 new and 119 relapsed cases among Singapore residents (citizens and permanent residents), and 1,381 new and 42 relapsed cases among non-residents (long- and short-term pass holders). The majority (86.3%) of cases had pulmonary TB with or without extrapulmonary involvement, while the remainder (13.7%) had exclusively extrapulmonary TB. The incidence of gastrointestinal TB in Singapore is similar to other published reports. In a retrospective review of 57 patients who were diagnosed with abdominal TB in a Singapore hospital between 2001 and 2007, the ileum was the most common region affected [5].

There is a close resemblance in the clinical, radiological, endoscopic, surgical, and histological features of CD and gastrointestinal TB. On endoscopy, gastrointestinal TB can present with segmental ulcers and colitis, inflammatory strictures, or hypertrophic lesions resembling polyps and masses. canon rare occasions it presents as pancolitis indistinguishable from ulcerative colitis. A Korean prospective study [6] found that intestinal TB usually has less than four segments involved, a patulous ileocecal valve, transverse ulcers, and more scars. In contrast, anorectal involvement, longitudinal ulcers, aphthous ulcers and a cobblestone appearance were all significantly more common in patients with CD than in patients with gastrointestinal TB. A new endoscopic scoring system to differentiate between CD and intestinal TB has been proposed by the authors, with a positive predictive value for CD of 95% and 89% for tuberculosis. However, it has not been validated for routine use.

In our practice, during colonoscopy with ileoscopy, multiple biopsy samples are taken from ulcer margins and sent for acid-fast bacilli smear, and cultures, as well as tuberculosis polymerase chain reaction (PCR) assay. Where it is not possible to confidently differentiate gastrointestinal tuberculosis from CD, a trial of 8–12 weeks of anti-tuberculosis therapy is recommended [2]. In patients showing no or partial symptom response at 8–12 weeks, a repeat colonoscopy should be done. To differentiate gastrointestinal tuberculosis from CD, a colonoscopy is suggested to document mucosal healing at the completion of anti-tuberculous therapy [2].

27.3 Available Clinical Care

We reviewed the available care in the tertiary hospitals in Singapore. We found that IBD teams that are made up of consultants, nurse practitioners, and nutritionists provide the majority of the care. These teams provide inpatient and outpatient care. For complex cases, they work collaboratively with colorectal surgeons and radiologists.

27.4 Colonoscopy with Ileoscopy: Surveillance

There was limited data on the prevalence and incidence of IBD related-colorectal cancer (CRC) in Asia. The only population-based study in the Asia-Pacific region was conducted in Korea (between 1970 and 2005), which showed that the period prevalence of CRC in patients with UC was 0.37% [7]. A multi-center retrospective study conducted in China (between 1998 and 2009) reported that the period prevalence of CRC in Chinese UC patients was 0.87% [8]. Both studies revealed a lower prevalence than that reported by Eaden et al. [9]. The cumulative risk of UC–CRC in the former study was 0.7% by 10 years, 7.9% by 20 years, and 33.2% by 30 years, whereas that reported in the latter was 1.15% by 10 years, 3.56% by 20 years, and 14.36% by 30 years, both of which were comparable to that of Western countries.

The goal of surveillance programs is early detection of CRC and mortality reduction in patients with IBD. Among the major IBD referral centers in Singapore, endoscopic screening and surveillance is offered as per international guidelines [10], i.e., all patients with a history of UC (including ulcerative proctitis) and Crohn's colitis are offered a screening colonoscopy approximately 8 years after the onset of clinical symptoms. Surveillance colonoscopy is offered for UC patients with left-sided or extensive colitis, and for Crohn's colitis involving more than one segment of the colon or at least one-third of the colon. Subsequent surveillance intervals depend on the risk factors for IBD-associated colorectal neoplasia (IBD–CRN). Patients with the highest risk of IBD–CRN (concomitant primary sclerosing cholangitis, extensive colitis, active endoscopic or histologic inflammation, a family history of CRC in a first-degree relative before 50 years of age, personal history of

dysplasia, presence of strictures on colonoscopy) are recommended for annual surveillance, whereas patients with the lowest risk are recommended for less frequent surveillance intervals, varying from 2 to 5 years.

Although the SCENIC consensus [11] suggested high-definition pancolonic chromoendoscopy for colorectal cancer surveillance in IBD, many centers are still practicing the traditional four-quadrant biopsies every 10 cm from cecum to rectum [12]. Endoscopically visible lesions detected in segments of the colon that are uninvolved with colitis are treated as sporadic adenomas, and we follow standard post-polypectomy surveillance recommendations. For lesions identified in an area of known colitis, we assess for endoscopic resectability. We refer the clearly demarcated lesions without endoscopic features of submucosal invasion to our expert endoscopist for resection. En-bloc resection is preferred whenever possible. An endoscopically detected dysplastic lesion that is not amenable to endoscopic resection is an indication for colectomy. Other indications for proctocolectomy include presence of dysplasia at the base of the lesion, endoscopically invisible high-grade dysplasia or multifocal low-grade dysplasia.

27.5 Conclusions

We see a rising incidence and prevalence of IBD in Asian countries in the last two decades. At present, the diagnosis of IBD remains challenging given the high incidence of TB in Asia. Endoscopy is widely used in the care of IBD patients in Singapore.

References

1. Ng SC, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific Crohn's and colitis epidemiology study. Gastroenterology. 2013;145(1):158–65.
2. Ooi CJ, et al. The Asia Pacific consensus statements on Crohn's disease part 1: definition, diagnosis and epidemiology. J Gastroenterol Hepatol. 2016;31(1):45–55. doi: 10.1111/jgh.12956.
3. WHO. Global tuberculosis report 2014. Geneva: World Health Organization, 2014. http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf (accessed May 16 2017).
4. The Ministry of Health, Singapore. Epidemiological News Bulletin. Oct–Dec;40(4):68–76. https://www.moh.gov.sg/content/dam/moh_web/Publications/Epidemiological%20News%20Bulletin/ENB04Q_14.pdf. (accessed May 17 2017).
5. Tan KK, Chen K, Sim R. The spectrum of abdominal tuberculosis in a developed country: a single institution's experience over 7 years. J Gastrointest Surg. 2009;13(1):142–7.
6. Lee YJ, Yang SK, Byeon JS, et al. Analysis of colonoscopic finding in the differential diagnosis between intestinal tuberculosis and Crohn's disease. Endoscopy. 2006;38:592–7.
7. Kim BJ, Yang SK, Kim JS, et al. Trends of ulcerative colitis-associated colorectal cancer in Korea: a KASID study. J Gastroenterol Hepatol. 2009;24:667–71.

8. Gong W, Lv N, Wang B, et al. Risk of ulcerative colitis-associated colorectal cancer in China: a multi-center retrospective study. Dig Dis Sci. 2012;57:503–7.
9. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48:526–35.
10. ASGE Standards of Practice Committee. The role of endoscopy in inflammatory bowel disease. Gastrointest Endosc. 2015;81(5):1101–21.
11. Laine L, Kaltenbach T, Barkun A, McQuaid KR, Subramanian V, Soetikno R. SCENIC guideline development panel. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastroenterology. 2015;148(3):639–51.
12. Rubin CE, Haggitt RC, Burmer GC, et al. DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. Gastroenterology. 1992;103:1611–20.

Chapter 28
Endoscopy in Inflammatory Bowel Disease: Western Perspectives-North America

Hans Herfarth and Todd Baron

Abstract Endoscopy is essential for the diagnosis and management of patients with inflammatory bowel diseases. Endoscopic procedures are used to make the initial diagnosis of inflammatory bowel disease (IBD), distinguish Crohn's disease from ulcerative colitis, evaluate disease extent and disease activity, assess response to therapy, survey for dysplasia, and provide endoscopic treatment. This review focuses on the purpose of different endoscopic procedures including upper and lower endoscopy, and capsule endoscopy as well as balloon enteroscopy in the evaluation and management of patients with IBD in the United States.

Keywords IBD • Crohn's disease • Ulcerative colitis • Colonoscopy • Capsule endoscopy • Balloon enteroscopy

28.1 Introduction

Endoscopy and radiological imaging are the fundamental basis for the diagnosis and management of suspected or established inflammatory bowel disease (IBD), in conjunction with supportive clinical, microbiological, and histological data. Whereas the esophagus, stomach, duodenum, terminal ileum, and colon are accessible by upper- and lower-GI endoscopy, complete visualization of the small bowel is only possible using capsule endoscopy (CE) or single- or double-balloon enteroscopy (SBE; DBE). In the U.S., endoscopic and radiologic imaging procedures for suspected IBD, Crohn's disease (CD), or re-evaluation of patients with established ulcerative colitis (UC) follow a classic sequence of combining both imaging techniques (Figs. 28.1 and 28.2). It is noteworthy that transabdominal

H. Herfarth (✉) • T. Baron
Division of Gastroenterology and Hepatology, University of North Carolina, Bioinformatics Bldg, CB#7080, Chapel Hill, NC 27599, USA
e-mail: hherf@med.unc.edu

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_28

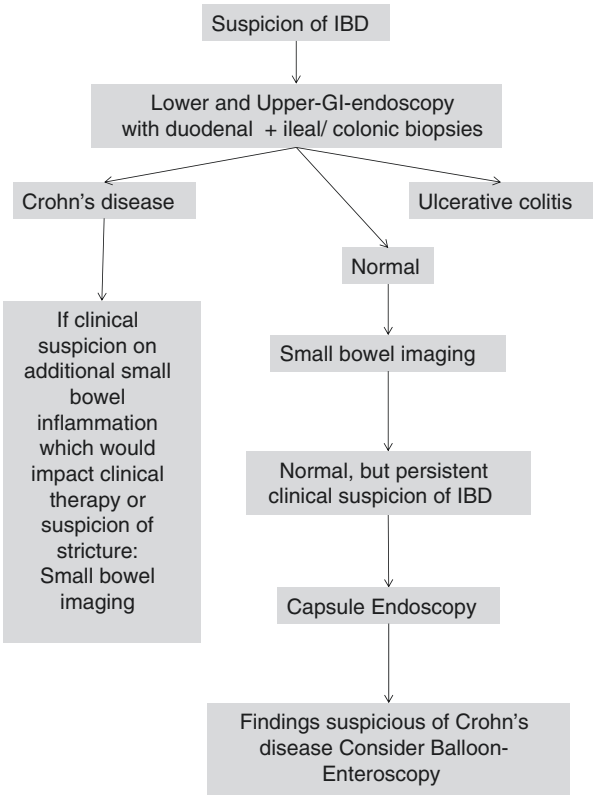


Fig. 28.1 Endoscopic and radiologic algorithm for patients with suspected IBD (adapted from [1])

ultrasound, which is commonly used as a first-line imaging technique in Europe for assessing small and large intestinal pathologies, is not incorporated in the diagnostic algorithms in the U.S.

28.2 Use of Colonoscopy and/or Upper-Endoscopy in the United States

Colonoscopy is the overall preferred/standard screening procedure for the confirmation of either CD or UC in patients with clinical suspicion of IBD. Sigmoidoscopy is only a diagnostic choice in established UC to evaluate disease activity and in patients with established IBD in whom there is a suspicion of superimposed infection such as CMV and Clostridium difficile [2]. Moreover, apart from radiologic analyses of the small bowel in patients with CD, colonoscopy is the method of choice for re-evaluation of disease activity of UC and CD, and in cases where there is loss of response to therapy. Also, colonoscopy is recommended for the

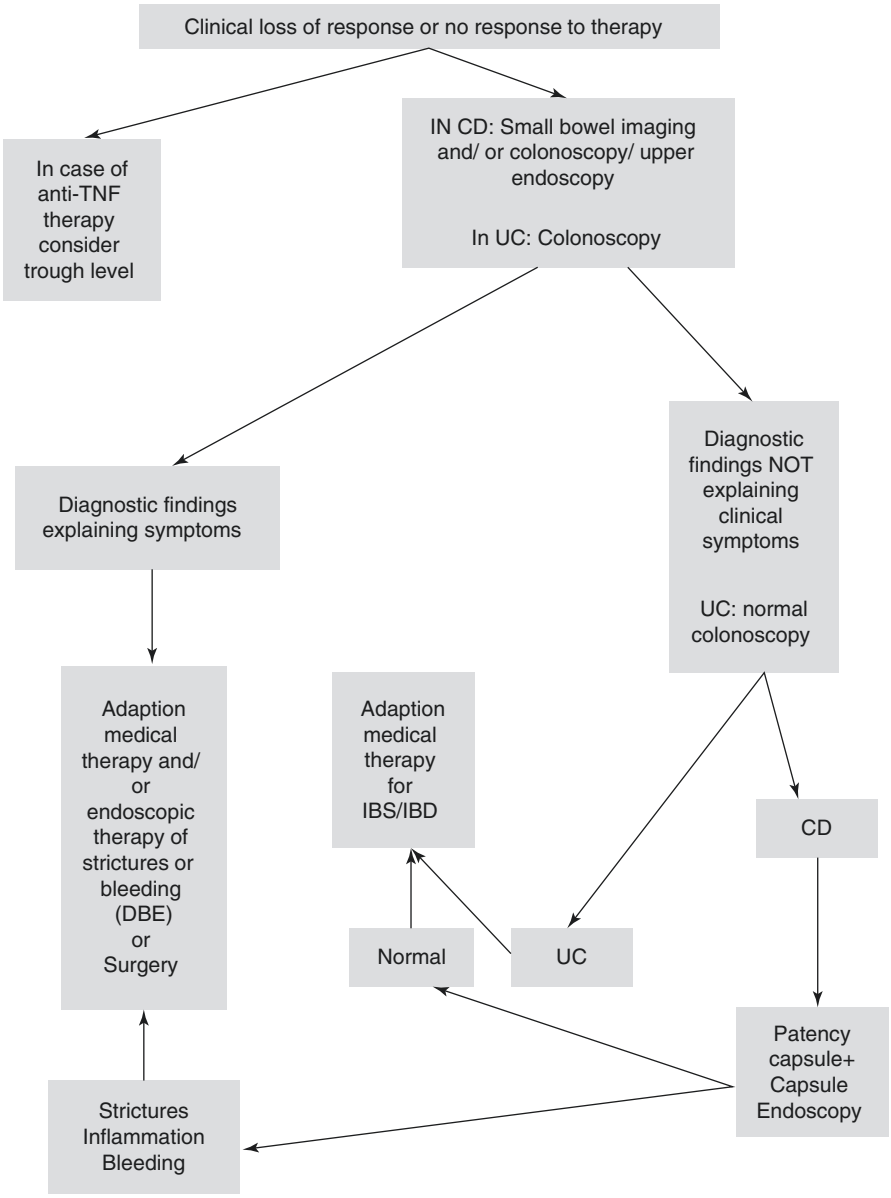


Fig. 28.2 Endoscopic and radiologic algorithm for patients with established IBD and clinical symptoms while receiving medical therapy (adapted from [1])

assessment of CD recurrence 6–12 months after resective surgery to adapt or modify medical therapy based on the endoscopic findings [3].

In adult patients in the absence of clinical signs for upper-GI involvement (e.g., epigastric pain), upper-GI endoscopy is usually not performed at the initial diagnostic evaluation for IBD. In contrast, in pediatric patients, CD often appears as a UC-like phenotype at colonoscopy; due to a relatively high percentage of upper-GI involvement in this age group an upper-endoscopy is always recommended as a staging procedure for suspected IBD in children [4].

In the US, a new strategy termed "Treatment to Target" is currently being passionately discussed [5, 6]. The aim of this strategy is the establishment of mucosal healing, using escalation of therapy in patients with persistent endoscopically visible inflammation until mucosal healing is achieved. There are no prospective studies that have proven such an approach, which requires frequent colonoscopies in patients with enduring endoscopic disease activity (every 3–6 months). In patients with small-bowel involvement this might consist of repeat radiological imaging procedures to re-evaluate the impact of therapeutic escalation.

28.3 CE in IBD

For the initial assessment of small-bowel involvement in patients with IBD, one has to keep in mind that neither computer tomography (CT) nor magnetic resonance imaging (MRI) are able to visualize superficial ulcers in the small bowel. CE has been proven to be superior to both imaging modalities in patients with suspected CD [7–9]. However, due to the risk of concurrent strictures even in clinically asymptomatic patients, a radiological evaluation of the small intestine is always recommended before performing CE [10]. The main problem of diagnosing CD in patients with otherwise negative upper and lower endoscopy workup is (a) the lack of histological verification of the findings, which can be only achieved with a balloon enteroscopy, and (b) the lack of validated "diagnostic criteria for small-bowel involvement. This is illustrated by a 12-month follow-up study conducted in an American tertiary IBD center, in which 102 patients with suspected CD underwent CE after normal or equivocal findings on colonoscopy and radiological small-bowel imaging [11]. Only 13% of the patients who were found to have small-bowel ulcerations were subsequently diagnosed with CD based on endoscopic or radiographic re-evaluations. The overall sensitivity of CE (defined as any visualized small-bowel ulcers) for the diagnosis of CD (within 12 months of CE) was 85%, the specificity was 73%, the positive predictive value (PPV) was 31%, and the negative predictive value (NPV) was 97%. The PPV increased to 50% if >3 ulcers were used as a criterion for CD on the initial capsule study. Given the high NPV of a normal CE study, the real value is the exclusion of

the diagnosis of CD in patients with suspected small-bowel inflammation and an otherwise negative previous workup.

As for patients with established CD, one retrospective single-center analysis which included 128 capsule endoscopies in patients with IBD reported a change in medication in 62% of the patients in the 3 months after the CE, with 40% commencing a new IBD medication based on the findings seen on CE [12].

28.4 Balloon Enteroscopy

SBE or DBE are available endoscopic modalities that can allow evaluation of the small bowel in patients with suspected or proven small-bowel CD. The advantages include the possibility to obtain biopsies and perform interventions such as dilation of strictures, which are sometimes not recognized by CT or MRI imaging [13, 14]. The disadvantages, compared to CE, are the need for sedation and the risk of perforation, which is estimated at around 1% in patients with IBD [10, 15, 16]. Also, DBE might be unsuccessful due to the presence of fixed bowel loops in the setting of previous surgery or inflammation. A recent retrospective analysis of five academic centers in the U.S. analyzed 98 DBE procedures performed over a 5-year period in 81 patients (47% known CD) [17]. In 17% of the patients, DBE was unsuccessful due to fixed bowel loops or inability to intubate the ileocecal valve. The overall diagnostic yield was 83%, which impacted the management in 79% of patients. Whereas the main indications for DBE in patients with established CD were abdominal pain (37%) and bleeding/anemia (39%), the indications in patients with suspected CD were abnormal radiologic imaging (44%) or abnormal CE (60%).

28.5 Specific Situations as Indications for Endoscopy

28.5.1 The Role of Endoscopy After Loss of Response to Anti-TNF Therapy

Loss of response to anti-TNF therapy occurs in a considerable number of patients with IBD [18]. Currently, there are no strict guidelines in the U.S. for management of this situation. It is generally recommended that an anti-TNF drug trough level be obtained (available in the U.S. for infliximab and adalimumab, but not yet for certolizumab pegol or golimumab). Based on the drug trough level and the presence or absence of anti-drug antibody, three different clinical scenarios for adapting therapy in these patients are possible [19]. Scenario 1: low or undetectable

anti-TNF trough levels and negative or very low anti-drug antibodies; scenario 2: low or undetectable anti-TNF trough levels and high anti-drug antibodies; scenario 3: high anti-TNF trough level. In the first two scenarios, the treatment decision may be made without an endoscopic evaluation, which is either to increase the dose and/or frequency of anti-TNF therapy and to consider adding an immunosuppressive (scenario 1) or change to another anti-TNF agent or out-of-class drug (scenario 2). In the third scenario, an endoscopic/colonoscopic evaluation is imperative.

28.5.2 Surveillance Colonoscopy for Long-Standing UC or Crohn's Colitis

Eight years after the initial diagnosis of left-sided or pan UC or a diagnosis of Crohn's colitis with involvement of >1/3 of the colon, patients should undergo surveillance colonoscopy with biopsies for dysplasia [2, 20]. Depending on the results, 1–3-yearly surveillance colonoscopies should be pursued. There are no specific recommendations for the follow-up time interval based on the degree of intestinal inflammation, as provided in the British Guidelines [21]. Also, adherence to the recommended programs in the U.S. seems to be suboptimal, and is as low as 25% [22].

The most recent 2015 American Society for Gastrointestinal Endoscopy (ASGE) guidelines recommend chromoendoscopy with pancolonic dye spraying and targeted biopsies, with consideration of two additional biopsies from each colon segment for histologic staging [2]. However, despite the superiority of this technique compared to conventional colonoscopy in detecting neoplasia in randomized trials, real-world experience suggests that chromoendoscopy is not superior [23]. Therefore, a conventional colonoscopy with random four-quadrant biopsies every 10 cm, limited to the greatest extent of endoscopic or histologic involvement documented by any prior colonoscopy and targeted biopsies of any suspicious lesions, is still considered a valid option.

28.5.3 Capsule Endoscopy in Patients with Suspected Strictures

CE can be performed in patients with established CD when imaging results from CT, MRI, or other radiological methods are not conclusive enough to explain symptoms (e.g., continuing diarrhea despite negative upper and lower GI-endoscopy and negative CT-enterography). Very short small-bowel strictures outside the reach of conventional upper and lower endoscopy are often not depicted by radiological imaging [13]. Thus, CE offers the possibility of not only visualizing but also "marking" the site of the stricture, and facilitates further radiological guided balloon-enteroscopic

or surgical approaches. In contrast, a patency capsule would start dissolving and would be not detectable 24–36 h after intake. The CE approach without patency capsule should be only performed in centers with accessible balloon-enteroscopy in case of capsule retention and should be coordinated with an experienced IBD surgeon. In our experience at the University of North Carolina, capsule retention occurred in 14 patients with suspected but not proven strictures [12]. Spontaneous clearance occurred in seven of the patients within 2 weeks, whereas the seven other patients underwent either surgical resection ($n = 5$) or endoscopic retrieval ($n = 2$).

28.6 Summary and Conclusion

In the United States, colonoscopy is the first-line diagnostic approach for patients with suspected or proven IBD. However, in patients with established small-bowel CD or suspicion of extraintestinal complications such as abscesses, either CT-enterography or MR-enterography is the preferred initial diagnostic approach. CE is only used if radiological evaluation of the small bowel is equivocal or negative despite a strong clinical suspicion of small-bowel CD, or in patients with persistent therapy refractory small-bowel CD. Double-balloon enteroscopy is rarely conducted as a first-line diagnostic approach, but rather is used to obtain biopsies to prove small-bowel CD. Balloon enteroscopy is also used in patients with established CD for endoscopic treatment of small-bowel strictures, to assess occult bleeding, or to retrieve retained capsule endoscopy video cameras.

References

1. Herfarth H. Update imaging in inflammatory bowel diseases. Dig Dis. 2013;31:345–50.
2. American Society for Gastrointestinal Endoscopy Standards of Practice Committee, Shergill AK, Lightdale JR, et al. The role of endoscopy in inflammatory bowel disease. Gastrointest Endosc. 2015;81:1101–21.
3. Swoger JM, Regueiro M. Evaluation for postoperative recurrence of Crohn disease. Gastroenterol Clin N Am. 2012;41:303–14.
4. Turner D, Levine A, Escher JC, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr. 2012; 55:340–61.
5. Bouguen G, Levesque BG, Feagan BG, et al. Treat to target: A proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol. 2015;13:1042–50.
6. Bouguen G, Levesque BG, Pola S, et al. Feasibility of endoscopic assessment and treating to target to achieve mucosal healing in ulcerative colitis. Inflamm Bowel Dis. 2014;20:231–9.
7. Jensen MD, Nathan T, Rafaelsen SR, et al. Diagnostic accuracy of capsule endoscopy for small bowel Crohn's disease is superior to that of MR enterography or CT enterography. Clin Gastroenterol Hepatol. 2011;9:124–9.
8. Schreyer AG, Golder S, Seitz J, et al. New diagnostic avenues in inflammatory bowel diseases. Capsule endoscopy, magnetic resonance imaging and virtual enteroscopy. Dig Dis. 2003;21:129–37.

9. Voderholzer WA, Beinhoelzl J, Rogalla P, et al. Small bowel involvement in Crohn's disease: a prospective comparison of wireless capsule endoscopy and computed tomography enteroclysis. Gut. 2005;54:369–73.
10. Herfarth HH, Long MD. Capsule and balloon endoscopy: when are they really needed in patients with inflammatory bowel diseases? Dig Dis. 2010;28:439–44.
11. Tukey M, Pleskow D, Legnani P, et al. The utility of capsule endoscopy in patients with suspected Crohn's disease. Am J Gastroenterol. 2009;104:2734–9.
12. Long MD, Barnes E, Isaacs K, et al. Impact of capsule endoscopy on management of inflammatory bowel disease: a single tertiary care center experience. Inflamm Bowel Dis. 2011; 17:1855–62.
13. Takenaka K, Ohtsuka K, Kitazume Y, et al. Comparison of magnetic resonance and balloon enteroscopic examination of the small intestine in patients with Crohn's disease. Gastroenterology. 2014;147:334–42.
14. Sinh P, Shen B. Endoscopic evaluation of surgically altered bowel in patients with inflammatory bowel diseases. Inflamm Bowel Dis. 2015;21:1459–71.
15. Alexander JA, Leighton JA. Capsule endoscopy and balloon-assisted endoscopy: competing or complementary technologies in the evaluation of small bowel disease? Curr Opin Gastroenterol. 2009;25:433–7.
16. Bourreille A, Ignjatovic A, Aabakken L, et al. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. Endoscopy. 2009;41:618–37.
17. Rahman A, Ross A, Leighton JA, et al. Double-balloon enteroscopy in Crohn's disease: Findings and impact on management in a multicenter retrospective study. Gastrointest Endosc. 2015;82:102–7.
18. Allez M, Karmiris K, Louis E, et al. Report of the ECCO pathogenesis workshop on anti-TNF therapy failures in inflammatory bowel diseases: definitions, frequency and pharmacological aspects. J Crohns Colitis. 2010;4:355–66.
19. Ordas I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10:1079–87.
20. Farraye FA, Odze RD, Eaden J, et al. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology. 2010;138:746–74.
21. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010;59:666–89.
22. Velayos FS, Liu L, Lewis JD, et al. Prevalence of colorectal cancer surveillance for ulcerative colitis in an integrated health care delivery system. Gastroenterology. 2010;139:1511–8.
23. Mooiweer E, van der Meulen-de Jong AE, Ponsioen CY, et al. Chromoendoscopy for surveillance in inflammatory bowel disease does not increase neoplasia detection compared with conventional colonoscopy with random biopsies: Results from a large retrospective study. Am J Gastroenterol. 2015;110:1014–21.

Chapter 29
Endoscopy in Inflammatory Bowel Disease: Western Perspective—Europe

James E. East and Simon P.L. Travis

Abstract Endoscopy for IBD in Europe has in the last decade been driven by an agenda focussed on endoscopic quality and quality assurance. This has affected endoscopy in IBD practice in two specific areas; the use of chromoendoscopy for dysplasia detection, and endoscopic scoring systems of disease severity.

Chromoendoscopy studies for dysplasia detection have been positive; however, it was not recommended until 2010 when the British Society of Gastroenterology (BSG) led change with a new guideline, subsequently supported by the European Crohn's and Colitis Organisation (ECCO) and European Society for Gastrointestinal Endoscopy (ESGE), which has become the standard of care in IBD in Europe. North America still lags behind Europe in this regard.

Validated scoring systems for colitis are key to ensure we speak an international "common language" between countries, but also to precisely convert research finding into clinical practice. Two validated scoring systems have become available recently, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS). Regulatory agencies including the Food and Drug Administration (FDA) and European Medicines Agency (EMA) are taking an active interest in scoring systems and outcome measures in clinical trials.

Quality and quality assurance are now embedded in IBD endoscopy in Europe by the use of chromoendoscopy and validated scoring systems. We need to evaluate whether this improves outcomes for patients.

Keywords Colonoscopy • Colorectal cancer • Colonic polyps • Inflammatory bowel disease • Quality • Chromoendoscopy • Scoring systems

J.E. East (✉) • S.P.L. Travis
Translational Gastroenterology Unit, Experimental Medicine Division, Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, UK
e-mail: james.east@ndm.ox.ac.uk

T. Hibi et al. (eds.), *Advances in Endoscopy in Inflammatory Bowel Disease*,
DOI 10.1007/978-4-431-56018-0_29

29.1 Introduction: Quality and Quality Assurance for Endoscopy in IBD

Endoscopy for IBD in Europe, and in the United Kingdom specifically, has in the last decade been driven by an agenda focussed on endoscopic quality and quality assurance. Colonoscopic quality has been a key area where routine metrics (key performance indicators, KPIs) are available. The adenoma detection rate has become particularly prominent, as it is clearly linked to outcomes including post-colonoscopy cancer rates [1]; however, other KPIs such as caecal intubation rate have also improved [2, 3]. This quality focus has also permeated thinking around endoscopy in IBD, resulting in change both in our approach to detecting and resecting dysplastic lesions, and in our need to find a "common language" to describe the lesions we see at endoscopy in IBD. This common language needs to be validated both within the international IBD community and between research and clinical practice.

29.2 Chromoendoscopy

Chromoendoscopy was first described in Japan in 1976 [4], but was slow to find favour in the West due to additional time and training needed, and the long learning curve for pit pattern classification [5]. In 2003–2004, however, a number of European research groups began to apply chromoendoscopy to dysplasia detection in ulcerative colitis to try and improve the yield of dysplastic lesions [6, 7]. Dysplasia detection at colonoscopy of flat lesions against an inflamed background was widely accepted as one of the most difficult diagnostic tasks at colonoscopy, so endoscopic visualisation was usually supplemented with quadrantic random biopsies every 10 cm to try and detect "flat" or "endoscopically invisible" dysplasia. Chromoendoscopy created a paradigm shift, with a doubling of dysplasia detection and obviating the need for "random" biopsies. Further studies from multiple centres confirmed the effect size; however, despite this evidence, chromoendoscopy for colitis surveillance did not become the routine in clinical practice, even in tertiary centres. The British Society of Gastroenterology led the way in 2010 for the widespread introduction of chromoendoscopy for IBD surveillance, with the publication of a clinical practice guideline which strongly endorsed the use of chromoendoscopy [8]. Furthermore, it advocated abandoning quadrantic biopsies when using chromoendoscopy, as well as risk stratification to select higher risk patients for more intensive surveillance, with less frequent surveillance for those at lower risk. It also advocated the concept of endoscopic resection for circumscribed dysplastic lesions in IBD. At a stroke, this radically changed the landscape for endoscopic surveillance in IBD in the United Kingdom, incorporating new evidence from a range of areas to improve quality. Interestingly, this change may be cost-saving due to fewer colonoscopies and fewer biopsies for an increased dysplasia detection rate [9].

29.2.1 International Guidelines

Although this appeared a major departure compared to guidelines in Europe and North America at the time, this approach was endorsed by the UK National Institute for Clinical Excellence (NICE) guidance, where chromoendoscopy was made mandatory as the standard of care [10]. Guidance from NICE is binding on healthcare providers in England and Wales, meaning they must either implement and fund the recommendation or give explicit local reasons for deviation. This government approval has meant UK endoscopists have had to engage with chromoendoscopy on a large scale. Subsequent to this, other major IBD and endoscopic societies in Europe including the European Crohn's and Colitis organisation (ECCO) and the European Society for Gastrointestinal Endoscopy (ESGE) have both updated guidance strongly supporting the use of chromoendoscopy in colitis surveillance [11, 12]. ECCO have also supported the concept of risk-based stratification and of resection of circumscribed dysplastic lesions. There therefore seems to be a European consensus emerging on the optimal way to perform surveillance, allocate resources, and to deal with the dysplasia that has been detected.

North America has, paradoxically, lagged behind both in terms of recommending let alone mandating chromoendoscopy for colitis surveillance, although the AGA does recommend chromoendoscopy for 'appropriately trained endoscopists' [13]. The recently developed guidance from the SCENIC group might redress this, although there remain questions around training and re-imbursement, as well as an unwillingness to stop quadrantic random biopsies. Europe has therefore led the way in implementing chromoendoscopy as the standard of care for colitis surveillance, to optimise detection quality. It remains to be seen whether this will translate into lower rates of colitis-associated colorectal cancer.

29.3 Endoscopic Scoring Systems in IBD

The second quality item that has been a focus in Europe as well as in North America has been on the language we use to describe the inflammation we see at endoscopy. In order to be a high quality and effective communication tool, an inflammation scoring system in colitis should have clearly defined items, be reproducible, responsive, usable in both research and clinical practice, and correlate with clinical outcomes. Scoring is important both for entry to clinical trials to ensure patients have active disease when treated, and to ensure that local investigators and central investigators agree on entry criteria. In one recent trial using a widely used, but unvalidated score (Mayo Clinic endoscopic sub-score), the primary end point was not met; however, after central reading and exclusion of patients who did not have sufficient inflammation to enter the trial, the primary end point was reached with a significant difference [14]. It is important that we can translate clinical situations in trials directly into clinical practice.

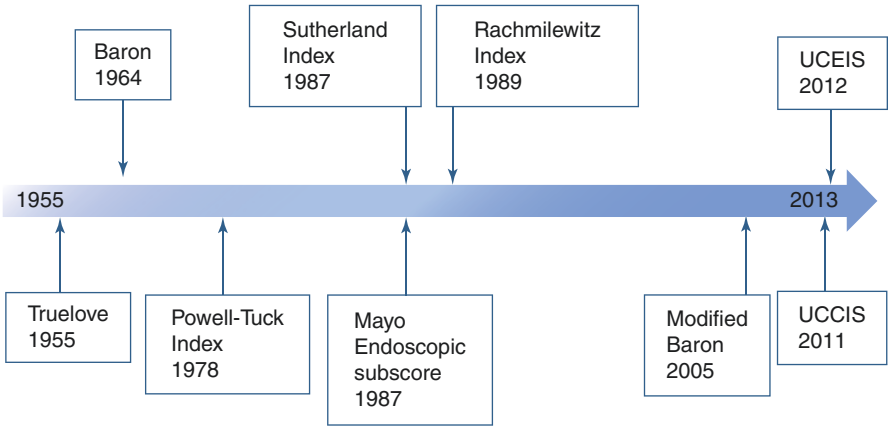


Fig. 29.1 Timeline showing development of scoring systems for inflammation in ulcerative colitis 1955–2014

The history of endoscopic colitis scores, starting with the sigmoidoscopic scoring of Truelove and Witts in 1955 developed around the first steroid trials in Oxford [15], has closely mirrored the development of new pharmacological approaches to colitis (Fig. 29.1) [16]. Clinicians, patients, pharmaceutical companies, and regulators need scores which are validated and reproducible in both academic and community practice and throughout the international IBD community, specifically between the West and Asia. This has led to the development of two new scores, with biostatistical input to ensure validity [17, 18].

29.3.1 Validated Scoring Systems

Two validated scoring systems now exist, the UCEIS and UCCIS [17, 18]. Both have been shown to have good inter and intra-observer agreement, and the scores account for ≥80% of the variability seen in visual analogue scores. Neither score has yet created a formal definition of endoscopic remission, although an international group of IBD specialists favour the UCEIS and a score of 0/8 [19]. ECCO highlight these scores in recent guidelines [12]. It seems likely both academically and clinically that validated scores will in time replace non-validated ones. The responsiveness of the UCEIS appears to be an advantage over the Mayo Clinic endoscopy sub-score, especially for early-phase clinical trials [20]. This is partly because of the 9-point range in the UCEIS in contrast to the 4-point range in the Mayo Clinic sub-score, but also because the UCEIS does not allow overlapping items for each level. The Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2015 started taking an active interest in scoring systems and outcome measures in clinical trials for ulcerative colitis, especially with regard to the application of central reading [21].

29.3.2 *Ulcerative Colitis Endoscopic Index of Severity (UCEIS)*

UCEIS is a straightforward 0–8 point score developed for flexible sigmoidoscopy, scoring the worst affected area. It went through four phases of development and validation, using different cohorts of investigators and videos ranging from normality to acute severe colitis just before colectomy [17]. It should be noted that the first published paper used a range of 3–11 for the score [22], although this was later changed for convenience to 0–8. The UCEIS was developed with anchor points assessed for reproducibility between observers, and interestingly has dropped friability and granularity, both of which were difficult to define reproducibly. Three factors are scored; vascular pattern, bleeding, and erosions and ulcers (Table 29.1). The score is the simple sum of the level for each of the three variables, which makes it simple to use and to remember, although appropriate

Table 29.1 Components of ulcerative colitis endoscopic index of severity (UCEIS) [17]

Descriptor (score most severe lesions)	Likert scale anchor points	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined or with blurring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliterated (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope that can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of the endoscope or visible oozing from the mucosa after washing intraluminal blood, or visible oozing from a hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤5 mm) defects in the mucosa of a white or yellow colour with a flat edge
	Superficial ulcer (2)	Larger (>5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared with erosions but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa with a slightly raised edge

Note. The worst affected area of the colon visible at sigmoidoscopy is scored. The simple sum of the UCEIS ranges from 0 to 8. The copyright of UCEIS is held by Watson Laboratories, a subsidiary of Actavis Inc., as successor in interest of Warner Chilcott and Procter & Gamble. The score is freely available for use, but the copyright protects the terminology

training is still needed. The scale is reproducible and responsive, and has been validated between international Western experts and community-based gastroenterologists, and is undergoing validation in Asia through the Asian Organisation of Crohn's and Colitis (AOCC). Higher scores have been shown to correlate with worse clinical outcomes [23]; other, longer-term outcomes in relation to the UCEIS are under study, as well as its relationship to histopathology and impact of clinical details on scoring [24]. A UCEIS training tool has been developed (www.ecco-ibd.eu).

29.3.3 Ulcerative Colitis Colonoscopic Index of Severity (UCCIS)

The UCCIS was based on the initial development of the UCEIS, but scores the entire colon in each of five colonic segments for vascular pattern, granularity, ulceration, and bleeding/friability. These scores are then each multiplied by a factor and added together to give a whole colon score from 0 to a maximum of 162 [18]. It is validated and correlated clinically with C reactive protein, albumin and haemoglobin. It offers the advantage of an assessment of whole-colon inflammatory burden, but is more cumbersome and requires full colonoscopy and a calculation to complete the score.

29.3.4 Endoscopic IBD Scores in Practice

Formal clinical scoring is still rarely used in Western clinical practice. Nevertheless, this is set to change with simple validated scores that link directly to trigger points for change "step up" in medication use in trials: it seems likely that endoscopic scoring will be more widely used in Europe and internationally. This would be more likely if incorporated into straightforward data entry in digital endoscopic reporting systems, to enhance quality, and directly and more precisely translate research into clinical care.

29.4 Summary

Endoscopy in IBD in Europe has developed significantly in the last decade, with quality and quality assurance becoming integrated as the standard of care for chromoendoscopy and a key aspect of scoring of inflammation. Integrating chromoendoscopy and validated scoring into routine clinical care and assessing the impact on outcomes remains a future challenge for Europe and the wider international IBD community.

References

1. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med. 2014;370(14):1298–306.
2. Bowles CJA, Leicester R, Romaya C, et al. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? Gut. 2004;53(2):277–83.
3. Morris EJ, Rutter MD, Finan PJ, et al. Post-colonoscopy colorectal cancer (PCCRC) rates vary considerably depending on the method used to calculate them: a retrospective observational population-based study of PCCRC in the English National Health Service. Gut. 2015;64(8):1248–56.
4. Tada M, Katoh S, Kohli Y, et al. On the dye spraying method in colonofiberscopy. Endoscopy. 1977;8(2):70–4.
5. Togashi K, Konishi F, Ishizuka T, et al. Efficacy of magnifying endoscopy in the differential diagnosis of neoplastic and non-neoplastic polyps of the large bowel. Dis Colon Rectum. 1999;42(12):1602–8.
6. Kiesslich R, Fritsch J, Holtmann M, et al. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. Gastroenterology. 2003;124(4):880–8.
7. Rutter MD, Saunders BP, Schofield G, et al. Pancolonic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. Gut. 2004;53(2):256–60.
8. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010;59(5):666–89.
9. Elsadani NN, East JE, Walters JR. New 2010 British Society of Gastroenterology colitis surveillance guidelines: costs and surveillance intervals. Gut. 2011;60(2):282–3.
10. Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas: NICE guideline. 2014. 2–2-0014. Ref Type: Electronic Citation. http://www.nice.org.uk/nicemedia/live/13415/57930/57930.pdf.
11. Kaminski MF, Hassan C, Bisschops R, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2014;46(5):435–49.
12. Annese V, Daperno M, Rutter MD, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. J Crohns Colitis. 2013;7(12):982–1018.
13. Farraye FA, Odze RD, Eaden J, et al. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology. 2010;138(2):746–874.
14. Feagan BG, Sandborn WJ, D'Haens G, et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology. 2013;145(1):149–57.
15. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2(4947):1041–8.
16. Cooney RM, Warren BF, Altman DG, et al. Outcome measurement in clinical trials for ulcerative colitis: towards standardisation. Trials. 2007;8:17.
17. Travis SP, Schnell D, Krzeski P, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology. 2013;145(5):987–95.
18. Samuel S, Bruining DH, Loftus Jr EV, et al. Validation of the ulcerative colitis colonoscopic index of severity and its correlation with disease activity measures. Clin Gastroenterol Hepatol. 2013;11(1):49–54.
19. Peyrin Biroulet L, Sandborn WJ, Sands B, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110(9):1324–38.
20. Levesque, B. G., Loftus, E. V., Jr., and Panaccione, R.. Responsiveness of endoscopic indices in the evaluation of ulcerative colitis. J Crohns Colitis. 2014; P150, Ref Type: Abstract.

21. Gottlieb K, Travis SP, Sandborn WJ, et al. Clinical trial endoscopy and central reading of endoscopy endpoints for inflammatory bowel disease. Inflamm Bowel Dis. 2015;21(10): 2475–82.
22. Travis SP, Schnell D, Krzeski P, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the ulcerative colitis endoscopic index of severity (UCEIS). Gut. 2012;61(4):535–42.
23. Corte C, Fernandopulle ANR, Cantuneau A, et al. Association between the ulcerative colitis endoscopic index of severity (UCEIS) and outcomes in acute severe ulcerative colitis. J Crohns Colitis. 2015;9(5):376–81.
24. Travis SP, Schnell D, Feagan BG, et al. The Impact of Clinical Information on the Assessment of Endoscopic Activity: Characteristics of the Ulcerative Colitis Endoscopic Index Of Severity [UCEIS] J Crohns Colitis. 2015;9(8):607–616.