Essentials in Ophthalmology
Series Editor: Arun D. Singh

Atul Kumar
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Ocular Tuberculosis

Springer

Essentials in Ophthalmology

Series Editor

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Ocular Tuberculosis

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ISSN 1612-3212 ISSN 2196-890X (electronic)
Essentials in Ophthalmology
ISBN 978-3-319-57519-3 ISBN 978-3-319-57520-9 (eBook)
DOI 10.1007/978-3-319-57520-9

Library of Congress Control Number: 2017942939

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Tuberculosis (TB) has protean disease manifestations. Most cases of tuberculosis are caused by *Mycobacterium tuberculosis*. Other organisms causing tuberculosis include *M. bovis*, *M. africanum* and *M. microti*, all of which together are grouped as *M. tuberculosis* complex. Mycobacteria are slow-growing, aerobic, acid-fast bacilli. Pulmonary tuberculosis is the most common manifestation of tuberculosis with airborne droplets being the most common mode of person-to-person transmission. An active case of TB is the most common source. About 15–20% of all cases of TB in immunocompetent patients are extrapulmonary TB (EPTB), whereas EPTB accounts for 50% of all cases of TB in immunocompromised patients. The most common site of extrapulmonary TB is lymph nodes, followed by pleural effusion. The host response and thus manifestation of the disease depend on host immune status and whether the infection is the primary exposure of the organism to the host immunity or a secondary response to an already sensitized host. The prevalence of tuberculosis is very high in most developing and underdeveloped nations. Thus clinicians in tuberculosis-endemic regions always consider ruling out tuberculosis as a differential for a plethora of disease manifestations. Such is also the case with ocular disease, and thus tuberculosis has been implicated as an aetiological agent for many ocular disorders. The difficulty in obtaining adequate ocular tissue for histopathological and microbiological analysis makes it difficult to prove or disprove the role of tuberculosis in many such ocular disorders. However, indirect evidence, presence of concomitant systemic disease, response to anti-tubercular therapy and new evidence based on modern molecular microbiological assays have enhanced our understanding of the association of tuberculosis with ocular disease.

Though we do have some definite answers, yet, the aetiology of many ocular diseases is still labelled as "probable tuberculosis". The issue gets further complicated when we try to relate an ocular disease manifestation to active tubercular infection vis-a-vis an immunological response.

In this text we discuss some of the controversies and provide the reader with a comprehensive update on the work done on many facets of ocular tuberculosis.

New Delhi, India

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Epidemiological Aspect of Ocular Tuberculosis

1

May Zun Aung Win and Soon-Phaik Chee

Introduction

Tuberculosis (TB) is an airborne infection caused by *Mycobacterium tuberculosis*. While 10% of individuals with infected TB become symptomatic, in about 90% the infection remains latent without manifestation of the disease for the rest of their lives. In 1999, the World Health Organization (WHO) declared tuberculosis a global emergency causing nearly three million deaths annually. In the same year, WHO reported that there were 3.7 million cases of tuberculosis of which 20% of patients came from Africa, 38% from Southeast Asia, 22% from Western Pacific, 6% from the United States, and 4% from the eastern Mediterranean [1].

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The incidence of TB in developed countries decreased in the nineteenth century. This decline was attributed to improved living conditions and the discovery of effective antibiotics. In developed countries, such as the United States, the prevalence of ocular TB is estimated to be around 1–2%, while in Spain it is significantly higher at 18% (see Table 1.1). In contrast in developing countries, there are approximately 8.4 million new cases of TB annually with a corresponding increased incidence of ocular TB [7].

Ocular TB was first diagnosed by Maitre-Jan in 1711. The current prevalence of ocular TB varies from 0.5% to 1.4% [8]. Ocular TB is defined as an infection by *M. tuberculosis* which can involve any part of the eye, superficial, intraocular, or the structures around the eye with or without systemic involvement [9]. In primary ocular TB which is rare, the eye is the portal of entry which may be the conjunctiva, cornea, or sclera. In secondary ocular TB, the ocular involvement occurs by hematogenous spread of the organism, of which tuberculous uveitis is an example [10]. Due to the rich blood supply of the uveal tract, the choroid is the most common site of ocular TB manifestation [11, 12].

Ocular TB often presents without clinical evidence of active pulmonary TB and may be the first and only manifestation of the infection [13]. Among the various forms of ocular TB, posterior uveitis is the most common [9].

A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_1

Table 1.1 Studies in which rates of ocular tuberculosis were reported in patients with pulmonary tuberculosis

Author	Year	Place	Percentage of ocular TB in pulmonary TB patients
Bouza et al. [2]	1997	Spain	18
Lara et al. [3]	2013	Philippines	6.8
Beare et al. [4]	2002	Africa	2.8
Donahue [5]	1967	United States	1.46
Biswas and Badrinath [6]	1995	South India	1.39

Epidemiology of Ocular TB in Patients with Pulmonary TB

Epidemiological data for ocular TB are rare due to the lack of standardized diagnostic criteria. Table 1.1 shows the rates of ocular TB among pulmonary TB patients.

In 1960, Woods reported that 20% of patients with pulmonary TB due to *M. tuberculosis* had uveitis [14]. In contrast in 1967, Danahue found that only 1.46% of pulmonary TB patients had concomitant ocular TB in the United States [5]. Surprisingly in 1997, a prospective study from Spain randomly examined 100 patients with pulmonary TB and diagnosed 18 patients (18%) with ocular TB [2].

Among the developing countries, Biswas and Badrinath in 1995 examined 1005 eyes of pulmonary TB patients in south India and found that 1.39% of patients concomitantly had ocular TB [6]. However, in another publication by Biswas et al. in 1997, they found that culture-positive ocular TB accounted for only 0.60% of the 1273 uveitis patients seen in his uveitis referral clinic [15]. In the Philippines, screening of 103 cases of pulmonary TB found seven patients (6.8% prevalence) with ocular TB in 2013 [3].

Thus, reports of the prevalence of ocular TB have been variable across time, patient populations, and geographical locations [16].

Ocular TB in Developed Countries

Currently, there is a lower prevalence of ocular TB cases in developed countries compared to developing countries (see Table 1.2). In Chile, Israel, the Netherlands, Portugal, and Turkey, the prevalence is very low, ranging from 0.7% to 2.7% [17–22]. In the United States, the percentage of ocular TB was 0.2% in 1987, reaching 0.6% in 1996 and then declining to 0.38% in 2014 [23–25]. Studies in the United Kingdom show a notable rise in prevalence from 0.28% in 1996 to 3.3% in 2015 [26, 27]. Japan is another country in which the prevalence increased from 0.2% in 1997 to 6.9% in 2003 and then settled at 1.4% in 2016 [28–30].

A study from Denmark suggested that ocular TB is an important cause of ocular morbidity where cases presented as chronic iridocyclitis, peripheral phlebitis, and disseminated choroiditis [47]. In Russia, ocular TB was on the increase especially with cases presenting as posterior uveitis [48]. Studies in Argentina, France, Italy, and Saudi Arabia reported high prevalence than other developed countries with prevalence ranging from 6.2% in France to 10.5% in Saudi Arabia [32, 35–37, 42].

Ocular TB in Developing Countries

Infectious uveitis accounts for a significant proportion of uveitis cases seen in the developing countries. Studies in Congo, Iraq, Lebanon, and Nepal found a high prevalence ranging from 4% to 11.4% [33, 43–45]. Myanmar has an alarmingly high prevalence of 32.4% in a study conducted in 2016 [46]. There is also a rising trend in India increasing from 5.6% in 2000 to 10.13% in 2004 [34, 38]. Surprisingly in China there is an apparent decrease from 4% in 1986 to 0.7% in 2005 [31, 40]. Studies from Tunisia, Iran, and Thailand reported almost similar percentage of ocular TB with 1.1%, 1.5%, and 2.2%, respectively [39, 41, 49].

The wide variability in the reported incidence of ocular TB in the various studies in both the developed and developing countries mentioned

Table 1.2 Prevalence of ocular tuberculosis in reported series from different countries by percentage

Author	Year	Country	Percentage of ocular TB patients
Abrahams and Jians [31]	1986	China	4
Henderly et al. [23]	1987	United States	0.2
Palmares et al. [21]	1990	Portugal	2.2
Weiner and Ben Ezra [18]	1991	Israel	0.7
Rothova et al. [19]	1992	Netherlands	1.4
Couto and Merlo [32]	1993	Argentina	6.8
Smit et al. [20]	1993	Netherlands	2.7
Rodriguez et al. [24]	1996	United States	0.6
Thean et al. [26]	1996	United Kingdom	0.28
Kotake et al. [28]	1997	Japan	0.2
Kaimbo et al. [33]	1998	Congo	6
Rathinam and Namperumalsamy [34]	2000	India	5.6
Mercanti et al. [35]	2001	Italy	7.02
Bodaghi et al. [36]	2001	France	6.2
Islam and Tabbara [37]	2002	Saudi Arabia	10.5
Wakabayashi et al. [29]	2003	Japan	6.9
Singh et al. [38]	2004	India	10.13
Soheilian et al. [39]	2004	Iran	1.5
Yang et al. [40]	2005	China	0.7
Sengun et al. [22]	2005	Turkey	1.3
Pathanapitoon et al. [41]	2008	Thailand	2.2
Hanmade et al. [42]	2009	Saudi Arabia	7
Hong et al. [25]	2014	United States	0.38
Al-Shakarchi [43]	2014	Iraq	11.4
Abdulaal et al. [44]	2014	Lebanon	5.7
Liberman et al. [17]	2014	Chile	2.3
Jones [27]	2015	United Kingdom	3.3
Weiner and Ben Ezra [18]	2016	Israel	0.7
Nakahara [30]	2016	Japan	1.4
Manandhar [45]	2016	Nepal	4
Win et al. [46]	2016	Myanmar	32.4

above may reflect the difference in prevalence of TB in these countries. However, these studies are also reported among different ethnic groups and more importantly in different eras. The diagnosis and detection techniques have also improved over time, with newer diagnostic tools being made available with the advancement of technology.

Ocular TB in the Immunocompromised

Patients who are immunosuppressed or human immunodeficiency virus (HIV) infected can develop active mycobacterial disease in the eye leading to rapid destruction of the ocular structures. HIV is a contributing factor for the reemergence of TB in recent years.

CD4 cells play a major role in the immune response, and susceptibility to TB in HIV-infected patients increases markedly when CD4 T cells are depleted.

In patients with HIV infection, the initial choroiditis may develop into a subretinal abscess, leading to a chorioretinitis involving the retina. The chorioretinitis can be extensive and involve the ciliary body causing cyclitis with hypotony and phthisis bulbi [50].

A prospective study in Africa found a 2.8% prevalence of choroidal granulomas in HIV

patients with pulmonary tuberculosis in 2002 [4]. In 2006, Babu et al. reported an incidence of 1.95% of ocular TB in 766 consecutive cases of HIV or acquired immune deficiency syndrome (AIDS). Of these, more than a quarter had bilateral involvement. Their ocular presentation included choroidal granulomas (52.63%), subretinal abscess (36.84%), panophthalmitis, conjunctival tuberculosis, and panophthalmitis [51].

Because of impaired cell-mediated immunity in HIV-infected patients, there is increased severity and susceptibility of TB when compared to patients with intact immune systems [5]. Therefore, ocular TB in HIV-infected patients may present with severe sight-threatening complications.

Gender

In a study by Shah et al. in 2016, researchers found 80% of TB uveitis patients to be male and 20% female [52]. Basu et al. in 2014 reported that 67.5% of the TB population was male and 32.5% female [53]. In a study by Sanghvi et al. in 2011, it was found that 59% of ocular patients were females and 41% male [54]. These studies represent a small sample of recent research publication with differing results, suggesting that there is no clear gender variation for ocular TB. These findings may reflect the social variations in these different population studies as the first two studies were from India and the last from the United Kingdom.

Laterality

Ocular TB often presents as a unilateral and asymmetric disease [55]. In a prospective study done in the Philippines, all pulmonary patients were diagnosed with unilateral ocular TB [3]. Both ocular and orbital TB are usually unilateral in presentation [56]. Most cases of military tuberculosis are bilateral. Thus, these variations may be related to the size of the inoculum during hematogenous spread.

Anatomical Location of Ocular TB

Tuberculous uveitis may present as anterior, intermediate, posterior, or panuveits [16]. The most common presentation of ocular TB is anterior uveitis and sclerokeratitis in a study by Demirci [55]. Retinal vasculitis, neuroretinitis, and choroiditis are other common manifestations in a study by Shah et al. [52] While tuberculous choroidal granulomas are a result of hematogenous spread of the organism, the cause of TB vasculitis with choroiditis patches is believed to be due to hypersensitivity reaction to bacterial protein. Posterior uveitis was the most common clinical presentation in a study from India [57].

A study from Saudi Arabia reported that panuveitis was the most common form of ocular TB [58]. In a study from Italian and Swiss centers, granulomatous uveitis was the most common presentation of ocular TB [59]. Torres and Calonge reported that cystoid macular edema was the predominant ocular presentation of TB [60]. In a study from the Philippines, posterior uveitis was the main finding in patients with ocular TB [3].

In an evaluation of anatomical classification of uveitis, Shah et al. found that 33% of cases had anterior uveitis, 33.3% intermediate uveitis, and 26.6% posterior uveitis, and only 6.6% presented as panuveitis [52]. In a study by Gupta et al., 43% of patients had panuveitis, while 36% had anterior uveitis, 11% had panuveitis, and another 11% had intermediate uveitis [57]. However, other reports found that disseminated choroiditis was the most common presentation [61–63].

Thus, ocular TB may present with different clinical features in different countries. This may be a result of various factors including the ethnic group, immune status and response of the patient, mycobacterial status (including drug-resistant strains), and size of inoculum.

Conclusion

Tuberculosis (TB) has reemerged as a global health problem in the recent years. Due to challenges faced in diagnosing ocular TB and the

lack of standardized diagnostic criteria, epidemiological data for ocular TB are few and unreliable. The incidence and clinical presentation of ocular TB varies vastly between developed and developing countries. It is important to have a good understanding of the epidemiological background of a patient and maintain a high index of suspicion for ocular TB. Ocular TB is a treatable disease, and delayed treatment can cause serious problems for the patient. Failure to diagnose ocular TB when proceeding with immunosuppression may have disastrous outcomes.

Compliance with Ethical Requirements May Zun Aung Win and Soon Phaik Chee declare that they have no conflict of interest. No human or animal studies were performed by the authors for this chapter.

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Pathogenesis and Pathology of Ocular Tuberculosis

2

Seema Sen

Tuberculosis affects one-third of the world population [1]. Extrapulmonary tuberculosis (TB) involving the pleura, lymphatics, bone, genitourinary system, meninges, or skin occurs in 15% of TB patients [2]. The incidence of ocular TB ranges from 1.4% to 5.74% [3]; it may occur in association with either pulmonary tuberculosis or in isolation, with no clinical or laboratory evidence of pulmonary infection [4]. The number of extrapulmonary tuberculosis cases has increased in recent times in immunocompromised individuals with AIDS and tuberculosis (2.8–11.4%) [3, 5].

The organism *M. tuberculosis* (MTB) is an obligate aerobic slow-growing, nonspore-forming, nonmotile bacteria. Humans are the only natural host, and infection is usually by airborne aerosol and enters into susceptible hosts through the lung and results in a latent infection in individuals with normal immune systems [3]. In 5% of newly infected persons, the pulmonary process progresses. Rarely lymphohematogenous spread of bacilli in large numbers may lead to miliary TB or other extrapulmonary manifestations [4].

Spread to the eye and other extrapulmonary sites usually occurs from hematogenous or adjacent spread of viable bacilli or as a local phenomenon of hypersensitivity to circulating tuberculoproteins [6]. The bacilli tend to localize in tissues that have high regional oxygen tension which includes the apices of the lungs, kidneys, bones, meninges, eye, and choroid [3]. Within the eye the preferred sites include the choroid and ciliary body where the oxygen tension is higher in comparison to other ocular structures [7].

Ocular TB is often misdiagnosed as retinoblastoma, squamous cell carcinoma, xanthogranuloma, or pseudotumor. Corneal or corneoscleral perforations may also occur. Its diagnosis is challenging in the absence of pulmonary disease [6].

Pathology of Ocular Tuberculosis

M. tuberculosis infection is usually chronic and insidious when it affects the eye and adnexa. It is usually a hematogenous spread of the organism. The three forms of disease include mycobacterial invasion of ocular tissues, hypersensitivity to antigen of MTB with viable mycobacteria, and hypersensitivity in the absence of viable bacteria [1].

Characteristic histopathological features in ocular tuberculosis include granulomatous inflammation involving the sclera, cornea, conjunctiva, iris, and ciliary body with central caseous necrosis and occasional or no acid-fast bacilli (Fig. 2.1a, b). The granulomas are composed of abundant epithelioid histiocytes, occasional giant cells of Langerhans type, and lymphomononuclear

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A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_2

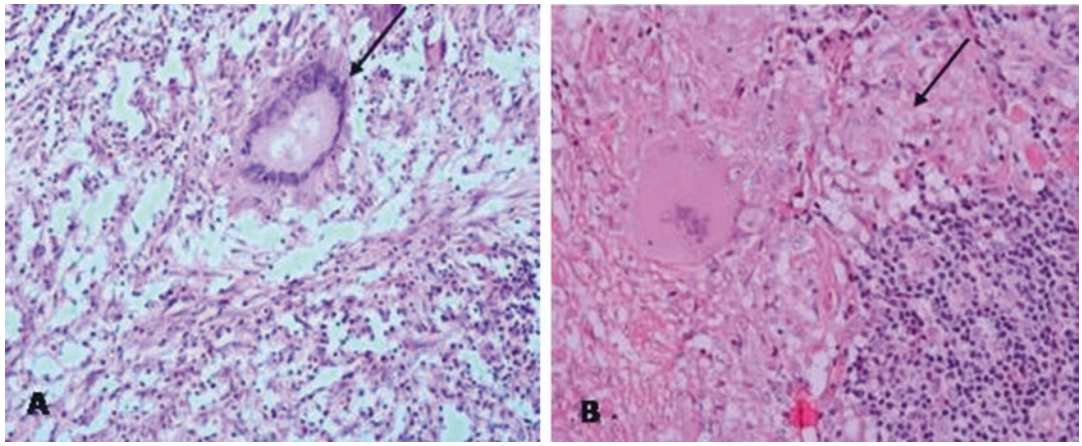

Fig. 2.1 (**a**) Granulomatous inflammation with giant cell reaction (*arrow*) (H&E ×100). (**b**) Higher magnification to show epithelioid cells (*arrow*) and lymphomononuclear surrounding the Langerhans giant cell (H&E ×200)

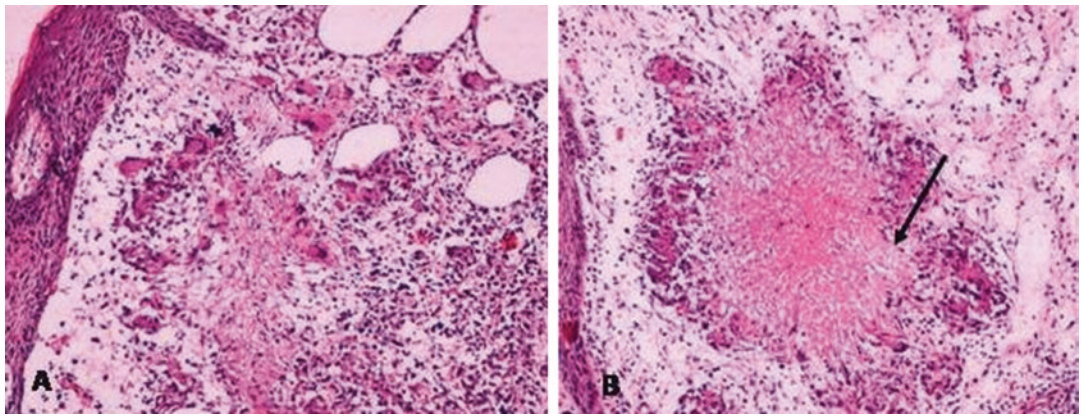

Fig. 2.2 (**a**) Subconjunctival necrotizing granuloma with giant cell reaction in a case of suspected eyelid tuberculosis (H&E ×100). (**b**) High-power view to show necrosis (*arrow*) in the center of granuloma (H&E ×200)

cells. Since the granulomas in immunocompetent individuals contain occasional bacteria, the staining may not reveal the presence of organisms. In such cases, the bacterial DNA may be detected by polymerase chain reaction (PCR).

Ocular tuberculosis is a unique form of extrapulmonary tuberculosis which can present with several clinical manifestations based on the virulence of the organism and immune status of the individual. Both ocular and orbital tuberculosis are usually unilateral [8]. The most common clinical presentation is posterior uveitis followed by anterior uveitis, pan uveitis, and intermediate uveitis. Although granulomatous uveitis is common, it may be nongranulomatous. The diagnosis of intraocular TB is difficult prior to enucleation.

The eyelid involvement is very rare and is usually secondary to orbital TB and may appear as a small nodule simulating a chalazion or as a draining sinus (Fig. 2.2a, b). Rarely primary conjunctival and eyelid tuberculous granuloma may occur [8–11].

Orbital or lacrimal gland (Fig. 2.3a, b) *and lacrimal sac* granuloma may occur secondary to infection with *M. tuberculosis* [12, 13]. These may be associated with preauricular lymphadenopathy. Children can present as preseptal cellulitis with a fistula or as abducens nerve palsy [14].

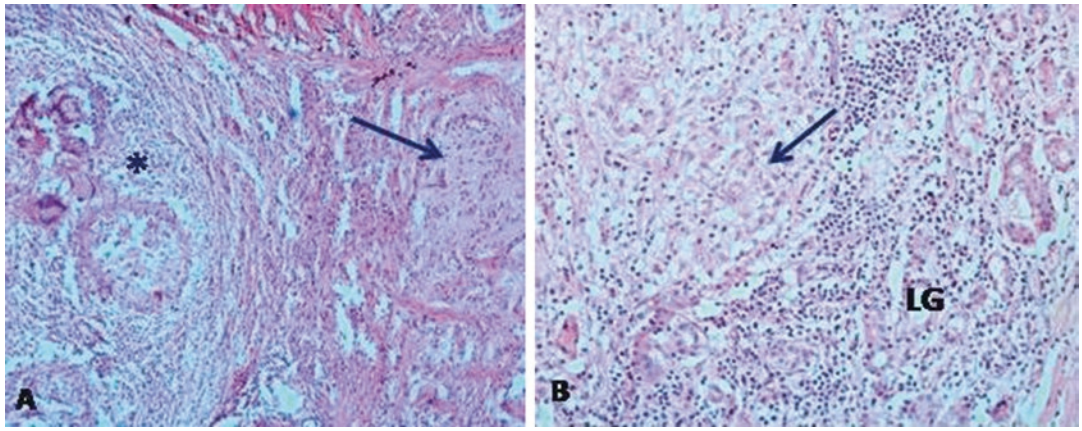

Fig. 2.3 (**a**) Granulomatous inflammation (*asterisk*) in lacrimal gland (*arrow* shows lacrimal gland acini) (H&E ×100). (**b**) Higher magnification shows epithelioid cell granuloma (*arrow*) and adjoining lacrimal gland (*LG*) (H&E ×200)

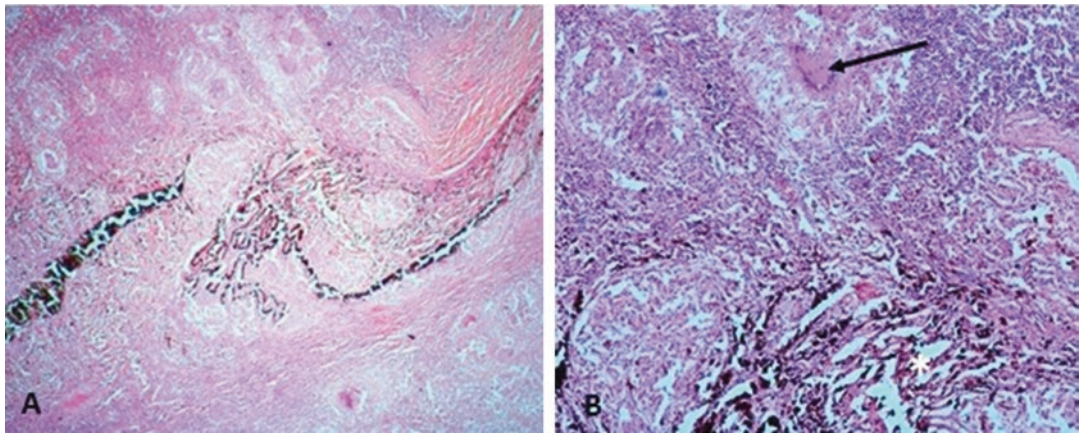

Fig. 2.4 (**a**) Tuberculous granuloma of the ciliary body with acute panophthalmitis. The vitreous shows necrotizing inflammatory reaction (H&E ×40). (**b**) Higher magnification to show granuloma with giant cell (*arrow*) and destroyed ciliary processes (*asterisk*) (H&E ×200)

Interstitial keratitis and phlyctenular keratoconjunctivitis represent a localized immunologic (hypersensitivity) response to the antigens of mycobacteria. Tuberculous scleritis presents as anterior scleritis mostly in the form of focal elevated nodules which may undergo necrosis and result in scleromalacia. Many of the cases of anterior segment are not associated with systemic manifestations of TB and appear localized to the eye [3, 10, 15].

Scleritis, both necrotizing and non-necrotizing, diffuse or nodular, may be associated with TB [16]. The diagnosis is often presumptive and rarely confirmed by histopathology or PCR following enucleation.

Anterior uveitis presents with insidious granulomatous uveitis which may be unilateral or bilateral. Iris lesions in tuberculosis appear as nodular areas at the pupillary margin, over the surface, or in the angle and are made up of epithelioid cells, giant cells, and lymphocytes with extensive caseation. Cyclitis is seen frequently and may cause caseating granulomas (Fig. 2.4a, b) [10, 17].

Posterior segment involvement is more common and may include features of endophthalmitis or panophthalmitis simulating intraocular tumors

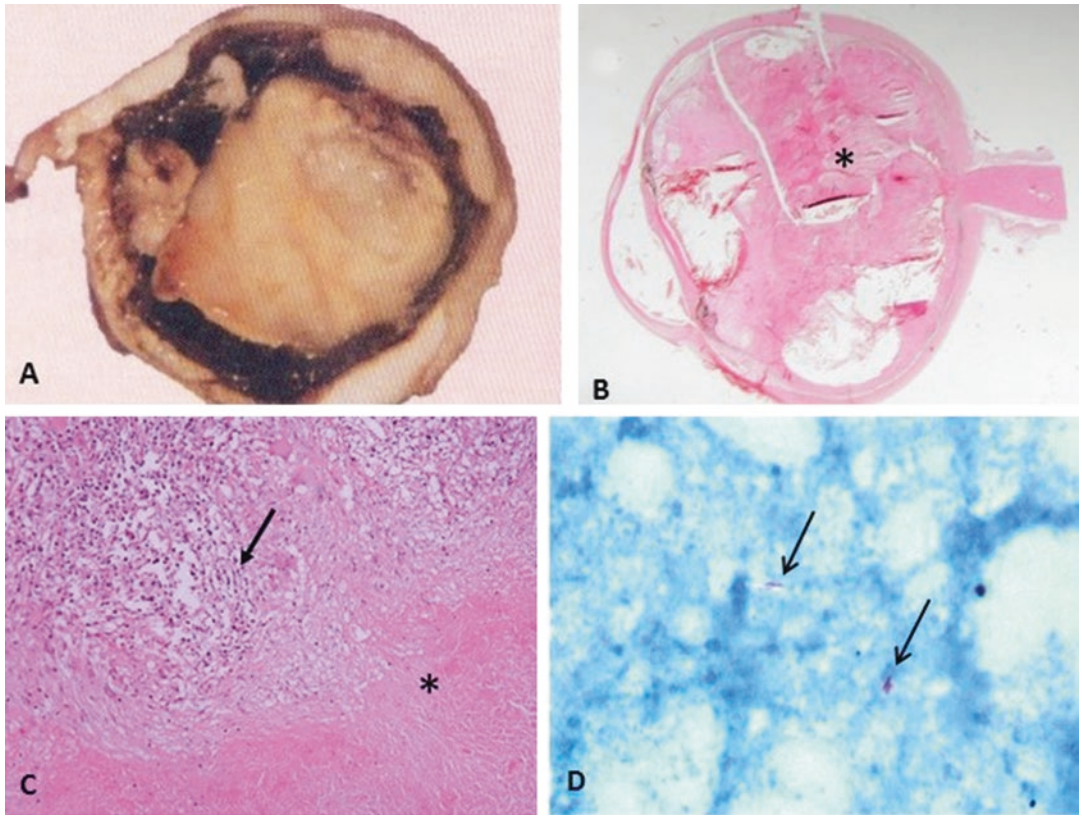

Fig. 2.5 (**a**) Gross specimen of enucleated eye ball shows yellowish white mass in vitreous cavity. (**b**) Low-power view to show the entire vitreous cavity replaced by necrotizing inflammatory mass (*asterisk*). (**c**) Tubercular endophthalmitis. Low-power view of necrosis (*asterisk*) with adjacent chronic granulomatous inflammatory infiltrate (*arrow*) (H&E ×200). (**d**) Ziehl-Neelsen acid-fast stain demonstrates acid-fast bacilli (*arrow*) in necrotic tissue (×1000)

including retinoblastoma (Fig. 2.5a–d) [18]. The retina and choroid are frequent targets with multifocal choroiditis being most common. Solitary choroidal tuberculoma (Fig. 2.6a) may occur in immunocompetent patients and in patients with disseminated tuberculosis [19–21]. Multifocal choroidal tubercles may occur anywhere in the posterior segment with retinal involvement. Vitritis is frequently associated with large choroidal tuberculomas. In the choroid these tuberculomas involve all the choroid layers including choriocapillaris (Fig. 2.6b). These are usually surrounded by choroidal vessels which get obliterated. The RPE initially is normal but can get disrupted in later stages. The granulomas are typical; however, the necrotic areas contain few bacilli.

Tuberculosis may present with several manifestations including retinal vasculitis and serpiginous choroiditis. Retinal vasculitis may occur in the absence of choroiditis or retinitis. This form of phlebitis in patients with healed TB may represent immune-mediated reaction to tuberculoproteins. The inflammation may spread anteriorly to involve the anterior chamber angle, limbus, and cornea resulting in globe perforation.

Pathogenesis of Ocular Tuberculosis

Pathogenesis of extrapulmonary tuberculosis can be extended to ocular tuberculosis. Due to absence or rare isolation of MTB from ocular samples, the role of immune-mediated and direct

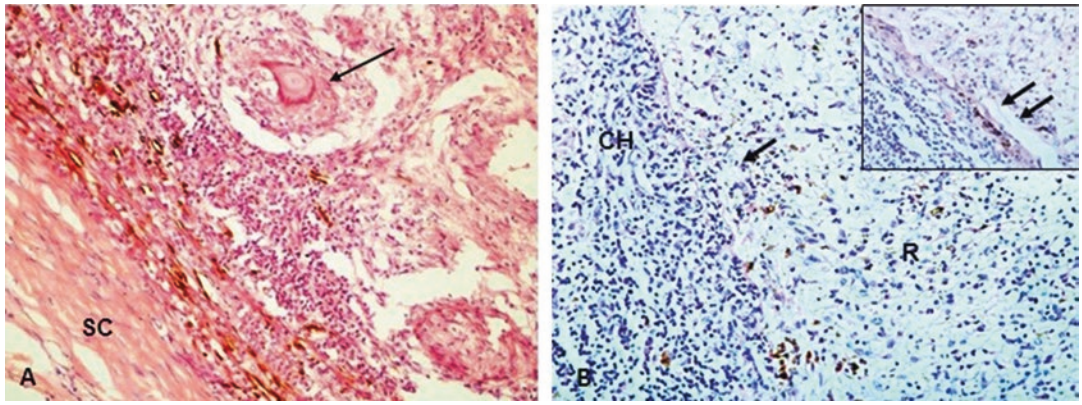

Fig. 2.6 (**a**) Choroidal granuloma (*arrow*) with lymphomononuclear infiltrate. Adjoining sclera (*SC*) (H&E ×200). (**b**) Tubercular retinitis. The retina (*R*) and choroid (*CH*) are replaced by intense chronic inflammatory cell infiltrate (H&E ×200). Inset shows RPE cells (*double arrow*) and Bruch's membrane (*arrow*) (H&E ×400)

bacterial-mediated inflammation is debated [22]. The mechanisms involved in pathogenesis include:

(i) Bacterial dissemination from the site of primary infection
(ii) Bacterial localization in ocular tissues
(iii) Bacterial reactivation and inflammation in these tissues

MTB is an obligate aerobic intracellular organism which invades tissues rich in oxygen. It enters the body through the respiratory system and spreads via the lymphatics or blood to other parts of the body [23]. Usually the bacteria are destroyed by alveolar macrophages or however they may grow destroying the alveolar macrophages resulting in initial nidus of developing tubercle [5].

An initial growth of MTB results in a *delayed-type hypersensitivity response* which is characterized by the formation of small necrotic lesions with solid caseous centers in infected area. After starting delayed-type hypersensitivity (DTH) and tubercle formation, stimulation of macrophages by CD4+ T_{DTH} cells enables the macrophages to kill bacilli inside of the tubercle lesions [23]. The growth of the bacteria becomes limited, and the number of viable bacteria becomes stationary [5].

If the cell-mediated immune response is poor, bacilli start re-multiplying in nonactivated and partly activated macrophages. The T cells are primed followed by initiation of adaptive immunity which takes 5–7 days. During this latent period, macrophages carrying *M. tuberculosis* or even free bacteria may disseminate to the eyes or other organs. Once localized to the ocular tissues, *M. tuberculosis* may remain latent for long periods without apparent clinical disease [5, 24, 25]. The organism preferentially infects macrophages and other reticuloendothelial cells. Choroid is the most common site in the eye [1]. The RPE is the most suited among various ocular cell types to harbor MTB within the eye. It has alveolar macrophage-like properties like phagocytosis and expression of TLRs (Toll-like receptors) and complement receptors [22]. Although retina and uvea are involved by inflammation in tubercular pan uveitis, MTB localizes preferentially in RPE [26]. These organisms sequestered within RPE may cause recurrences.

TB choroidal granulomas in guinea pigs have shown evidence of tissue hypoxia with VEGF upregulation in RPE. However, AFB are rarely identified [27]. In most adults who are not HIV positive, ocular TB develops from postprimary reactivated lesion [5].

Although MTB evades killing if a good CMI develops, the bacteria are destroyed in the phagosomes on fusion with lysosomes, thereby exposing bacteria to acid pH, reactive nitrogen species, and lysosomal enzymes [26]. *M. tuberculosis* evokes an inflammatory response from the host to control the infection which may cause extensive

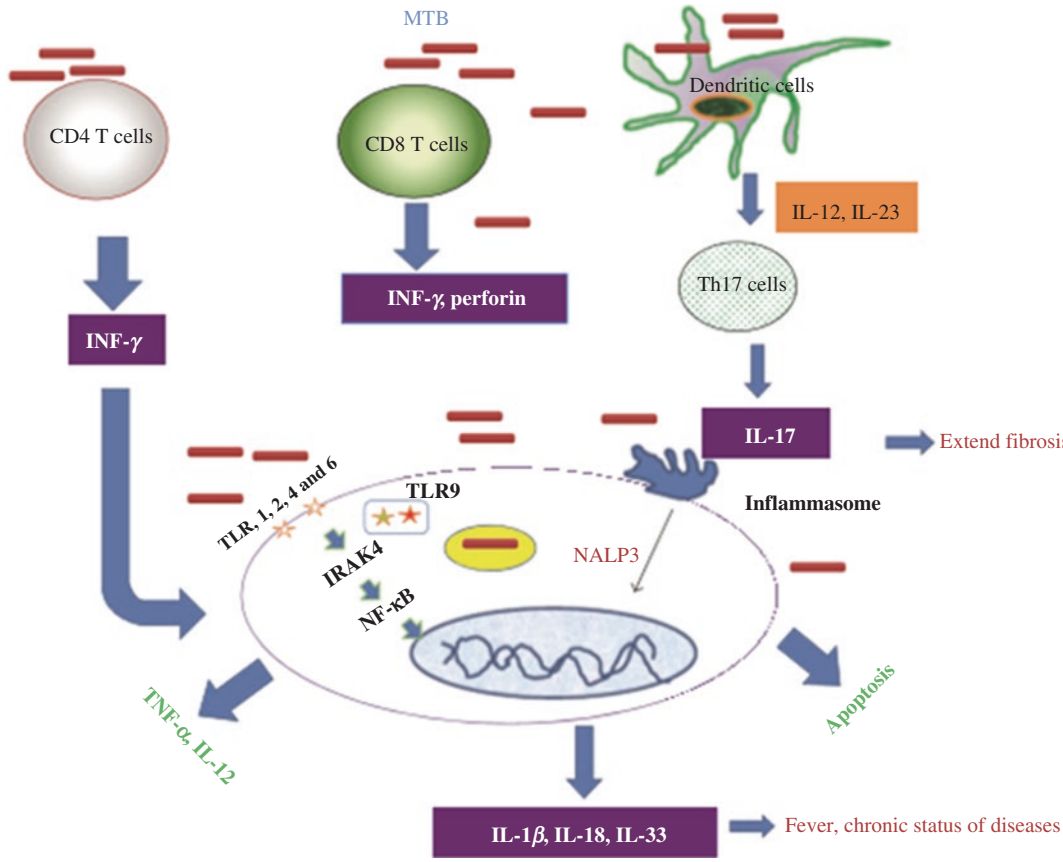

Fig. 2.7 Immunopathogenesis of tuberculosis. MTB causes immune cells T4 cells, T8 cells, DCs, and Th17 cells to be activated. Th1 cytokines are released by the T cells. Macrophages are activated by IFN-γ, MTB, IL-12, and TNFα, and they also undergo apoptosis – a major host protection strategy against MTB infection (From Mortaz et al. [23], which is published under a Creative Commons Attribution License https://creativecommons.org/licenses/by/3.0/)

tissue damage [1]. The progression of the lesion may get halted at subclinical stage.

The rare isolation of mycobacteria has led to the development of an alternative hypothesis in pathogenesis of intraocular TB. Garip et al. [28] have hypothesized that antigen mimicry between tubercular and retinal antigens could be a cause of uveitis in latent TB patients. Supporting features of this hypothesis include demonstration of significantly increased IL-6, rather than TNF-α, IL-12, and interferon gamma that characterize TB [22].

Immunopathogenesis of Ocular Tuberculosis (Fig. 2.7)

Initial immune response to *M. tuberculosis* results in the development of cell-mediated immunity and also hypersensitivity to mycobacterial antigens. Macrophages, T cells (CD4 and CD8), cytokines IFN γ, IL-12, TNF α, and IL-6 are most important in immune response to MTB.

The immune response to active MTB is initiated with bacterial recognition by macrophage

and dendritic cells through TLRs. Activated macrophages via TLRs stimulate production of IL-12 and TNF-α. IL-12 causes a Th1-cell-mediated adaptive immune response which recruits CD4+ cells further and is responsible for controlling the infection [1]. Mycobacteria have a unique ability to delay the initiation of T-cell-mediated adaptive immune response by 2–3 weeks. This is due to the failure of dendritic cells to migrate to regional lymph nodes [22]. The immune response to MTB results in response from T cells, neutrophils, B cells, and NK cells. The mycobacterial antigens are presented by the macrophages and dendritic cells via MHC class II molecules on their surface to CD4 Th1 cells [2, 22].

Cellular Immunity to MTB

- *Macrophages and monocytes*: MTB is a facultative intracellular parasite in macrophages. Entry into the macrophage is gained by phagocytic receptors like complement toll-like and mannose receptors followed by delivery of bacteria to phagolysosome. Nonpathogenic MTB get degraded by acidification of the phagosomes by hydrolases at low ph. Virulent MTB restrict fusion of vacuole with lysosome resulting in blockage of phagosome maturation which assures intracellular survival and replication of MTB. In macrophages activated by IFN-γ, phagosome maturation is blocked. Within the phagolysosome MTB is deprived of essential nutrients and exposed to antimicrobial peptides and reactive oxygen or nitrogen intermediates. Macrophages may also undergo TNF-α-mediated apoptosis. Apoptosis contributes to host defense by removing the MTB growth by direct antimicrobial effects [23]. In resting macrophages MTB blocks phagosome maturation which assures intracellular survival and replication. Helper T cells recruit and activate new monocytes and macrophages [29–31].
- *CD4 Th-1 cell* is the most well-studied cell in the pathogenesis of tuberculosis and is very important in the formation of granulomas. CD4+ T cells are helper T cells which secrete various interleukins (IFN-γ and IL-2) responsible for activating macrophages for protection against mycobacteria. IFN-γ specifically activates macrophages and stimulates them to kill mycobacteria [23, 32, 33].
- *Dendritic cell response*: Dendritic cells are very important antigen-presenting cells of the innate immune system with the ability to stimulate memory T lymphocytes. After phagocytosis by alveolar macrophages and resident dendritic cells, dendritic cells are able to move to the local lymph nodes and present the antigen to the T cells. This is very important to generate a cell-mediated immune response. On exposure of dendritic cells (DCs) to MTB, IL-12p70 and IL-23 are produced which are critical in TB pathogenesis (Fig. 2.7).
- *The role of IL-23 and IL-17* has emerged recently. IL-23 is essential for expression of both Th17 and IL-17 response to human mycobacterial infection. IL-23 and IL-17 act in a complex manner to control inflammation caused by TB (Fig. 2.7). During TB infection IL-17 can mediate accumulation of both neutrophils and mononuclear cells.
- *Gamma/delta T cells* also play an important role by lysing macrophages with mycobacteria and by producing IFN-γ in the initial stages of immune response [34].
- *The CD8+ T cells* can recognize antigens on non-phagocytic cells as epithelial cells.
- *NK cells and B cells* play a role in immunity against TB. NK cells are important in host immune response to MTB. NK cells have the ability to lyse host cells infected with MTB.
- MTB also induces activation of *regulatory T cells (T reg)* which have inhibitory and anti-inflammatory functions.
- Another important CD4+ cell is Th17 cells which are proinflammatory cells which mediate immunity against extracellular bacteria and fungi especially at mucosal surfaces [2].
- *Polymorphonuclear cells*: Neutrophils reach the site of MTB infection promptly where they phagocytose bacilli effectively.
- *Humoral immunity*: IFN-γ an inflammatory cytokine stimulates the antimicrobial activity of macrophages and regulates antigen presentation

through MHC class II molecules by upregulating mRNA and protein expression [23].

MHC type II-restricted CD-4$^+$ T cells, MHC class I CD-8$^+$T cells, and macrophages are important in the protective immunity against MTB. Decrease in the number or function of these cells results in reactivation of the infection.

Immunity to MTB is associated with Th1 activity through TNF-α, IFN-γ, and IL-12 release. TNF-α neutralization reactivates the disease, and genetic defects of receptors for IFN-γ or IL-12 increase susceptibility to MTB. Immune response starts with pattern recognition of microbial structures called pathogen-associated molecular patterns (PAMPs). Dectin and TLR4 are important in IL-17 induction by TB.

Recent Advances in the Diagnosis of Ocular TB

Diagnosis and treatment of active TB are important for preventing blindness [35]. A definitive diagnosis of ocular tuberculosis is made when there is granulomatous eye involvement with the presence of AFB (microscopy or culture) or PCR-based detection of genomic DNA [22, 25]. Only 60% cases with histopathology findings suggestive of ocular tuberculosis may have positive Tuberculin skin test (TST), and 57% may have normal chest x-rays [36].

Demonstration of AFB by microscopy or culture, although standard, is prolonged and cumbersome and may not be positive in low yield of organisms. PCR from intraocular fluids including aqueous, vitreous, subretinal fluid, or rarely chorioretinal biopsy or IS6110 or other conserved sequences in MTB genome although sensitive and extremely useful for early diagnosis of intraocular TB is not recommended due to false positivity [3].

IFN-γ release assay which measures IFN-γ production by T cells in response to MTB antigen is more specific and rapid than TST. However, it lacks specificity to distinguish between latent and active TB.

Quantitative PCR (qPCR) has been evaluated and found to be useful in making a diagnosis suggestive of active ocular tuberculosis in combination with clinical symptoms [37].

Compliance with Ethical Requirements Seema Sen declares no conflict of interest. No human or animal studies were carried out by the author for this chapter.

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Imaging Studies for Ocular Tuberculosis

3

Atul Kumar, Rohan Chawla, and Ruchir Tewari

Ocular tuberculosis has protean manifestations which can involve both the anterior and posterior segments of the eye. Ophthalmologists are fortunate as ophthalmic imaging today is quite advanced and most ocular pathologies can be seen and documented. Thus ocular imaging and investigations play an important role in assessing various ocular disorders. However, the various ocular manifestations of tubercular uveitis are not exclusive to tuberculosis. Though the ocular investigations may suggest a diagnosis of tuberculosis, it cannot be established beyond doubt. It is finally the ophthalmologist who has to correlate the history, ocular and systemic investigations and circumstances of the patient to make a diagnosis of ocular tuberculosis. Response to antitubercular therapy is generally taken as confirmatory evidence of tubercular aetiology. Due to a high prevalence of tuberculosis in India, it is all the more imperative and all the more challenging to correctly establish a diagnosis of ocular tuberculosis. Tuberculosis, time and again, has proven to be the great masquerader and, even today, does not fail to surprise.

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Fundus Fluorescein Angiography

Fundus fluorescein angiography (FFA) plays an important role in the assessment of retinal and choroidal pathology. It helps in the evaluation of various lesions based on their intrinsic vascular pattern. The effect of the lesion on the expected normal pattern of fluorescence at the location of the lesion and its surroundings also gives a clue regarding its aetiology. It may also help in the detection of additional associated/secondary effects of the lesion, such as associated vasculitis, presence or absence or cystoid macular oedema and development of secondary retinal or choroidal neovascularisation. This helps in comprehending the full scope of the disease process, assessing disease activity and monitoring response to treatment.

The fundus image, primary fluorescein angiographic pattern of the lesion and its secondary/associated effects help us to point towards an aetiological diagnosis. The commonest uveal manifestation of systemic tuberculosis is a choroidal tubercle. A tubercle is basically a well-defined patch of choroiditis secondary to tubercular bacilli. Tubercles are usually multiple, involve the posterior pole and appear as yellowish-white deep nodules. The active inflammatory lesion in the choroid blocks the normal choroidal fluorescence in the early phase of fluorescein angiography, thus appearing hypofluorescent. With passage of time there is a centripetal

A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_3

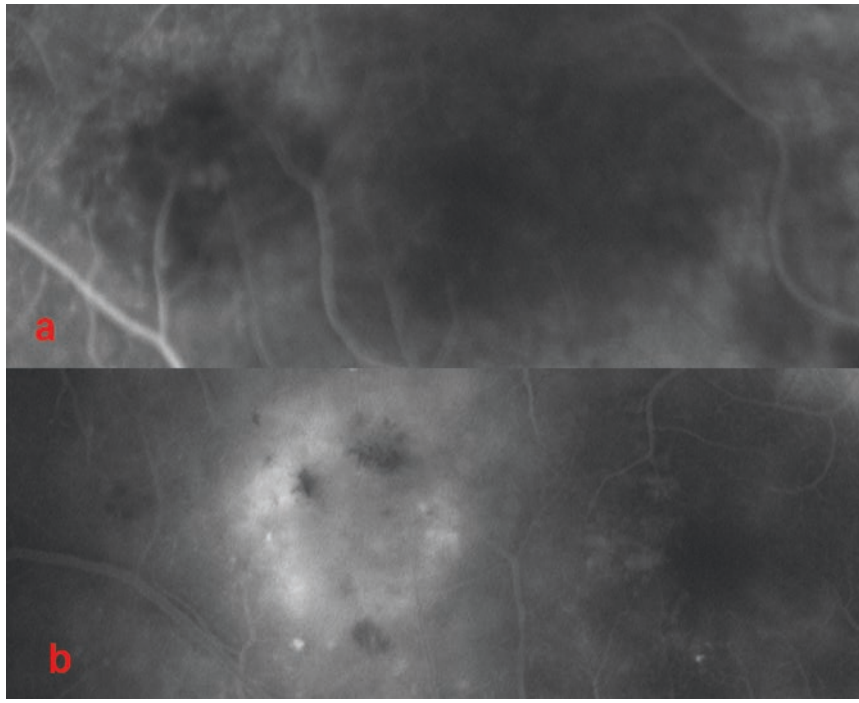

Fig. 3.1 (**a**) Venous phase fluorescein angiogram of a choroidal tubercle showing a hypofluorescent tubercle with mild hyperfluorescence at its margins. (**b**) Late-phase fluorescein angiogram showing diffuse hyperfluorescence of the tubercle due to slow centripetal increase in fluorescence

increase in fluorescence of the lesion with the lesion becoming hyperfluorescent in the late stages, due to dye entering the lesion from its surroundings (Fig. 3.1a, b) [1, 2]. A healed lesion usually presents as a transmission defect with early hyperfluorescence that does not increase in size or intensity and fades away in later stages. This pattern is not pathognomonic of tubercular choroiditis and can be seen in many types of multifocal/unifocal choroiditis lesions.

Another common manifestation is a choroidal granuloma or a "tuberculoma", which is usually solitary. Tuberculoma is a large granulomatous mass-like lesion in the choroid that appears as a raised nodule at the posterior pole and may mimic a choroidal tumour. It usually does not have its own separate vascular supply. Thus, again in the early phases it would block choroidal fluorescence. However, in the late phases, it may become intensely hyperfluorescent due to large amount of dye accumulating in the lesion. Being an inflammatory choroidal pathology, a tuberculoma may also be associated with an exudative detachment. In late phases dye would pool in this space and further enhance the f luorescence seen around the choroidal mass (Fig. 3.2) [1, 2].

Some large granulomas may start to fluoresce earlier than usual with increasing intensity of the fluorescence in later phases along with a dilated capillary bed [1]. We have also seen subretinal fibrotic changes developing during the healing of large tubercular granulomas (Fig. 3.3) [3].

Few common differential diagnoses of tubercular granulomatous mass lesions are haemangioma, melanoma and metastasis. A haemangioma has its own intrinsic large blood-filled spaces separated by septae. This gives it a very characteristic appearance of patchy adjacent areas of hyperfluorescence and hypofluorescence from

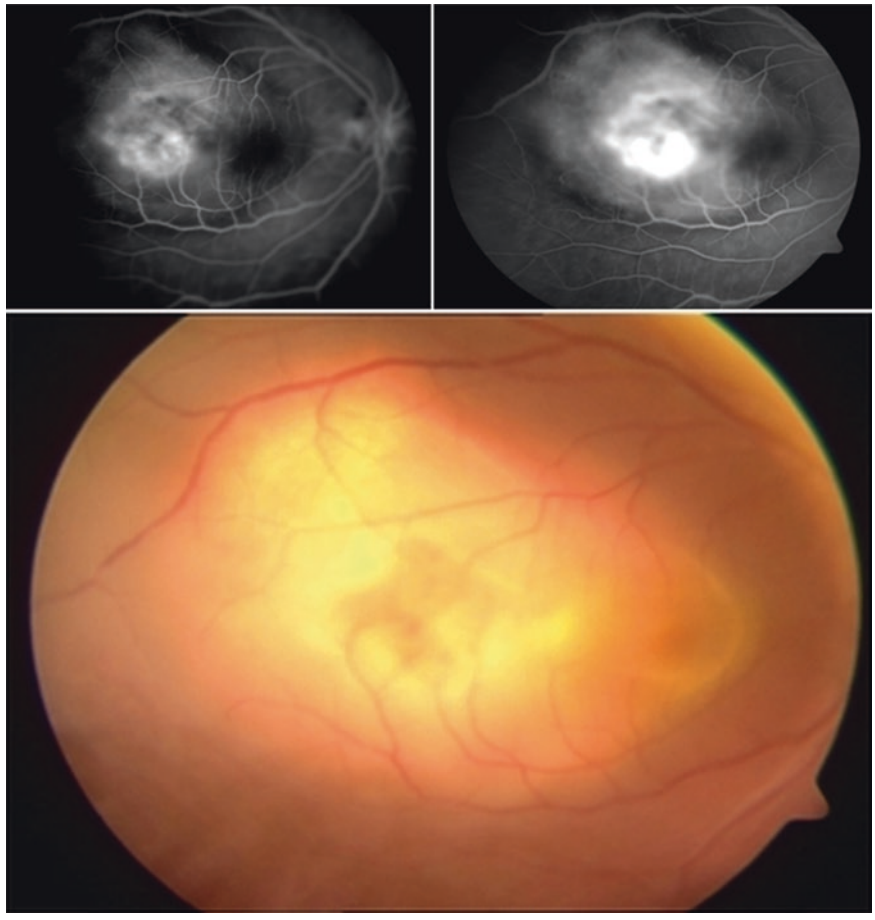

Fig. 3.2 Composite image of the fundus and fluorescein angiography of a choroidal tuberculoma. Note the hyperfluorescence seen in the tuberculoma due to leakage of dye into the lesion. There is associated surrounding hyperfluorescence due to pooling of dye in the surrounding neurosensory detachment

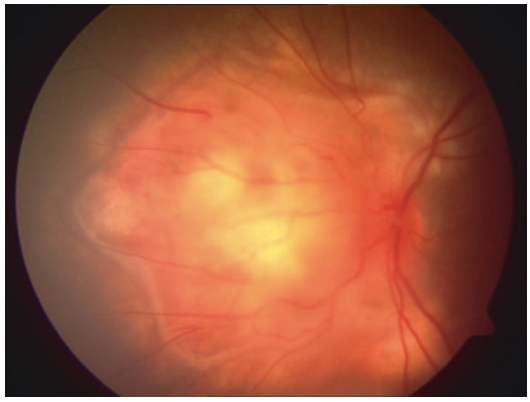

Fig. 3.3 A healing choroidal tuberculoma with evidence of evolving subretinal scarring at the margins of the lesion

very early phases of the angiogram. The entire mass never becomes intensely hyperfluorescent (Fig. 3.4a–c) [4].

A melanoma can have its own blood supply and show a characteristic "double circulation" sign from the early phases. Apart from this, a melanoma also does not have very characteristic features on fluorescein angiography [5].

Metastasis also appears as slowly filling hyperfluorescent lesions on FFA. We have found multiple punctate hyperfluorescent dots surrounding such lesions in many of our cases. These could be due to local infiltration of the tumour cells (Fig. 3.5a–c).

Fig. 3.4 (**a**) Fundus image of a peripapillary orange mass suggestive of a circumscribed choroidal haemangioma (*black arrows*) (**b**) Arteriovenous phase fluorescein angiogram of the mass shows patchy hyperfluorescence (**c**) Late-phase fluorescein angiogram of the mass shows persisting patchy hyperfluorescence. Marked increase in the fluorescence is not seen

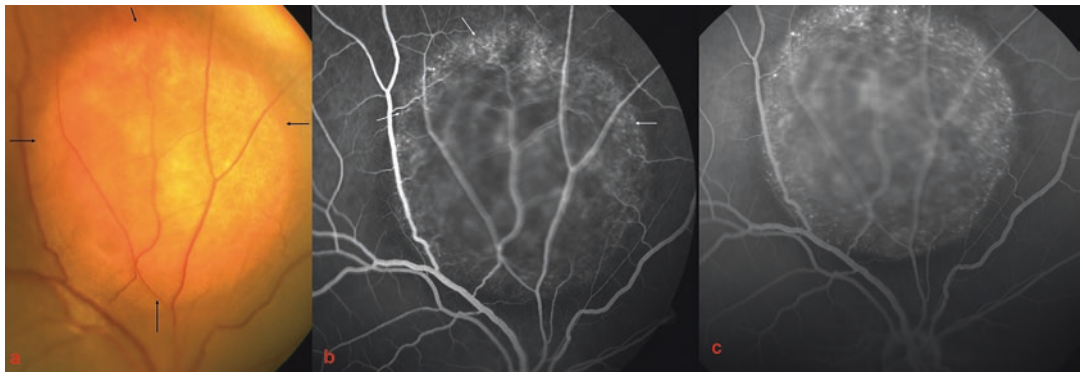

Fig. 3.5 (**a**) Fundus image of a peripapillary yellowish-orange mass (*black arrows*). (**b**) Venous phase fluorescein angiogram of the mass shows slowly increasing fluorescence in the mass with a peripheral rim of punctuate hyperfluorescent dots (*white arrows*). (**c**) Late-phase fluorescein angiogram of the mass shows a further increase in fluorescence of the mass with persistence of the rim of hyperfluorescent dots

As stated before though some of these features may suggest a particular aetiology, there are no definite diagnostic features of a tubercular granuloma on fluorescein angiography. In fact a sarcoid granuloma could entirely simulate a tubercular granuloma on fluorescein angiography.

Tuberculomas may sometimes be associated with deep retinal and subretinal haemorrhages. In such cases fluorescein angiography may be important to rule out development of a secondary choroidal neovascularisation or a retinal angiomatous proliferation-like lesion. An early inflammatory neovascularisation of the disc may also be picked up in cases of tubercular aetiology [1, 2].

Fluorescein angiography is also helpful in the evaluation of the associated vasculitis seen in some cases. Presence of vitritis, significant exudation and perivenular infiltration into adjacent choroid forming pigmented perivenular scars in cases of vasculitis have been associated with tubercular aetiology [6–9]. We have seen occlusive vasculitis in tubercular cases, especially if there is associated retinitis (Fig. 3.6a–c) [6]. During the healing stage of tubercular retinitis, periarterial plaques (Kyrieleis arteriolitis) have also been seen (Fig. 3.7). In fact, Kyrieleis arteriolitis was first described in a case of suspected tubercular retinitis [10]. However, it is again not pathognomonic of tubercular aetiology and may be seen in a variety of cases of retinitis during the phase of resolution.

Ultrawide field imaging that captures around 200 degrees or nearly 80% of retinal surface

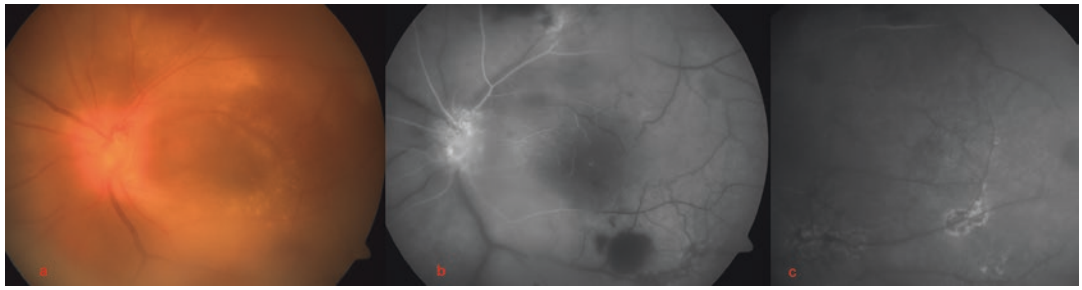

Fig. 3.6 (**a**) Fundus image of a case of diffuse tubercular chorioretinitis. (**b**) Arterial phase angiogram showing partial filling of the arteries, suggestive of occlusive arteriolitis and an early neovascularisation of the disc. (**c**) Temporal fluorescein angiogram showing incomplete filling of the vessels with a pigmented paravenous patch of chorioretinitis

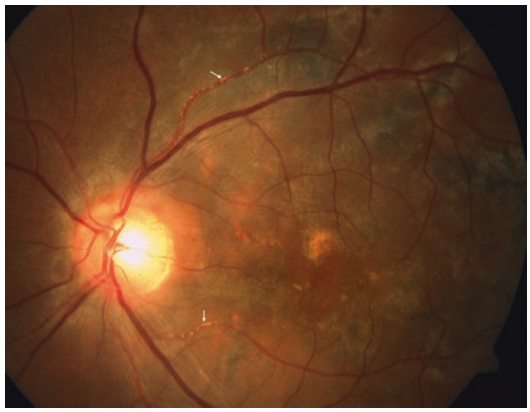

Fig. 3.7 Periarterial plaques (Kyrieleis arteriolitis) (*white arrows*) seen during the healing stage of a case of tubercular chorioretinitis

area (SLO, Optomap P200Tx, Optos PLC, Dunfermline UK) has further enhanced our ability to image even the most peripheral fundus lesions. It provides valuable information in cases with choroidal lesions and associated vasculitis [11]. The exact extent and location of the granulomas and their response to therapy can be assessed more easily. Moreover, the ability to detect peripheral areas of neovascularisation, leakage and capillary nonperfusion enables us to assess associated peripheral vasculitis and helps in better planning of laser photocoagulation for such lesions [11–15].

Few authors have described tubercular choroiditis manifesting as serpiginous-like choroiditis [16–18]. In such cases the active edge of the lesion is initially hypofluorescent with increasing fluorescence in late phases with diffuse staining of the advancing edge. The lesions usually have an amoeboid pattern of extension which is well delineated on FFA. An inactive healed lesion may either present as a window defect or blocked fluorescence due to reactive hyperplasia of pigment epithelium that shows delayed staining [19].

Macular oedema may complicate choroiditis, retinal vasculitis and intermediate uveitis associated with tubercular involvement. It may present in a cystoid pattern with hyperfluorescence in the late phases of the angiogram or a diffuse oedema [1]. These changes are also seen on fluorescein angiography. In fact we have found Ultra wide field angiography (UWFA) a good tool to simultaneously pick up both the peripheral and central changes on fluorescein angiography in cases of uveitis. This is all the more helpful in cases where the pupil in small due to synechia [12].

Indocyanine Green (ICG) Angiography

Indocyanine green (ICG) angiography involves the use of ICG dye along with longer wavelength of light to capture fundus images. ICG is different from sodium fluorescein as it is much more protein bound (98% compared to 80%) and fluoresces in the infrared spectrum. Moreover, ICG leaks only from the choriocapillaris and stays in the choroidal stroma for long, unlike fluorescein

dye that leaks from choroidal as well as retinal vessels. Blockage of fluorescence in FFA from RPE further compounds evaluation of choroid that is overcome in ICG angiography [20].

In cases of choroiditis, especially Vogt-Koyanagi-Harada syndrome, it may help to detect subtle subclinical lesions. It has been proposed as the investigation of choice to monitor response to therapy in such cases of choroiditis. Experience with ICG in cases of tubercular aetiology is limited. Herbort et al. [20] described two different ICG presentations with hypofluorescent lesions in all phases of angiography being ascribed to full-thickness choroidal involvement or atrophy and early hypofluorescent lesions becoming hyperfluorescent in mid and later phases due to partial choroidal thickness involvement. Tayanc et al. [21] reported two cases of ocular tuberculosis with choroidal granuloma wherein ICG was performed. The first case showed two hypofluorescent lesions in the choroid although only one lesion was seen clinically. The second case had a hypofluorescent lesion much bigger in size than the clinically visualised lesion. In both cases, hypofluorescence persisted throughout the angiogram. With treatment both cases showed decrease in hypofluorescence of the lesions. The role of ICG was further evaluated in tubercular chorioretinitis by Wolfensberger et al. [22] who described four different clinical signs in such cases. Gupta et al. reported cases with large granulomas wherein early hypofluorescence in the entire lesion was followed by late hyperfluorescence in the periphery and persisting hypofluorescence in the central dense core [23]. ICG angiography has also been utilised in delineating the hypofluorescent active edges in serpiginous-like choroiditis [17].

Fundus Autofluorescence

Fundus autofluorescence (FAF) is a noninvasive imaging technique that details the health of the RPE. As RPE and choriocapillaris are the proposed major sites of involvement in tubercular serpiginous-like choroiditis (SLC), FAF can play an important role in assessing disease activity and resolution of such lesions.

FAF has several advantages over both FFA and ICGA. Besides being noninvasive, it is easier to interpret than FFA in cases where there are active lesions interspersed between healed regions. Similarly, it overcomes the shortcomings of ICGA which cannot differentiate between active and healed lesions as both appear hypofluorescent on it.

Gupta et al. [24] have described different stages in the resolution of SLC lesions using FAF imaging. The acute stage (stage 1) shows an ill-defined amorphous lesion with halo-like hyperautofluorescence and ill-defined margins. With resolution, the lesion progresses through different stages with increasing hypo-autofluorescence in an outward-in fashion. The central stippled hyper-autofluorescence has been shown to persist until the entire lesion becomes hypo-autofluorescent (stage 4). This marks the end of activity and RPE atrophy.

Optical Coherence Tomography (OCT)

OCT technology, since its inception, has evolved immensely. Beginning with time domain technology, we have now moved on to commercially available spectral domain and now swept-source OCT that provide much better resolution and deeper penetration. With advancement in technology, our ability to characterise pathological changes at a microscopic level in vivo has greatly improved. We can now obtain images from the level of the posterior hyaloid to the choroidal-scleral interface with swept-source OCT. These have further enhanced our understanding of choroidal pathologies and their response to therapy. Introduction of OCT angiography (OCTA), a dyeless angiography, has improved pickup rates of choroidal neovascularisation. Spectral domain OCTA can also image choroidal vasculature. This will further enhance our understanding of how these choroidal lesions affect the choroidal vasculature.

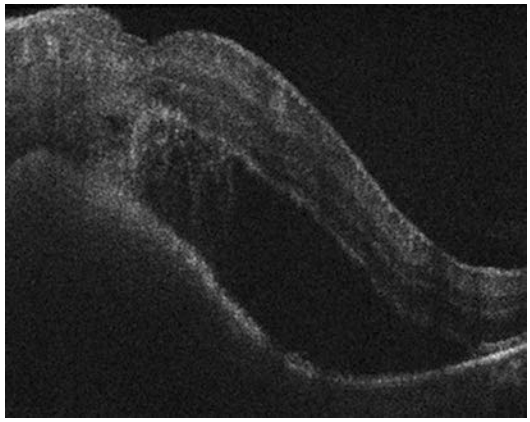

Fig. 3.8 OCT scan through the fovea of a case of tubercular choroidal abscess. A hyporeflective choroidal mound is noted elevating the fovea. There is a neurosensory detachment at the fovea. The fluid under the fovea shows some amount of hyper-reflectivity which suggests that the fluid is not clear

Macular oedema may complicate various forms of uveitis associated with ocular tuberculosis. OCT plays an important role in assessing macular involvement and its response to treatment. Three different forms of macular oedema have been associated with tubercular infection, namely, cystoid macular oedema, diffuse macular oedema and serous retinal detachment (Fig. 3.8) [25]. Increased thickness of macula corresponds with poor visual acuity. As the oedema responds to treatment, there is a decrease in thickness and improvement in visual acuity. We have found en face imaging using swept-source OCT to best highlight the presence and extent of cystoid macular oedema.

The structural relationship between the choroidal granuloma and overlying neurosensory retina has been described using SD-OCT. Pirraglia et al. [26] described SD-OCT findings in intraretinal tuberculous granuloma that showed a single, rounded, hyper-reflective lesion in the neurosensory retina with a partially hyporeflective core that was surrounded by a hyper-reflective area and surrounding neurosensory retinal detachment. The hyper-reflective dots in the outer retinal layers were ascribed to RPE proliferation that appeared granular. They also found the RPE-choriocapillaris complex under the retinal lesion to exhibit non-homogeneous localised thickening without any retinal elevation.

Salman et al. described features of a tubercular granuloma on SD-OCT. They reported a distinctive feature of attachment between the RPE-choriocapillaris layer and the neurosensory retina over the granuloma that was referred to as the “contact” sign. This was seen to be associated with surrounding subretinal fluid and inflammatory infiltrate in the deeper retinal layers.

Recent studies utilising enhanced depth imaging (EDI) protocols and swept-source (SS) technology have provided new insights about the disease. Invernizzi et al. [27] used EDI-OCT to report internal choroidal patterns in tubercular granulomas that were found to be lobulated and non-homogeneous. They reported the granulomas to show increased transmission effects. They also proposed that EDI-OCT helped in identifying smaller or barely visible granulomas and also enabled their differentiation from the normal large choroidal vessel lumens. OCT has also been found to be sensitive in differentiating choroidal tumours from granulomas as the latter tend to have a smooth contour and moderate thickness as opposed to the former that lead to various contour changes and greatly increased choroidal thickness [28, 29].

Mehta et al. [30] studied choroidal sublayers using EDI-OCT in sarcoid and tubercular granulomas. They reported greater contribution of Sattler’s medium vessel layer to increased submacular choroidal thickness in sarcoid granulomas as compared to tubercular granulomas. Although they did not provide a cut-off limit, this finding could prove crucial in challenging cases.

OCT may also demonstrate development of a secondary choroidal neovascularisation as a hyperreflective subfoveal membrane complex with subretinal and intraretinal fluid accumulation [31].

Bansal et al. [32] documented resolution of SLC lesions using SD-OCT and its correlation with fundus autofluorescence. Acute SLC lesions that were diffusely hyper-autofluorescent corresponded on OCT to outer retinal layer hyperreflectivity with involvement of retinal pigment epithelium (RPE), photoreceptor outer segment tips (POST), ellipsoid region, external limiting membrane (ELM) and outer nuclear layer (ONL) with a minimal involvement of inner retinal layers.

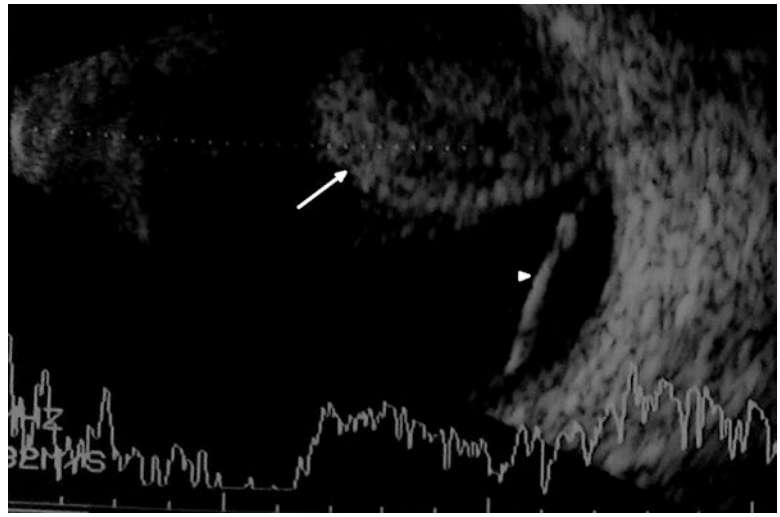

Fig. 3.9 Ultrasound A&B scan image of a case of a tuberculoma showing a well-defined mass with low-to-moderate internal reflectivity (*white arrow*). An associated exudative detachment is also visible (*white arrowhead*)

With onset of resolution, the hyper-reflective regions were seen to be replaced by irregular elevations of outer retinal layers. With further resolution a loss of outer retinal layers with increased choroidal backscattering was noted. Rifkin et al. demonstrated choroidal infiltration with elevation of the RPE in active areas of tuberculous serpiginous-like choroiditis on EDI-OCT.

Recently introduced OCT angiography is also being utilised to study presumed tubercular lesions and their complications. Optical coherence tomography angiography (OCTA) findings in a case of secondary neovascularisation associated with tuberculous serpiginous-like choroiditis were recently reported. OCTA was found to be effective in clearly delineating the lesion of CNV and detailing the involvement of retinochoroidal layers with branching vascular networks.

Thus, OCT, in its various avatars, plays a major role in diagnosis, management and assessment of response to treatment and picking up secondary complications in different scenarios pertaining to tubercular uveitis.

Ultrasonography

Ultrasonography (USG) is a useful additional investigation for evaluation of choroidal masses. USG of a tubercular granuloma displays a lesion with variable moderate to low internal reflectivity (Fig. 3.9) [33]. Some tubercular masses may show well-defined anechoic areas within the mass lesion. This is due to the presence of large areas of caseous necrosis in some of these granulomas.

Ultrasound B-scan may again be helpful in ruling out other causes of choroidal masses. A choroidal haemangioma has a very typical appearance of a mass with a sloping convex surface with uniform moderate internal reflectivity (Fig. 3.10) [34]. On B-scan a melanoma appears as a mushroom-shaped mass lesion arising from the choroid with or without associated choroidal excavation [35] (Fig. 3.11). On A scan, a high initial spike is seen at the surface of the mass followed by low internal reflectivity. This is also referred to as a high angle kappa. Metastases are generally placoid lesions which are not too elevated. However, a definite diagnosis of metastasis cannot be made on USG B-scan alone [35]. An osteoma will show a typical area of very high reflectivity with shadowing due to its calcium content (Fig. 3.12) [36]. Sometimes patients with focal nodular posterior scleritis may simulate a choroidal granuloma. In such cases a T-sign or presence of fluid in the subtenon's space is suggestive of a diagnosis of posterior scleritis (Fig. 3.13). These cases may also be associated with exudative neurosensory detachments at the macula which can be easily picked up on OCT [37].

Ultrasound biomicroscopy (UBM) is a variation of the normal ophthalmic echography that

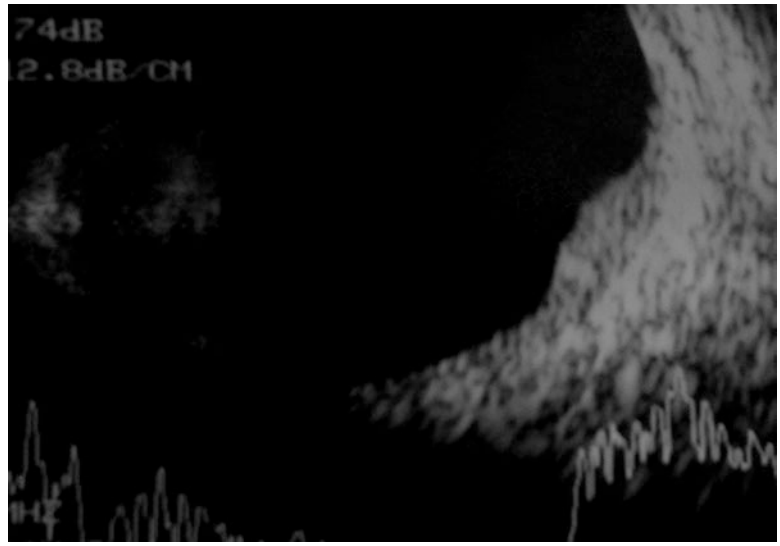

Fig. 3.10 Ultrasound A&B scan of a mass with relatively uniform moderate internal reflectivity and smooth sloping margins merging with the adjacent chorioretinal layer. Such a picture is suggestive of a choroidal haemangioma

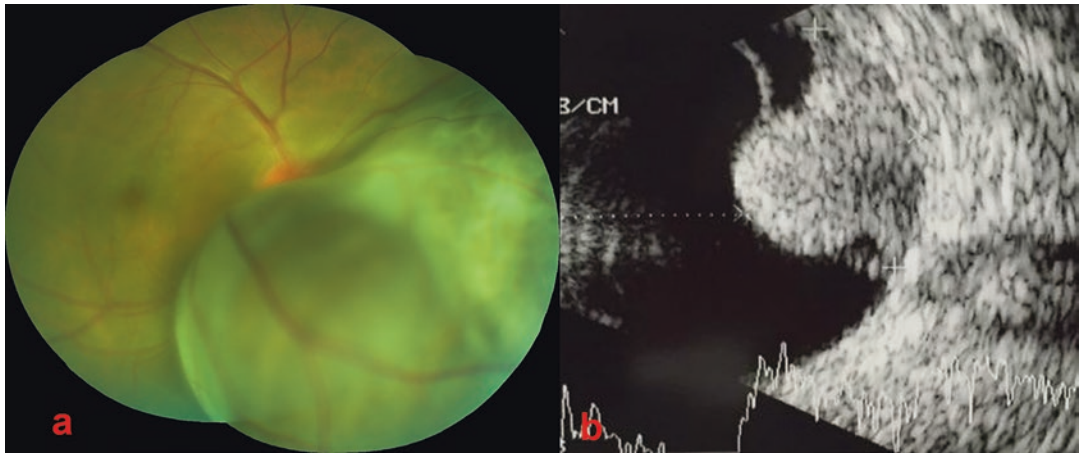

Fig. 3.11 (**a**) Fundus image of a pigmented elevated mass lesion suggestive of a melanoma. (**b**) Ultrasound A&B scan of the mass showing a mushroom-shaped solid lesion arising from the choroid, suggestive of a melanoma

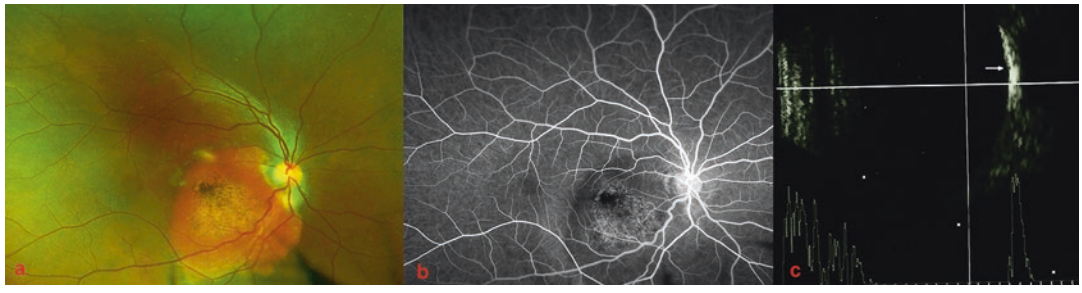

Fig. 3.12 (**a**) Optos fundus image showing an orange peripapillary lesion with central pigmentary change. (**b**) Fluorescein angiography of the same lesion showing window defects in the area of the pigmentary changes with a surrounding relatively hypofluorescent halo. (**c**) A highly reflective choroidal lesion with posterior shadowing is seen on ultrasound A&B scan. This confirms the diagnosis of a choroidal osteoma

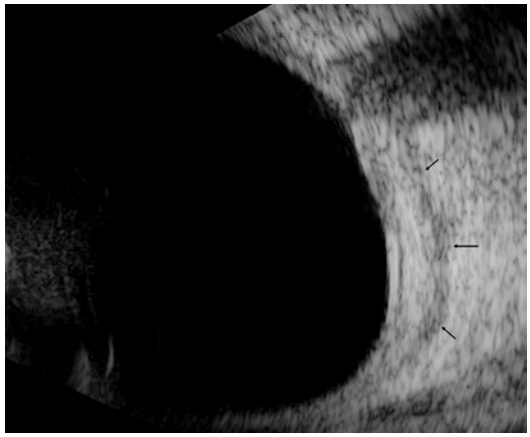

Fig. 3.13 Ultrasound B-scan showing fluid in the subtenon's space (*black arrows*) adjacent to the optic disc

utilises a 50 Mhz probe instead of the usual 10 Mhz probe. It lacks deep penetration but enables better resolution. It is found to be useful in the identification and characterisation of ciliary body and pars plana involvement in cases of tubercular uveitis [38].

Compliance with Ethical Requirements Atul Kumar, Rohan Chawla and Ruchir Tewari declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

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4 Laboratory and Radiological Investigations in the Diagnosis of Ocular Tuberculosis

Randeep Guleria and Vijay Noel Nongpiur

Introduction

Ocular tuberculosis implies any infection by *Mycobacterium tuberculosis (MTB)*, in or around the eye. Ocular tuberculosis has historically been further classified into "primary" and "secondary" ocular tuberculosis: primary, when the disease affects the eye with little or no systemic involvement, and secondary, where a haematogenous spread from a distant site or seeding from an adjacent area (such as the paranasal sinuses) occurs. Secondary ocular tuberculosis can also occur as a cross-reactive immune response by the host to tuberculosis of a distant site, affecting the intraocular tissues [1, 2]. In areas with low TB endemicity, such as the USA and Europe, the estimated prevalence of ocular tuberculosis is around 1–4%, whereas in highly endemic areas like India and the Middle East, the prevalence may be as high as 10–26% [3]. The HIV pandemic and emergence of drug-resistant strains of MTB has generated a renewed interest in the disease.

Uveitis is the most common presentation of ocular tuberculosis [1] and can present as anterior, intermediate, posterior and even panuveitis. Posterior uveitis is most commonly seen. Previously, tuberculosis was identified as the most common cause of granulomatous uveitis. However, over the last few decades, other important disease entities such as sarcoidosis, toxoplasmosis and histoplasmosis are increasingly being recognised as other causes of granulomatous uveitis [4]. However, in endemic countries like India, tuberculosis still remains the commonest causes.

Less common ocular manifestations of tuberculosis include retinal vasculitis, which may cause vascular occlusion and periphlebitis. Tubercular conjunctivitis may present as a unilateral, chronic conjunctivitis. Phlyctenular keratoconjunctivitis is a type IV hypersensitivity reaction, often to tuberculin protein, and can be associated with a conjunctival mass or ulceration. Episcleritis and scleritis have also been reported [1].

Investigations

Ocular tuberculosis remains a diagnostic challenge even today. The disease is notoriously variable in its clinical presentation, and in a majority of cases, there may not be any other systemic evidence of tuberculosis [3]. Residence in a tuberculosis-endemic area or migration from such an area and a history of contact with a tuberculosis patient are clinical pointers to suggest

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A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_4

ocular tuberculosis in patients with suspicious ocular findings. Cultures of intraocular fluids are more often negative, and obtaining biopsies for a histopathological diagnosis is difficult and, at times, impossible. Hence, arriving at a confident diagnosis of ocular tuberculosis requires a combined clinical, laboratory and radiological approach. Over the last few years, a lot of advancements have been made in the immunological and molecular diagnosis of tuberculosis. This has helped in a more rapid and accurate diagnosis of tuberculosis including drug-resistant tuberculosis.

Laboratory investigations for the diagnosis of ocular tuberculosis include:

(a) Immunological tests – the Mantoux (tuberculin skin test) and interferon-gamma release assays (QuantiFERON-TB Gold/TB SPOT) (Chap. 5)
(b) Molecular assays – nucleic acid amplification techniques (PCRs, RT-PCRs, LAMP) and genotypic methods such as the GeneXpert MTB/RIF
(c) Imaging modalities – systemic radiological investigations like chest X-ray, HRCT and MRI; ocular imaging modalities like fluorescein (FFA) and indocyanine angiography (ICGA), optical coherence tomography (OCT) and OCT angiography (Chap. 3)

Molecular Assays

Molecular methods for the diagnosis of ocular tuberculosis are particularly challenging. The disease is often paucibacillary in nature, and at times, the inflammation in the ocular tissues is immune mediated [5], with a low yield of mycobacteria.

Traditional PCR methods using a single gene target (protein IS6110) reported a low sensitivity (33–66%) for the diagnosis of ocular tuberculosis [6]. Newer, multiplex PCR assays that use multiple target genes (IS6110, MPB64 and protein B) have reported a higher yield. These assays have reported a sensitivity of 77% and specificity reaching 100% for the diagnosis of ocular TB [7].

Genotypic assays such as the GeneXpert MTB/RIF have been approved by the WHO for the diagnosis of extrapulmonary tuberculosis. The GeneXpert assay is a fairly rapid automated molecular assay, with a run time of 90 min. It also has the added advantage of being able to detect mutations of the *rpo* gene, a marker of rifampicin resistance. However, in a study comparing the GeneXpert and the MTBDRPlus line probe assay in the diagnosis of ocular tuberculosis in 11 patients of multifocal serpiginoid choroiditis, the GeneXpert assay showed a lower sensitivity compared to the latter [8].

Imaging

Radiographic imaging such as chest X-ray and CT scan, especially high-resolution CT (HRCT), is useful for assessing systemic involvement of tuberculosis. Chest radiographic features that suggest active pulmonary tuberculosis include infiltrates and cavities, predominantly in the upper lobes, though in immunocompromised patients these lesions may be present even in the lower lobes. Miliary tuberculosis has a characteristic X-ray picture where the entire lung appears studded with small nodules that resemble millet seeds. Extrapulmonary tuberculosis such as tubercular effusions can also be picked up on the X-ray. A CT scan of the chest has a much higher pickup for visualising parenchymal and pleural pathologies; in addition, mediastinal lymphadenopathy with necrosis can be picked up on contrast-enhanced scans. These findings may be very suggestive of active tuberculosis in the chest. MRI and contrast-enhanced MRI are useful for imaging neurological and musculoskeletal involvement of tuberculosis such as CNS tuberculosis and spinal tuberculosis and can be done if CNS tuberculosis is suspected on clinical grounds (Fig. 4.1).

Diagnostic Approach

The traditional bacteriologic diagnostic methods rely on the detection of acid fast bacilli (AFB) by either the Ziehl-Neelsen or the auramine-rhodamine

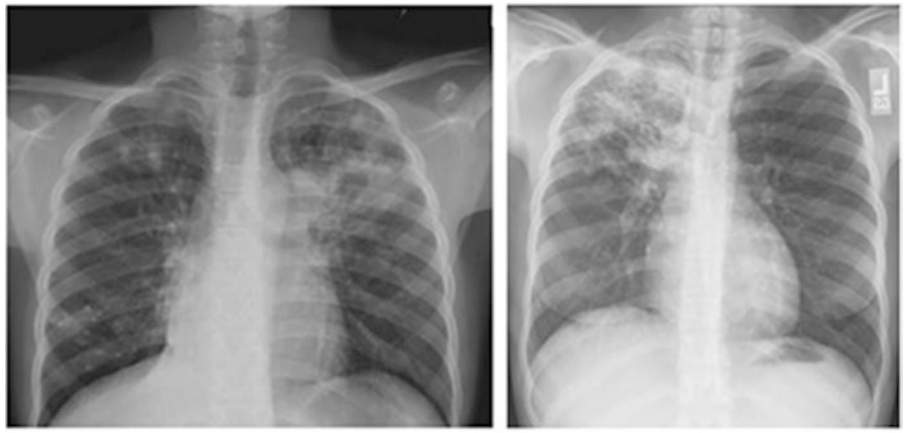

Fig. 4.1 Chest radiograph in pulmonary tuberculosis. (**a**) Left upper zone consolidation and cavitation. (**b**) Right upper zone infiltrates and foci of consolidation

stain. Although roughly 50% of active pulmonary tuberculosis may show smear positivity in sputum samples, the sensitivity of these tests in ocular fluids is low. The IGRAs, though more sensitive than the TST, are still unable to distinguish between latent and active tuberculosis.

Molecular tools such as the nucleic acid amplification tests, PCR and GeneXpert MTB/RIF have emerged as promising tools. They have the added advantage of the ability to detect drug resistance. However, ocular fluid samples availability is usually low, affecting the amount of DNA load and hence the sensitivity and specificity of these assays. Moreover, comparative studies with the gold standard (culture) are still lacking.

Histopathological demonstration of necrotising granulomas in ocular tissue may support the diagnosis of tuberculosis, but in the absence of AFB, the diagnosis of tuberculosis cannot be confirmed. Also, obtaining ocular tissue for histological examination may not be possible in all cases, especially in posterior uveitis.

A reasonable understanding of the available diagnostic tests, particularly their strengths and weaknesses, individualised to the clinical picture, allows for a judicious use of these modalities in a particular clinical setting to achieve a diagnosis (Table 4.1).

The combination of clinical symptoms and radiological and laboratory investigations is used to categorise a patient into three categories: *definite intraocular tuberculosis*, where AFB or tubercular DNA has been demonstrated from ocular samples in the presence of suggestive clinical and radiologic features; *probable ocular tuberculosis*, where there is a supportive evidence of tuberculosis (IGRA/TST and/or radiological features) and a favourable response to an empiric antitubercular therapy (ATT) trial in the absence of a definite evidence of tuberculosis; and *unlikely intraocular tuberculosis*, where the investigation results do not support a diagnosis of intraocular tuberculosis.

Compliance with Ethical Requirements Randeep Guleria and Vijay Noel Nongpiur declare that they have no conflict of interest. No human or animal study statements were carried out by the authors for this chapter.

Table 4.1 Advantages and disadvantages of various investigative modalities for tuberculosis

Type	Mechanism	Advantages	Disadvantages
Immunologic			
Mantoux test	Tests skin hypersensitivity to mycobacterial purified protein derivative	Low cost Widely available Good marker of cell-mediated immunity	Not specific to active MTB Not able to distinguish latent from active TB May be positive to BCG vaccination Interpretation is dependent on the person reading the size of induration May be negative in immune suppressed
Interferon-γ release assays	Tests release of γ after in vitro stimulation of patient's lymphocytes with Mycobacterium tuberculosis (MTB) antigens	More specific for MTB Not influenced by BCG Not subject to reading bias	Higher cost Unable to distinguish latent from active TB
Radiological			
Chest X-ray (CXR)	Assess evidence of pulmonary involvement in tuberculosis, either active or healed	Low cost Widely used Useful when a diagnostic pattern is found	Radiation exposure Findings may not be specific to tuberculosis Normal study does not rule out ocular TB
Chest CT	Assess evidence of pulmonary involvement in tuberculosis, either active or healed	More sensitive than CXR More useful for visualising lymphadenopathy	Radiation exposure High cost Not specific for tuberculosis Normal study does not rule out ocular tuberculosis
Microbiological/histological			
AFB smear	Identifies acid-fast-stained bacilli in clinical specimens	Widely used Useful for specimens with large bacillary load (e.g., sputum)	Low sensitivity Other organisms may also show acid-fast positivity
Culture	Detects growth of MTB after seeding in culture media	Gold standard for diagnosis of MTB infection	Cumbersome Results may take up to 6 weeks in solid media
Histopathology	Granulomatous inflammation supports the diagnosis. The presence of AFB is diagnostic	Allows evaluation of damage to tissue	Risks related to the degree of invasiveness of the procedure done to obtain tissue Low sensitivity
Molecular			
Nucleic acid amplification	Detects presence of MTB DNA in clinical specimens (PCR based)	High specificity Better sensitivity than AFB smear Results obtained quickly Able to detect drug resistance	High cost Limited availability Variable sensitivity

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5 Tuberculin Skin Test and Interferon-γ Release Assays in the Diagnosis of Ocular Tuberculosis

Nicole Shu-Wen Chan and Soon-Phaik Chee

Introduction

Despite the World Health Organization's advances in prevention and treatment over the last 15 years, tuberculosis (TB) remains a major global threat with 9.6 million new cases and 1.5 million deaths in 2014, ranking it as the leading cause of death alongside with the human immunodeficiency virus [1].

Ocular TB is defined as an infection by *Mycobacterium tuberculosis* in the eye, around the eye, or on its surface [2]. Primary ocular TB in which *M. tuberculosis* enters the body through the eye is rare. Secondary ocular TB occurs due to hematogenous seeding from a distant site, with direct invasion of tubercle bacillus causing local destruction and inflammation. Ocular TB may also be immune-mediated, in which there is a hypersensitivity reaction to the *M. tuberculosis* from distant foci in the body. This hypersensitivity causes inflammation despite the absence of the bacterium in the eye [3–6]. Phlyctenulosis, retinal vasculitis, and interstitial keratitis are examples of ocular pathology associated with *M. tuberculosis* infections believed to be hypersensitivity reactions [5, 7–9].

The diagnosis of ocular TB remains a complex issue as tuberculous infection can present with clinical features of virtually any type of extra−/intraocular inflammation [10–12]. When ocular TB presents with rare manifestations such as a lid abscess, chronic blepharitis, atypical chalazia, mucopurulent conjunctivitis with regional lymphadenopathy, infectious keratitis, or scleritis, material obtained for culture and biopsy can establish the diagnosis.

Ocular TB more commonly presents as tuberculous uveitis, likely due to the extensive vascularity of the uveal tract that makes it susceptible to the hematogenous spread of *M. tuberculosis* [6, 13, 14]. The most common sign of ocular TB is a choroidal mass assumed to be secondary to hematogenous dissemination, followed by choroiditis where the widespread inflammation is likely due to hypersensitivity [5, 6, 8, 9, 15–20].

However, tuberculous uveitis is often diagnosed late and undertreated for two reasons [21]. Firstly, it can present with a wide spectrum

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A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_5

of ocular manifestations. Secondly, investigations for the definitive diagnosis of tuberculous uveitis such as mycobacterial cultures using the Lowenstein–Jensen media, acid-fast bacilli smears, and polymerase chain reaction-based analyses on ocular fluid samples are often of low sensitivity [10, 22–25]. This may be due to the immune-mediated mechanism of inflammation, the small inoculum of *Mycobacterium tuberculosis* in the eye, and the low volumes of intraocular samples [23]. Doing a uveal biopsy for culture and histopathology is not only impractical and invasive [6], but the source of biopsy is also often unknown to the clinician because most infections are occult. Most uveal biopsies do not show any evidence of *Mycobacterium tuberculosis* [26, 27], and some may argue that the ocular inflammation may not be attributable to the source of TB infection even if it is found. It remains unknown if tuberculous uveitis results from a direct mycobacterial infection or a hypersensitivity reaction.

As unequivocal evidence of the infection is often not available [10], the diagnosis of "presumed" tuberculous uveitis is made adhering to published criteria in patients with suggestive clinical features (broad-based posterior synechiae, granulomatous inflammation, serpiginous choroiditis, retinal vasculitis) [28] and with a positive tuberculin skin test (TST), a positive interferon-γ release assay (IGRA), lesions suggestive of pulmonary TB on a chest X-ray (CXR), and/or evidence of associated systemic TB infections in the absence of any other underlying disease [10]. It is important to exclude other infectious and noninfectious causes including sarcoidosis before making the diagnosis of presumed tuberculous uveitis.

As the lungs are the main site of tuberculous involvement regardless of whether in primary infection, reactivation of dormant microbes, or reinfection [29], a chest radiograph is often done to look for evidence of active or healed/primary or reactivated tuberculosis. However, ocular tuberculosis may occur in the absence of evidence of pulmonary disease [30–32]. Chest radiographs are normal in the majority of patients with ocular TB [10, 19, 25, 27], and radiologic evidence of post-inflammatory lesions such as hilar lymphadenopathy and parenchymal scarring may not be specific for TB [33]. While there has been much research on the various diagnostic tests for *M. tuberculosis*, a common problem is the lack of a comparative gold standard to confirm the sensitivity and specificity of each test [34]. Moreover, using response to antituberculosis treatment may also be difficult in non-endemic regions as up to 40% of patients with ocular TB might not respond to ATT [35]. In such cases, clinicians often rely on the TST and IGRAs to aid the diagnosis of tuberculous uveitis.

Tuberculin Skin Test (TST)

The tuberculin skin test (TST) [36] or Mantoux test dates back to the nineteenth century and is still widely used in the diagnosis of TB today. It measures the degree of type IV delayed hypersensitivity reaction to a mixture of over 200 antigens derived from *M. tuberculosis*. T cells sensitized by previous infection are recruited to the site of intradermal injection and release lymphokines that recruit other inflammatory cells and induce induration through local vasodilatation, edema, and fibrin deposition.

The standard TST consists of an intradermal injection of 5 tuberculin units of purified protein derivative [37] to produce a wheal 6–10 mm in diameter. The skin induration, which may occasionally have vesiculation and necrosis, is measured 48–72 h later [38] and indicates whether the individual has been exposed to the tubercle bacilli. The TST does not measure immunity to TB, and the size of the induration does not correlate with the likelihood of current active TB disease but is correlated with the future risk of developing TB disease [39]. However, the formation of vesicles, bullae, or necrosis indicates a high degree of tuberculin sensitivity and thus the presence of TB infection [40]. Ocular hypersensitivity has been found to directly correlate with cutaneous hypersensitivity [41]. An induration of <5 mm is considered a negative result, and various thresholds of 5, 10, and 15 mm are used based on the individual's risk profile (see Table 5.1) to determine if the result is considered positive [27, 36, 42]. Although the recommended TST cutoff diagnosis

Table 5.1 Interpretation of the induration reaction in tuberculin skin test

Measurement of induration (mm)	Interpretation
<5	Negative result
≥5	Positive result in individuals who are: – HIV positive – End-stage renal failure patients – Organ transplant recipients and other immunosuppressed patients on cytotoxic immunosuppressive agents (e.g., cyclophosphamide, methotrexate) – On long-term systemic corticosteroid therapy (> 6 weeks) and those on prednisone ≥15 mg/day or equivalent – Recent contacts of active tuberculosis cases – Found to have nodular or fibrotic changes on chest X-ray consistent with old healed tuberculosis
≥10	Positive result in individuals who are: – Intravenous drug users – Residents and employees of high-risk congregate settings (e.g., nursing homes, hospitals, prisons) – Mycobacteriology lab personnel – From countries with high prevalence of tuberculosis and have arrived within the last 5 years – With medical conditions (e.g., diabetes, leukemia) that put them at high risk – Less than 4 years old – Infants/children/adolescents exposed to adults in high-risk categories
>15	Positive result in individuals who have no known risk factors for tuberculosis

HIV human immunodeficiency virus

is 10 mm for latent TB infection [36], the TST cutoff for diagnosis depends on the endemicity of TB. In countries with higher incidence of TB, a higher cutoff such as >15 mm reduces the chances of false-positive results and unnecessary antituberculosis treatment [38].

As the predictive value varies on the local incidence of TB and the BCG vaccination policy, routine use of the TST in patients with uveitis is mandatory in countries such as India [43] but considered unhelpful in some countries such as the United States [44].

Although the TST is inexpensive, it has several disadvantages. It requires multiple visits; is subjective with inter-reader variability, unstandardized in the timing at which the induration is measured (can vary from 48 to 72 h); has a low specificity; and may be difficult to interpret due to confounding factors.

Due to the nonspecific nature of the mycobacterial antigens and cross-reactivity, the TST may give a false-positive response in individuals infected with nontuberculous mycobacterium (NTM) or vaccinated with bacillus Calmette–Guérin (BCG) [37, 45]. In BCG-vaccinated individuals, the larger the size of induration reaction and risk factors for TB including contact history with a TB patient, family history of TB, and a country of origin with a high incidence or prevalence of TB increases the likelihood of a true-positive result [10]. The induration is also likely a true-positive result with increasing interval between the vaccination and skin testing as BCG vaccination-induced reactions wane over the first 7 years [46] and seldom persist beyond 10 years after vaccination [47].

The TST may also be difficult to interpret in the presence of certain comorbidities. For example, patients with psoriasis have enhanced response to the TST where the induration has a positive correlation with the psoriasis area and severity index [48], and the exaggerated skin hypersensitivity such as in Behçet's disease may act as a pathergy test, resulting in a false-positive response [49].

As the TST measures the cutaneous type IV hypersensitivity reaction, individuals with impaired cellular immunity such as young children, the elderly, and the immunocompromised including those with the human immunodeficiency virus (HIV) infection, diabetes, renal disease, and iatrogenic immunosuppression [50, 51] may have false negative responses. As the TST can be falsely negative in 10–20% of patients with proven tuberculosis with no apparent immunosuppression [52–55], a negative TST result does not exclude ocular TB.

Interferon-γ Release Assays (IGRAs)

A more recent addition to the diagnostic armamentarium are the interferon-γ release assays (IGRAs), which are sensitive, specific, and objective ex vivo assays for previous exposure to *M. tuberculosis* [56]. IGRAs measure in vitro interferon-γ (IFN-γ) released in response to stimulation by the TB antigens: early secretory antigenic target (ESAT)-6 and culture filtrate protein-10 (CFP-10) [57]. These peptides are coded by a deoxyribonucleic acid (DNA) region in the *M. tuberculosis* genome that is absent in BCG strains and most environmental mycobacteria (with the exception of *M. kansasii*, *M. szulgai*, *M. marinum*, *M. flavescens*, and *M. gastri*) [58–60].

Commercially available IGRAs include T-SPOT.TB (Oxford Immunotec, Oxford, UK) and QuantiFERON-TB Gold In-Tube (QFT) (Cellestis Inc., Carnegie, VIC, Australia). In T-SPOT.TB, ESAT-6 and CFP-10 are used to harvest viable peripheral mononuclear blood cells that release IFN-γ, which are counted with a T-cell-based enzyme-linked immunospot (ELISPOT) assay [61]. The QFT on the other hand is a whole-blood assay that quantifies IFN-γ produced by previously sensitized T cells in response to ESAT-6, CFP-10, and TB7.7 using an enzyme-linked immunosorbent assay (ELISA) [62–65].

Comparison of IGRAs with the TST

As both the TST and IGRAs are indirect tests that indicate a cellular immune response to recent or remote sensitization with mycobacterial antigens, neither test can distinguish between individuals with latent, active, and previous TB infection, nor do they have a high accuracy for predicting active TB [66].

Although the intensity of QFT response does not help to differentiate active from latent TB infection [67], a QFT >2 IU/mL indicates a higher likelihood of the response of the ocular TB to antituberculosis treatment [68]. IGRAs provide greater specificity for *M. tuberculosis* [23, 69, 70] in pulmonary TB [45, 61, 70, 71] and, unlike the TST (see Table 5.2), do not give false-positive results in individuals vaccinated with the BCG or infected with most NTM. IGRAs may thus be preferred in patients with previous BCG vaccination. In addition, IGRAs have a lower rate of false negatives than the TST in rheumatic patients taking steroids or disease-modifying antirheumatic drugs (DMARDs) [72].

However, IGRAs are not superior to the TST in sensitivity in diagnosing latent TB infections [70, 73, 74] and should not be used as a screening test or first-line investigation in tuberculous uveitis [23, 56, 75], especially in populations where TB is not endemic. Nevertheless, they are a useful adjunct in the diagnosis of tuberculous uveitis when used together with clinical signs suggestive of tuberculosis and TST in BCG-vaccinated populations [57]. A positive IGRA result strongly supports the diagnosis, while a negative IGRA result should be interpreted with caution as it does not exclude the diagnosis [23, 56].

Like the TST, the use of IGRAs in pediatric [76–79] and elderly patients [80] has its limitations. Given the variable T-cell IFN-γ response in children, a substantial proportion of children do not have a determinate IGRA result [81], which is likely due to the immature immune system and primary or acquired immune deficiencies [79, 81]. Similarly, as immunosenescence begins at 50 to 55 years of age [82], an age-related waning of T-cell function [80] is associated with decline in the functional activity of the peripheral blood mononuclear cells, reduced diversity of T cells, and a decreasing trend in IFN-γ production from T cells in response to mitogen and *M. Tuberculosis* antigens in whole blood [61, 80, 82, 83].

Although IGRAs are objective and require only a single visit [84], they have substantial intra-patient variability particularly in settings with low incidence of TB [64, 85–90] that is largely due to sample processing factors such as delays in incubation and variations in blood volume [86, 87, 90–110]. Reversions and conversions around the existing cut-point should thus be interpreted with caution [111]. Moreover, IGRAs require higher material costs, specialized equipment, and trained personnel to analyze the results since the samples are time and temperature sensitive [88].

Table 5.2 Comparison between the tuberculin skin test and the interferon-γ release assays (T-SPOT.TB and QuantiFERON-TB Gold In-Tube)

	Tuberculin skin test	Interferon-γ release assay	
		T-SPOT.TB	QuantiFERON-TB Gold In-Tube (QFT)
Principle	Measures the degree of type IV delayed hypersensitivity reaction to purified protein derivative	Counts the number of viable peripheral mononuclear blood cells that release IFN-γ using a T-cell-based enzyme-linked immunospot assay	Whole-blood assay – quantifies IFN-γ produced by previously sensitized T cells
Sensitivity (95% CI) [74]	0.709 (0.658–0.761)	0.500 (0.334–0.666) More sensitive than QFT in immunocompromised individuals and children ≤5 years old	0.642 (0.593–0.691)
Specificity (95% CI) [74]	0.683 (0.522–0.844)	0.906 (0.882–0.929)	0.996 (0.989–1.000)
False positives			
Cross-reactivity with			
– NTM infections	Yes	No	
– BCG vaccination	Yes	No	
Misc	Enhanced response in comorbidities (e.g., psoriasis) or exaggerated skin hypersensitivity (e.g., Behcet's disease)		
False negatives	Impaired cellular immunity: young children, elderly, immunocompromised (e.g., HIV, diabetes, immunosuppression)		
In individuals			
– On steroids or DMARDs	Higher rate of false negatives	Lower rate of false negatives	
– With low T-cell numbers		Better resolution of samples than QFT	Tends to give "indeterminate" results
		Tends to have "equivocal" results in individuals <13 years old or >55 years old	
Ability to distinguish between latent and active tuberculosis	Unable to distinguish	Unable to distinguish	
Objectivity	Less objective	More objective	
Reproducibility	Inter-reader variability; non-standardized timing (varies from 48 to 72 h) of measurement of induration	Intra-patient variability (due to delays in incubation and variations in blood volume)	
Cost	Inexpensive	More expensive (varies from country to country)	
Logistical considerations			
Specialized equipment	Not required	Required	
Trained personnel	Nurses, physician	Laboratory technicians	
Convenience	Requires 2–3 visits	Single visit	

CI confidence interval, *NTM* nontuberculous mycobacterium, *BCG* bacillus Calmette–Guérin, *DMARDs* disease-modifying antirheumatic drugs, *HIV* human immunodeficiency virus

Choosing Between the T-SPOT.TB and QFT

Although similar, the T-SPOT.TB may be preferred to the QFT and vice versa, depending on patient demographics. In studies comparing both IGRAs, the T-SPOT.TB was found to be more sensitive for *M. tuberculosis* infection, especially in immunocompromised individuals [83, 112] and children aged 5 years or younger [38, 113]. This is because the T-SPOT.TB has a better resolution of samples compared to the QFT, which may give "indeterminate" results in individuals with inadequate T-cell numbers. However, the QFT was found to be significantly more accurate than the T-SPOT.TB in identifying true-positive tuberculous uveitis cases among discordant cases [114].

Unlike the QFT which has a distinct cutoff value, the T-SPOT.TB has a range of cutoff values (negative <4 spots and positive >8 spots), resulting in an "equivocal" T-SPOT.TB result if the number of spots is more than the negative cutoff value but less than the positive cutoff value (i.e., between and inclusive of 5–7) [73, 83]. If the T-SPOT.TB result is equivocal, the clinician may repeat the T-SPOT.TB or do the QFT [76]. Individuals less than 13 years old or more than 55 years old are especially likely to have an "equivocal" T-SPOT.TB result [76], and in a setting where TB is moderately endemic, doing the QFT may be preferred as the equivocal T-SPOT.TB may be a false positive. These patients have a high likelihood of a negative QFT result and are unlikely to have latent TB infection [76].

Approach to the Diagnosis of Ocular Tuberculosis

Although there have been several attempts to recommend guidelines for diagnosis of ocular TB, there is currently no clear consensus on the most appropriate and cost-effective diagnostic strategy [115, 116]. This may be due to the varying prevalences of TB across developed and developing countries, as well as the local cost of performing IGRAs in the respective countries. In developing countries, the TST is generally preferred over IGRAs [117], and the use of IGRAs for active TB is not recommended due to the poor specificity given the high background prevalence of latent TB infection [118–121].

Common Diagnostic Strategies

Clinicians commonly adopt one of the four diagnostic strategies: firstly, a two-step approach of TST first, followed by IGRA; secondly, both the TST and IGRA simultaneously at presentation; thirdly, TST only; and lastly, IGRA only [116]. The UK-based National Institute for Health and Care Excellence (NICE) guidelines advocate a two-step approach using TST and chest radiography as first-line investigations, with subsequent confirmatory IGRA testing in cases with positive TST results or in those whom the TST is unreliable [122]. In contrast, the US Center for Disease Control and Prevention (CDC) guidelines recommend one-step IGRA-only testing for the diagnosis of TB infection [123].

A study compared the above four strategies for the diagnosis of tuberculous uveitis and found that it was the most cost-effective to do both the TST and IGRA at presentation and least cost-effective to do an IGRA only [124]. It cited two main advantages that likely outweighed the cost of performing both tests simultaneously. Firstly, the dual strategy had higher predictive power which reduced the number of false-positive results and the associated unnecessary costly treatment. Secondly, patients who were initiated on antituberculous treatment based on the positive results from both tests had a decreased likelihood of recurrence of uveitis and lower ocular morbidity [35]. However, this study was conducted in a country with a high cost of IGRA. In countries with a lower cost of IGRA, the two-step approach strategy which the NICE guidelines recommend is more cost-effective than the single-test strategy [124]. If a single-test strategy is used, doing IGRA only may be more cost-effective than TST for the screening of latent TB infection in immigrants from high-risk countries [125].

Although many studies have explored the use of IGRAs in tuberculous uveitis [3, 56, 75, 126–130],

their role in the diagnosis and testing strategy of latent TB or tuberculous uveitis is still uncertain [35, 114, 130]. However, based on two systematic reviews, IGRAs should not be used to diagnose active TB in adults because a positive IGRA result may not indicate active TB and a negative IGRA result may not rule out active disease. IGRAs should only be used as an adjunct test in the diagnosis of active TB and should not replace the standard microbiological and radiographic tests [120, 131]. Although IGRAs should ideally be performed prior to the TST, they may still be done in patients who have done the TST as the TST is unlikely to affect the QFT result [65, 76] and the boosting effect is likely to be insignificant if T-SPOT.TB is performed within 3–7 days after the TST [108]. As prevalence of TB affects the interpretation of IGRAs, Harada et al. (2004) [132] suggested that the cutoff value of QFT be reset at a lower level in the context of high prevalence of TB.

Gupta et al. (2007) [10] proposed a diagnostic criteria for intraocular TB, based on clinical signs, ocular investigations, systemic investigations, exclusion of other uveitis entities, and therapeutic test. The algorithm by Vasconcelos-Santos et al. (2009) [130] applies mainly to regions where TB is non-endemic and proposes the use of TST and chest radiograph as the initial investigations, with subsequent options of IGRA, computed tomography of the chest, and/or a trial of antituberculosis therapy depending on the TST and chest radiograph results.

Ang et al. (2009, 2012) [56, 57] recommend a combination of IGRA with TST as performing both tests increases the diagnostic accuracy and avoids negative or indeterminate solo test results [23]. If both the TST and IGRA cannot be performed due to cost or logistical issues, the investigation of choice depends on the prevalence of tuberculous uveitis in the population. IGRA is preferred in populations with low prevalence as it is more specific [114], while the TST is preferred in populations with high prevalence of tuberculous uveitis or in patients in whom there is already a high index of suspicion for tuberculous uveitis [23].

However, doing both the TST and IGRA may give rise to discordant results even in countries with low BCG vaccination. Individuals with concordant positive TST and IGRA results have the highest incidence of progression to TB, compared to those with discordant results. Those with positive IGRA and negative TST have a slightly higher risk of progression to TB as the results tend to represent new or active infections, whereas positive TST and negative IGRA are associated with previous BCG vaccination especially in the young [56].

Other Techniques

Besides the TST and IGRAs, other tests include microbiological investigations, molecular techniques, and diagnostic imaging.

Direct Evidence

Direct evidence of *M. tuberculosis* from tissue or fluid samples can establish the diagnosis of ocular tuberculosis.

Acid-Fast Smear

The traditional direct microscopy of smears of infected tissue or fluid of acid-fast bacilli (AFB) after acid-fast staining, usually with Ziehl–Neelsen or auramine–rhodamine stain, is a rapid method of diagnosing tuberculosis. However, at least 10^6 organisms/ml of sputum are required for detection on a smear [133].

Culture of Intraocular Fluid/Tissue

Culture of *M. tuberculosis* on Lowenstein–Jensen (egg-based) medium is regarded as the gold standard for the diagnosis of tuberculosis [69]. The cultures are incubated for 6–8 weeks, and visible colonies are identified by Ziehl–Neelsen stain. Cultures also enable the viable mycobacteria to be tested for antibiotic resistance. However, the process is prolonged and cumbersome. Costly semiautomated and automated systems with liquid media may allow earlier results [69].

Histopathologic Examination

Histopathologic examination of tissue sections with evidence of necrotizing granulomatous inflammation may support a diagnosis of tuberculosis [43, 134]. However, if no AFB are seen, the diagnosis of ocular TB cannot be confirmed unless results of other investigations, such as culture or nucleic acid amplification tests (NAATs), are positive [19, 135].

The main drawback of the acid-fast smear, Lowenstein–Jenson mycobacterial culture, and histopathologic examination is the low yield of organisms in intraocular fluids and biopsies. Moreover, intraocular biopsies are also invasive and difficult to obtain. Although these methods are often not helpful in the diagnosis of intraocular TB, they may be useful in lesions with abundant caseation necrosis or in those presenting with endophthalmitis which may have a higher yield of AFB [134, 136].

Polymerase Chain Reaction

The use of molecular techniques to detect the DNA of MTB in ocular fluid/tissue is a challenging task due to the paucibacillary nature of the disease [137] and a possible immune-mediated mechanism of intraocular inflammation [26] which may be related to cytokine responses in the eye [138]. Nucleic acid amplification tests (NAATs) such as polymerase chain reaction (PCR) [139], quantitative real-time (RT) PCR [140], multiplex PCR (MPCR), and loop-mediated isothermal amplification test (LAMP) [141] amplify mycobacterial DNA severalfold, enabling rapid detection of the mycobacterial genome.

They are emerging as important tools for timely and accurate diagnosis of ocular TB as PCR can be performed with very small sample sizes of intraocular fluids, which may be aqueous [17, 31, 139, 142, 143], vitreous humor [139, 144–146], subretinal fluid [147, 148], or, rarely, tissue obtained by chorioretinal biopsy [149–152]. As the target gene is absent in 20–40% of *M. tuberculosis* isolates [153], several studies using single gene targets for the detection of MTB DNA in ocular fluid sample showed poor sensitivity of PCR (ranging from 33.3% to 66.6%) [139]. However, studies using two or more gene targets yielded significantly better diagnostic sensitivities [154], with a multiplex PCR (MPCR) using three target genes yielding a sensitivity of 77.8% and specificity of up to 100% for diagnosis of ocular TB [137].

In addition to detecting *M. tuberculosis* DNA in active lesions, real-time PCR may also detect the presence of DNA from possibly dormant mycobacteria in normal tissues of latently infected individuals [155–157], although its use has not been reported in the diagnosis of ocular TB as of yet.

Genotypic methods such as the GeneXpert MTB/RIF (Xpert) (Cepheid, Sunnyvale, CA) assay potentially provide information on drug resistance, which may be the reason for recurrence in patients with recurrence of ocular TB despite effective antitubercular therapy, without a need for culture [158].

Imaging

Besides the chest radiograph, other diagnostic imaging modalities include computer-assisted tomography (CT) scans and positron emission tomography/computed tomography (PET-CT) scans. CT scans may help to delineate concomitant hilar, parenchymal, or pleural disease in highly suspected cases where plain chest radiographs are normal or inconclusive [29, 159]. More recently, PET-CT scans have been shown to be useful in identifying pulmonary and extrapulmonary lesions in patients with presumed ocular TB, which can be biopsied to establish the diagnosis [160, 161]. However, the high cost and lack of availability limit its use for routine investigation.

Conclusion

In a patient with clinical features typical of tuberculous uveitis, positive tuberculin skin test and/or interferon-γ release assay results are commonly used to aid the diagnosis of presumed tuberculous uveitis, especially if there is no evidence of associated systemic infection. The TST is widely used

particularly in TB-endemic countries because of its sensitivity and low cost, while IGRAs provide greater specificity for *M. tuberculosis* infection in individuals infected with nontuberculous mycobacterium or previous BCG vaccination. As there is currently no clear consensus on the approach to diagnosing ocular tuberculosis, the choice of investigation(s) depends on the local prevalence of TB, cost-effectiveness, and the patient demographics.

Compliance with Ethical Requirements Nicole Shu-Wen Chan and Soon-Phaik Chee declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this article.

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Management of Ocular Tuberculosis

6

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Introduction

TB is one of the leading causes of morbidity and mortality worldwide. The causative agent of tuberculosis is *Mycobacterium tuberculosis* (MTB), discovered by Robert Koch in the year 1882. The World Health Organization (WHO) declared TB as a global health emergency in the year 1993. India is the country with the highest burden of TB. The World Health Organization statistics for 2015 gave an estimated incidence figure of 2.2 million cases of TB for India out of a global incidence of 9.6 million [1]. The estimated TB prevalence in India for the year 2015 is about 2.5 million cases [2].

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Ocular Tuberculosis

Ocular tuberculosis is a form of extra-pulmonary tuberculosis. It can occur in isolation or in conjunction with pulmonary tuberculosis [3]. Tuberculosis bacilli get disseminated from the lung or any primary foci of tuberculous infection in the body, through haematogenous or lymphatic route to distant sites including the eye, where it remains dormant [4]. Ocular tuberculosis can be either intraocular tuberculosis or involving the ocular adnexa. Intraocular tuberculosis is an important cause of uveitis and accounts for about 10.5% of uveitic cases [5]. Extra-pulmonary disease is more common in immunocompromised patients [6]. Ocular tuberculosis can be caused either by an active infection or secondary to type IV hypersensitivity reaction. Active infection results from reactivation of the dormant bacilli, leading to haematogenous spread and direct invasion into local ocular tissues [7], and type IV hypersensitivity is due to an immune-mediated reaction to the latent MTB infection elsewhere in the body [7, 8]. Polymerase chain reaction analysis of ocular fluid has vital role in establishing the diagnosis of ocular tuberculosis.

Antitubercular treatment (ATT) drugs are being used around the world under various national TB control programmes and have helped to decrease the prevalence of disease, but still TB remains the greatest killer of human beings.

A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_6

ATT leads to rapid killing of the tubercle bacilli leading to cure of the disease .One of the first drugs used for treatment of TB was streptomycin in the 1950s [9]. Later in the 1960s development of isoniazid and rifampicin and their use lead to considerable decrease in the number of TB cases.

Challenges in Management of Ocular Tuberculosis

Inability to isolate the bacilli from ocular samples leads to poor result from cultures of aspirates. Lack of associated systemic features in case of intraocular tuberculosis can create problems in management as chest physicians may be reluctant to start ATT in these patients. There is no consensus amongst ophthalmologists all over the world regarding diagnostic criteria and treatment guidelines in endemic and non-endemic countries leading to confusion. Wide spectrum of clinical features with varied presentations can further complicate the management [10]. Delay in diagnosis and commencing antitubercular treatment (ATT) and management of ocular inflammation only with immunosuppressive and oral steroids may result in sight- and life-threatening consequences [8]. Even the short-course chemotherapy under the DOTS strategy, as advised by WHO, is not applicable for the treatment of ocular tuberculosis, as patients show variable response to treatment. The US Food and Drug Administration has currently approved ten drugs and recommended a course of 9 months of ATT for treatment of extra-pulmonary disease including ocular tuberculosis [3].

Pharmacokinetics and Pharmacodynamics of Anti-TB Drugs

Isoniazid, rifampicin and pyrazinamide were discovered 50–60 years ago, when the concept of pharmacokinetics and pharmacodynamics (PK-PD) was not well established in drug discovery. In order to reach within the non-vascularised granulomas from the circulation, these drugs have to diffuse into the necrotic foci and cross the lipid-rich cell walls of bacilli to target at molecular level. The plasma concentration of anti-TB drugs is not predictive of intralesional concentration. There are many factors responsible for poor chemotherapeutic penetration within the granulomas. Granuloma was initially considered as a protective mechanism to wall off the infective pathogen. But recent studies have shown that it actually forms a remote and shielded compartment within which the bacilli expands, disseminates and colonises [3, 11]. Thus damage in TB is more immune response driven than directly due to the bacilli. Initially the granuloma is cellular and highly vascularised. As it matures, the core becomes necrotic, called as the caseum. Vascularisation gradually gets destroyed within the caseum but persists in the surrounding cellular rim and the fibrotic wall [12]. In a cellular granuloma, the bacilli are predominantly intracellular; however in a necrotic granuloma, there are large number of extracellular bacilli [13, 14]. The anti-TB drugs penetrate the caseum by passive diffusion through the cellular rim in the absence of any active or facilitated transport mechanism due to poor vascularity [15]. Reduced vascularity within the granuloma impedes the drug delivery and also reduces the oxygen and nutrient supply. This decreases the cell proliferation, increases the metabolic quiescence of bacilli and increases the drug tolerance [15]. These slow-growing and non-replicating bacilli exhibit phenotypic tolerance which makes them recalcitrant to anti-TB drugs [12]. This subpopulation of bacilli within the granuloma which are slow growing and non-replicating have an altered cell wall due to which they often go undetected by Ziehl-Neelsen staining. Compromised vascularity of granuloma also reduces the access of circulating T lymphocytes and fails the immunity [16].

The concentration of isoniazid, rifampicin and pyrazinamide is low within the cellular granulomas as compared to their plasma levels [17]. Although the rate of penetration is rapid for all four anti-TB drugs, these drugs equilibrate quickly within the granulomas, but the dynamics of distribution is very complex. Isoniazid and pyrazinamide are prodrugs and their immediate

bioactivation is responsible for discrepancies in the levels of radio-labelled forms of these drugs measured by radioactive studies. Distribution of these drugs within the granulomas has been studied with matrix-assisted laser desorption/ionisation mass spectrometry (MALDI-MS) [18]. As compared to the poor diffusion of other drugs, pyrazinamide has good accumulation within the necrotic foci, where the phenotypically tolerant bacilli tend to persist. Therefore removal of pyrazinamide from ATT after initial months causes increase in duration of therapy and thereby leads to poor compliance [19, 20]. Second-line drugs like moxifloxacin attain high levels within the macrophages and lymphocytes but have subtherapeutic levels in the caseous foci due to nil or very minimal penetration within the necrotic foci where the phenotypically tolerant bacilli persist. This leads to development of antibiotic resistance mutation within the bacilli [21].

The intracellular drug uptake is also very variable. In vitro macrophage uptake and in vivo assays of concentration of these drugs within infected cells are unlikely to be predictive of actual intracellular concentration. Activation of macrophage increases uptake of fluoroquinolones. Thus in order to increase the efficiency of anti-TB drugs, it is important to increase the uptake and finally the intracellular retaining capability. Newer drug formulation is using liposomes and nanoparticles for targeted drug delivery. A ligand for macrophage receptors is added on the surface of liposomes and nanoparticles, which are then phagocytosed by macrophages and thereby intracellularly deliver the drugs. This also reduces the systemic drug levels and toxicity [22, 23]. Intracellular levels of fluoroquinolones is markedly reduced in quiescent bacilli [24]. Inflammation leads to increase production of endogenous polyamines in the macrophages. Polyamines decrease the permeability of drugs within the bacilli and thereby contribute to phenotypic tolerance. Increase efflux of drugs from the bacilli, when it grows, is also responsible for reduced intrabacterial drug concentrations. [25, 26] Finally bioactivation within the bacilli also plays a very important role in determining the conversion of prodrugs into active forms. In *Mycobacterium smegmatis*, stochastic variations have been described in the expression of katG gene enzyme, which activates the prodrug isoniazid into active form [27]. Prodrug pyrazinamide also gets converted to active form pyrazinoic acid by enzyme pyrazinamidase [28, 29]. Thus kinetics of bioactivations needs to be well understood to establish the PK-PD correlations. Pharmacokinetics deals with the factors responsible for differential and suboptimal drug distribution, and pharmacodynamics deals with the factors responsible for phenotypic tolerance and resistance in bacilli. Both PK-PD factors are responsible for inefficiency, drug resistance and prolonged duration of present ATT regimen and have to be dealt with in order to formulate effective therapy.

Treatment

Medical treatment as recommended by the Centers for Disease Control and Prevention (CDC) consists of a course of therapy which includes isoniazid, rifampicin, pyrazinamide and ethambutol [3]. The combination therapy is highly effective in susceptible population. The role of ATT, when pathogenic mechanism is immunogenic, remains controversial. In adults, the four drug regimens consist of the following drugs: isoniazid-H, 5 mg/kg/day; rifampicin-R, 10 mg/kg/day; ethambutol-E, 15 mg/kg/day; and pyrazinamide-Z, 20–25 mg/kg/day. Mechanism of action of antitubercular drugs is described in Table 6.1.

As per the Centers for Disease Control and Prevention recommendations, isoniazid, rifampicin, pyrazinamide and ethambutol for an initial 2-month period and then ethambutol and pyrazinamide are stopped and other two drugs are continued up to 4–7 months [3]. Many studies have reported that ATT should be prescribed at least for 6 months and maximum for up to 12–15 months [5]. Duration of therapy becomes an issue when after the initiation of therapy poor clinical response is noted.

Table 6.1 The mechanism of action of antitubercular drugs

Name of the drug	Mechanism of action
Isoniazid	It is a prodrug bioactivated by katG present in MTB which causes inhibition of mycolic acid synthesis. Most potent bactericidal drug in ATT regimen [7]
Rifampicin	Bactericidal against both dividing and dormant bacilli. Inhibits b-subunit of mycobacterial RNA polymerase Its rapid onset of action is due to its lipophilic nature, which is responsible for its penetration into macrophages and its activity against non-replicating persisters [30]
Ethambutol[a]	Inhibits arabinogalactan synthesis in MTB cell wall [5]
Pyrazinamide[b]	It is also a prodrug, which gets bioactivated by an enzyme – pyrazinamidase – present in MTB; exact mechanism of action is not known [6]

[a]Rifampicin can cause resistance when used alone. Combination of ethambutol reduces rifampicin resistance [5]
[b]Pyrazinamide has been reported to reduce the duration of treatment [6]

Monitoring of Response

In pulmonary tuberculosis and other forms of extra-pulmonary tuberculosis, it is easy to monitor the response because of the availability of clinical specimens in the form of sputum and tissue specimens, respectively. However, in the case of ocular tuberculosis, as intraocular tissues are not easily available, response is analysed completely based on clinical evaluation. It is important to assess the therapeutic response to ATT and monitor ocular toxicity of these drugs without compromising on the therapeutic effect. In case of favourable response within 2 months, ATT for 6 months might be enough. Patients who do not respond to ATT even at 2–3 months might need second line of therapy or alternative treatment along with complete systemic re-evaluation by an infectious disease specialist [5]. The end point for the therapy is assessed by the ophthalmologist in terms of resolution of intraocular inflammation. In case of poor response, a severe form of disease or an alternate diagnosis should be considered. If there is no reduction in intraocular inflammation after the 2-month initiation phase, the utility of continuing ATT should be reassessed as the likelihood of intraocular tuberculosis is low. Gupta et al. referring to their unpublished data have demonstrated resolution of intraocular inflammation in nearly 95% of their patients after 6–15 months of treatment with four drug regimens [31]. There are clear-cut guidelines for patients with pulmonary tuberculosis who are defaulters or previously treated cases who relapse in various tuberculosis control programmes all over the world. In case of intraocular tuberculosis, the role of restarting ATT in previously treated patients or in case of reactivation of previous lesions is not yet clear.

Side Effects of ATT Therapy [4, 5]

1. Unspecified symptoms
2. Rashes
3. Generalised weakness
4. Reduced libido
5. Hepatotoxicity associated with isoniazid and pyrazinamide
6. Eighth nerve toxicity associated with streptomycin
7. Optic neuritis – associated with ethambutol. However it has dose- and duration-dependent complication. It has to be used with caution in patients with renal insufficiency and in cases when dose is exceeding 15/mg/kg. It is recommended to check at least visual acuity and colour vision by physicians. It is also important to educate the patient regarding self-assessment of visual symptoms
8. Neurotoxicity is seen with isoniazid - It can cause peripheral neuritis, insomnia, increased agitation, urinary retention and seizures (these side effects can be reduced by pyridoxine supplementation, as they occur due to relative pyridoxine deficiency)

All these side effects can lead to compliance issues. Poor compliance in turn leads to

Table 6.2 Mechanism of action of second-line drugs

Drugs	Mechanism of action
P-Aminosalicylic acid	Antimetabolite interfering with incorporation of para-aminobenzoic acid into folic acid acting as folate synthesis antagonist
Cycloserine	Structural analogue of D-alanine and inhibits incorporation of D-alanine into peptidoglycan pentapeptide through inhibition of alanine racemase
Clofazimine	Unknown but might involve DNA binding. Possesses direct antimycobacterial and immunosuppressive properties
Amoxicillin and/or clavulanic acid	Amoxicillin inhibits cell wall synthesis. Clavulanic acid is a b-lactamase inhibitor
Clarithromycin	Inhibition of protein synthesis through binding to 50S ribosomal RNA as aminoacyl translocation reactions and the formation of initiation complexes is blocked
Rifabutin	Inhibits bacterial RNA synthesis by binding strongly to the b-subunit of bacterial DNA-dependent RNA polymerase
Thiacetazone	Not clearly elucidated

poor response to therapy, increased chances of recurrences and development of drug-resistant tuberculosis.

Jarisch-Herxheimer Reaction Paradoxical worsening of tuberculosis is a well-known entity especially in extra-pulmonary tuberculosis. The proposed mechanism of the reaction is the release of mycobacterial antigens after antitubercular treatment (ATT) and delayed hypersensitivity leading to worsening of clinical condition. Systemic manifestation of JRH includes fever, headache and sweating and is most commonly associated with treatment of syphilis, leptospiral infection and Lyme disease. Paradoxical reaction improves significantly after increasing the steroids to curb the inflammatory response [32].

Second-Line ATT Roles of second-line ATT are as follows: Efficacy of fluoroquinolones (levofloxacin and moxifloxacin) against intracellular and dormant MTB is good. It prevents drug-resistant TB and shortens TB treatment when combined with existing anti-TB drugs (Table 6.2) [5, 6].

Novel Drug Delivery System for Antitubercular Treatment

Nanotechnology-related rational drug delivery has improvised the therapeutic success and also has reduced the systemic toxicity and frequency of drug administration. In spite of emergence of newer antitubercular antibiotics, the real challenge is to target the intracellular pathogen. Most of the antibiotics are unable to actively pass through the cell membranes. Antitubercular drugs are loaded in the carrier system so that, once they get endocytosed by the phagocytic cells, they can prolong the release of the drugs and decrease the frequency of doses and drug toxicity (Table 6.3).

Role of Steroids and Immunosuppressives

One of the main aims of therapy for intraocular tuberculosis is to control the intraocular inflammation for which oral steroids are mainstay of treatment. Gupta et al. showed superior clinical outcomes following concurrent treatment with steroids and anti-TB treatment in patients with uveitis in comparison to patients who received ATT alone [33]. When ocular tuberculosis is misdiagnosed as some other uveitic entity, inflammation may recur in spite of steroid therapy or ocular disease may worsen, as underlying tubercular aetiology is not taken care of. Antitubercular drugs decrease the microbial as well as antigen load by actively killing the microbes. The decrease in antigen load in turn leads to fewer chances of hypersensitivity and recurrences. Steroids are well known to modify the immune response and decrease the inflammation and chances of recurrences when given along with antitubercular drugs. However few studies have reported no role of corticosteroid treatment in

Table 6.3 Novel drugs delivery systems containing anti-TB drugs

Carrier	Drugs	Features
Liposomes	Streptomycin, gentamycin, sparfloxacin, amikacin, clofazimine, isoniazid, rifampicin, pyrazinamide, rifabutin, capreomycin	They are the most widely studied carrier They have macrophage-specific antibacterial drug delivery Conventional liposomes are carriers for passive drug delivery Lung-specific stealth liposomes/PEGylated liposomes contain O-stearoyl amylopectin (O-SAP) and monosialogangliosides/ distearoyl-phosphatidylethanolamine-poly(ethylene glycol) (DSPE-PEG) as targeting moiety for active targeted delivery of isoniazid and rifampicin. They achieve higher levels of accumulation in the lung and show reduced uptake and accumulation in the liver and spleen as compared to conventional liposomes
Niosomes	Rifampicin	Micron-sized rifampicin-loaded niosomes contain Span 85 as surfactant
Nanoparticles (NPs) and microparticle	Isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin, rifabutin, ofloxacin, moxifloxacin, ciprofloxacin	PBCA NPs-poly(n-butyl cyanoacrylate) and PIBCA NPs-poly(isobutylcyanoacrylate) are non-biodegradable and PLGNPs-poly (DL-lactide-co-glycolide) is biodegradable Alginate NPs are produced by ionotropic gelation Solid lipid nanoparticles (SLNs) have good stability on nebulisation. These NPs are involved in passive drug delivery PLGNPs surface grafted with lectins are carriers for active targeted delivery of drugs. Lectins increase the intestinal mucoadhesion of nanoparticles and drug absorption and bioavailability
Polymeric micelles	Rifampicin, isoniazid, pyrazinamide	These are submicroscopic aggregates of surfactant molecules resulting in liquid colloid. Micelles have improved antitubercular activity
Dendrimers	Rifampicin	Dendrimers are carriers for active targeted delivery of drugs. They are low-molecular-weight macromolecules with well-defined, regular hyper-branched, three-dimensional structure. Mannose on the surface significantly reduces the haemolytic toxicity of nanocarriers and drug It also sustains the drug release. Surface modification improves the selective uptake of the drug-loaded nanocarriers by cells of immune system.

tuberculous optic neuropathy [34], poorer visual outcome in cases of initiation of corticosteroids prior to ATT [8], reactivation of latent TB with concurrent use of ATT and corticosteroids [5] and higher rate treatment failure in patients on immunosuppressants [35].

Factor Associated with Poor Visual Outcome [5]

1. African ethnicity
2. Age > 50 years
3. Female gender
4. Longer duration of uveitis
5. Delay in diagnosis (>500 days)
6. Presence of intermediate uveitis
7. Posterior uveitis or panuveitis
8. Administration of corticosteroid therapy prior to/after administration of ATT

Treatment of Drug-Resistant TB

Two types of drug-resistant tuberculosis are multidrug-resistant tuberculosis (MDR-TB) or extensively drug-resistant tuberculosis (XDR-TB). If drug susceptibility test demonstrates MDR-TB (resistance to isoniazid and rifampicin) and XDR-TB (resistance to fluoroquinolones and one of three injectable aminoglycosides, amikacin, kanamycin and capreomycin), modifications to

Table 6.4 Groups of drugs to treat MDR-TB

Group	Drugs (abbreviations)
Group 1: First-line oral agents	Pyrazinamide (Z) Ethambutol (E) Rifabutin (Rfb)
Group 2: Injectable agents	Kanamycin (Km) Amikacin (Am) Capreomycin (Cm) Streptomycin (S)
Group 3: Fluoroquinolones	Levofloxacin (Lfx) Moxifloxacin (Mfx) Ofloxacin (Ofx)
Group 4: Oral bacteriostatic agents	Para-aminosalicylic acid (PAS) Cycloserine (Cs) Terizidone (Trd) Ethionamide (Eto) Prothionamide (Pto)
Group 5: Agents with unclear role in treatment of drug-resistant TB	Clofazimine (Cfz) Linezolid (Lzd) Amoxicillin/clavulanate (Amx/Clv) Thioacetazone (Thz) Imipenem/cilastatin (Ipm/Cln) High-dose isoniazid Clarithromycin (Clr)

the antitubercular regimen must be made in consultation with a TB specialist. Improper drug regimens, inadequate duration of therapy and treatment defaulters have led to an emerging global problem of MDR-TB and XDR-TB. The drugs available for this form of disease are rifabutin, fluoroquinolones, interferons, amikacin, capreomycin, ethionamide and linezolid [4, 36].

Table 6.4 shows groups of drugs with which to treat MDR-TB.

New Technologies for Tuberculosis Control: A Framework for Their Adoption, Introduction and Implementation (Geneva, World Health Organization, 2007)

Treatment of MDR-TB is complex and the drugs are divided in different groups on the basis of their efficacy and clinical uses. All the first-line drugs are classified in Group 1 except streptomycin. These drugs are best tolerated and most potent. If susceptibility is proved, these drugs can be used in MDR-TB as these drugs are potent and less costly. If resistance is detected to both streptomycin and kanamycin, capreomycin should be used. Group 3 and 4 drugs are used whenever susceptible strains are there. Group 5 drugs are used in patients with XDR-TB. They are used in consultation with an expert in the treatment of drug-resistant TB.

Newer Drugs

As per CDC guidelines, bedaquiline fumarate is a FDA-approved drug for combination therapy for cases of confirmed pulmonary MDR-TB (for adults >18 years) only due to its potential side effects. Its half-life is 4–5 months, and hence it has to be stopped 4–5 months prior to adjunctive treatment in order to avoid extended period of exposure to low levels of single drug leading to drug resistance. It has to be used for 24 weeks and sometimes longer depending upon the case.

Recommended dose for week 1–2 is 400 mg (4 tablets of 100 mg) orally once daily and for week 3–24 is 200 mg (2 tablets of 100 mg) thrice daily per week, for a total of 600 mg per week. Its side effects include nausea/vomiting, dizziness, headache, haemoptysis, increased blood amylase, rashes, arthralgia, myalgia, chest pain, anorexia, fatigue, dark-coloured urine and jaundice.

The treatment for drug-resistant tuberculosis is complex and should always be done in consultation with an infectious disease specialist. Along with these drugs, a lot of other investigational new drugs are under trial to keep up with the problem of drug-resistant TB.

Treatment of Ocular Tuberculosis in Immunocompromised Patients

All HIV-infected patients need to start on concomitant antitubercular and antiretroviral drugs. Challenges include pill burden, patient compliance, drug interactions especially between rifampicin and non-nucleoside reverse transcriptase inhibitors, overlapping drug toxic effects (especially hepatotoxicity), immune reconstitution inflammatory syndrome (IRIS) and risk of developing

multidrug-resistant and extensively drug-resistant tuberculosis with high mortality rates [37].

Baseline isoniazid resistance is responsible for failure and development of acquired rifampicin resistance. Rifampicin resistance is mainly due to intermittent dosage of ATT drugs twice or thrice weekly [38–40].

WHO recommends to start ATT in all HIV-infected individuals with active tuberculosis (regardless of CD4 cell count) once tuberculosis treatment is tolerated, usually within 2–8 weeks [41, 42]. It is recommended to administer daily treatment at least during intensive phase for patients with CD4 cell counts 100 cells/μL [3, 12].

Treatment of Ocular Tuberculosis in Paediatric Patients

As per the National Guidelines on Diagnosis and Treatment of Paediatric Tuberculosis in consultation with the Indian Academy of Paediatrics during January–February 2012, recommended ATT regimen includes rifampicin (450 mg/day if BW ≤ 50 kg or 600 mg/day if BW >50 kg), isoniazid (5 mg/kg/day), ethambutol 378 (15 mg/kg/day) and pyrazinamide (20–30 mg/kg/day). TB preventive therapy/chemoprophylaxis with INH 10 mg/kg has to be provided for 6 months to the following children:

1. Asymptomatic children under 6 years of age, smear positive, after ruling out active disease and irrespective of BCG vaccination or nutritional status
2. All HIV-infected children who had exposure to TB case or Mantoux positive (≥5 mm) in the absence of active disease
3. All Mantoux-positive children on immunosuppressive therapy (e.g. children with nephrotic syndrome)
4. Child born to mother diagnosed with TB during pregnancy after ruling out congenital TB

Conclusions

Ocular tuberculosis is a difficult disease to treat. Till date no periocular form of antitubercular drugs has been introduced. A multidisciplinary approach is needed for the management of these patients involving the chest physician and an infectious disease specialist. Assessment of response to therapy is necessary to monitor therapy. Management of cases with drug resistance is challenging. Newer drugs with increased efficacy and capability to eliminate the bacilli will be of help to manage the cases of ocular tuberculosis more efficiently. Tuberculosis is a disease which has a cure and we should counsel the patients well about the duration of therapy and side effects of therapy, so that the number of defaulters is less and more number of patients undergo treatment for adequate time duration to prevent drug resistance. The ocular morbidity due to tuberculosis can be decreased by timely identification of disease and appropriate antitubercular therapy.

Compliance with Ethical Requirements Nitin Kumar, Eliza Anthony, Parthopratim Dutta Majumder, Ranju Kharel (Sitaula) and Jyotirmay Biswas declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

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Tubercular Uveitis

7

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Introduction

Uveitis by definition is inflammation of the middle ocular coats. This coat of the eye is probably more susceptible to inflammation as it is highly vascular. However, once significant inflammation sets in the uveal tissue, it can spill over to other coats of the eye also. Sometimes the inflammation itself may start in the other layers such as a primary retinitis and then secondarily involve the choroid. The inflammation may be autoimmune in nature or incited by an infective agent. It is very important for uveitis specialists to be able to differentiate between an infective uveitis and an autoimmune uveitis. The treatment paradigm of most infective uveitis involves giving anti-infective therapy first, followed by anti-inflammatory therapy in the form of steroids or immunosuppressants. Failure to recognise infective aetiology could potentially be devastating as direct immunosuppressive therapy might flare up such cases. Thus it is important for ophthalmologists to recognise the morphological differences of infective uveitis. Tuberculosis is one such cause of infectious uveitis.

Tuberculosis (TB) is an airborne communicable disease and the most common single cause of morbidity and mortality worldwide caused by *Mycobacterium tuberculosis* (M.TB) or related mycobacterial species [1–3]. Tuberculosis primarily affects lungs. It may also affect other organ systems and is then referred to as extrapulmonary tuberculosis. Ocular tuberculosis represents a form of extrapulmonary TB and encompasses any infection in or around the eye or on its surface. The incidence of extrapulmonary form of tuberculosis has increased in recent years, especially in immunocompromised patients. More than 50% of patients with AIDS and tuberculosis show extrapulmonary involvement, especially in patients with low CD4 counts [4, 5]. Tuberculosis is one of the most common public health problems in developing countries like India. Due to the high prevalence of tuberculosis in endemic countries and a resurgence of tuberculosis in immunocompromised patients, it has become an even greater public health problem. Intraocular TB may also emerge as an important cause of ocular inflammation in susceptible individuals posing various diagnostic and therapeutic challenges to ophthalmologists.

Maitre-Jan described the first case of tubercular disease of the eye as an iris nodule leading to corneal perforation [6]. Von Michel in 1883 provided the first description of histopathologically proven

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A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_7

Table 7.1 Clinical presentation of intraocular tuberculosis

Anterior uveitis	Granulomatous iridocyclitis, non-granulomatous iridocyclitis, iris nodules, ciliary body tuberculoma
Intermediate uveitis	Granulomatous uveitis, non-granulomatous uveitis with 'snowbanking' exudates over pars plana or peripheral retina
Posterior uveitis	Disseminated choroiditis (choroidal tubercles), focal choroiditis (choroidal tuberculoma), subretinal abscess, multifocal serpiginous-like choroiditis, retinitis, retinal vasculitis, neuroretinitis and optic neuropathy
Scleritis	Diffuse or focal nodular anterior and posterior scleritis
Panuveitis	Endophthalmitis (may also lead to panophthalmitis)

tuberculosis of the eye [7]. In India, the incidence of ocular involvement is variable, with a reported ocular morbidity of 1.39% amongst patients with active pulmonary and extrapulmonary tuberculosis [8]. Ocular tuberculosis is one of the most common infectious uveitis in tropical countries.

Clinical Spectrum of Intraocular Tuberculosis

Intraocular tuberculosis has varied clinical features and is a great mimicker of various uveitic entities. The presentation depends on various factors like host immunity and the immune response against the organism, the locus of primary infection and virulence of the organism. Uveitis is said to be the most common presentation of ocular tuberculosis [9]. Various manifestations of intraocular tuberculosis are tabulated in Table 7.1.

Diagnostic Challenge

Most forms of extrapulmonary tuberculosis are paucibacillary [10]. Cases of ocular tuberculosis, like other forms of extrapulmonary tuberculosis, may also be paucibacillary in nature [11]. This implies that the number of bacilli found at the site of infection is low. It is also not easy to get appropriate samples in adequate amount from ocular tissues for routine diagnostic methods. This makes it difficult to diagnose the disease using routine methods of detection of the acid-fast bacilli. In many cases the diagnosis may be made only on clinical manifestations based on a high index of suspicion. It is thus imperative for ophthalmologists to know different morphological presentations of tubercular uveitis.

Tests like Mantoux and IGRA may help support a diagnosis of tubercular uveitis in non-endemic regions. However, in endemic regions the high positivity rate of these tests in the general population [12] may reduce their diagnostic specificity for active tubercular infection. Reaction to purified protein derivative (PPD) or Mantoux test suggests delayed hypersensitivity reaction to tubercular protein by recruiting previously sensitised T-cells to the site of injection. Thus, the test has a poor predictive value for active disease irrespective of size of reaction [13] and needs to be interpreted carefully, especially in endemic areas. Interferon gamma release assay (IGRA) is an in vitro diagnostic aid to measure the cell-mediated immune reaction to *Mycobacterium tuberculosis*. This is of two types: in tube test and spot test. The test is based on quantification of interferon gamma released from lymphocytes sensitised by M.TB in whole blood incubated with purified protein derivative from M.TB and M.TB antigens like ESAT-6 and CFP10. A systemic review and meta-analysis on IGRA for active pulmonary TB in low- and middle-income countries concluded that neither of the tests (tuberculin skin test and IGRA) had value for diagnosis of active TB in adults, especially with HIV co-infection [14]. Some patients of suspected ocular tuberculosis may lack any evidence of active systemic tuberculosis elsewhere in the body. Hence, as of now a high index of suspicion based on typical manifestations supported by modern molecular microbiological assays and a therapeutic response to treatment is finally what a treating ophthalmologist has to rely on to diagnose tubercular uveitis. Due to all these limitations, some morphological manifestations of presumed ocular tuberculosis (due to active tubercular infection) might be

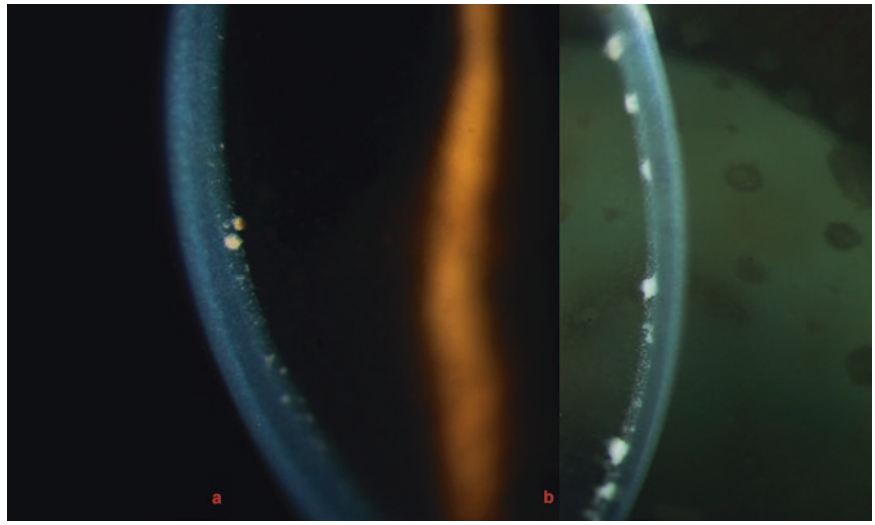

Fig. 7.1 (**a**, **b**) Slit lamp images showing large keratic precipitates deposited at the posterior aspect of cornea

controversial. In this text we aim to describe most morphologies of uveitis where tuberculosis has been incriminated as the causative agent and also discuss some of these controversies.

Anterior Uveitis

Cases of uveitis in which the inflammation primarily involves the iris or ciliary body are categorised as having anterior uveitis. This may be acute or chronic and granulomatous or non-granulomatous. Cases of granulomatous anterior uveitis typically have larger keratic precipitates (Fig. 7.1a, b). There may be associated nodular lesions on the iris and angle (Fig. 7.2). These cases have a tendency to form more anterior and posterior synechiae. Some cases may also show neovascularisation of the iris. Cases of non-granulomatous uveitis generally have fine cellular anterior chamber reaction with fine keratic precipitates and more of an acute course with a lesser tendency towards a chronic disease. However, some of the non-granulomatous cases also might present with frequent relapses on stopping steroids and become chronic and steroid dependent.

Typically tubercular anterior uveitis has been described as being granulomatous with large mutton fat keratic precipitates and posterior synechiae formation [15–18]. However, the presentation can be quite variable. Tubercular non-granulomatous anterior uveitis has also been described [19]. In some severe cases, a hypopyon may also be seen (Fig. 7.3) which may be pigmented [20].

Iris involvement is also variable in cases of tubercular anterior uveitis. Multiple iris nodules may be seen as in any granulomatous anterior uveitis [17, 21]. Iris nodules seen near the pupillary

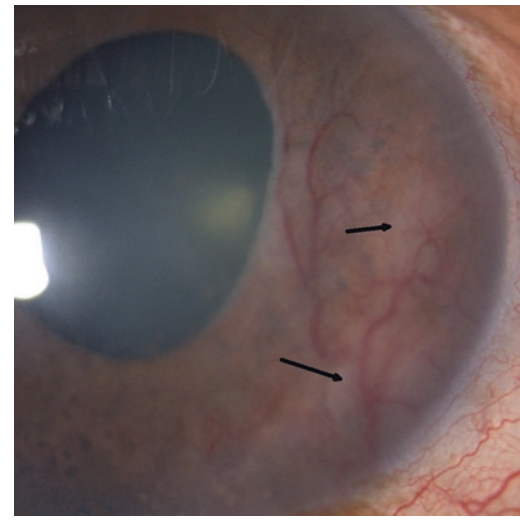

Fig. 7.2 Anterior segment photograph showing nodular iris lesions (*black arrows*) with early development of neovascularisation of the iris

border are referred to as Koeppe's nodules and those on the surface of iris are called Busacca's nodules [22]. Though both can be seen in tubercular anterior uveitis, they are not diagnostic of tubercular aetiology. In some cases of tubercular uveitis, nodules have also been seen near the iris root. Presence of broad-based synechiae (Figs. 7.4 and 7.5) has been suggested by some authors as a sign suggestive of tubercular aetiology [23]. The intraocular pressure may be normal or elevated.

Herpetic uveitis is another infective cause of uveitis which may sometimes appear similar to tubercular uveitis due to the presence of raised intraocular pressure and blood-stained hypopyon. Presence of patches of iris atrophy rather than nodules and a reduced corneal sensation in such cases favours a diagnosis of herpetic aetiology.

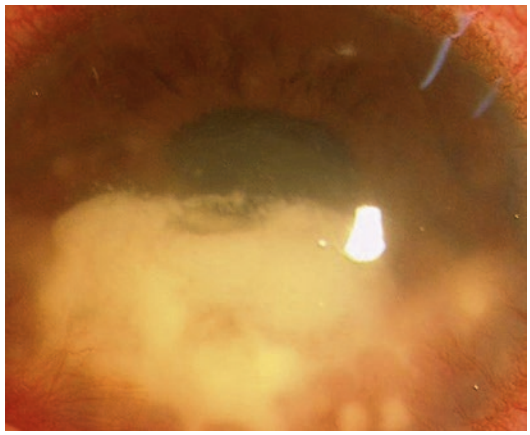

Fig. 7.3 Anterior segment photograph showing a hypopyon in a case of tubercular endophthalmitis

It is very important to rule out tuberculosis as the aetiology of anterior uveitis, especially for ophthalmologists from regions where tuberculosis is endemic. The authors of this chapter belong to a region where tuberculosis is endemic. The approach of the authors towards diagnosis and management of tubercular anterior uveitis is summarised below.

When should tubercular aetiology be suspected in a case of isolated anterior uveitis?

1. If a patient is found to have granulomatous uveitis with broad-based synechiae with nodular lesions on the iris or angle.
   (a) A contrast-enhanced CT scan of all such patients must be done. If it shows typical tubercular lesions, then we would consider this uveitis as tubercular. If it shows hilar lymphadenopathy, then we should try to exclude sarcoidosis by an e*ndobronchial ultrasound*-guided *transbronchial* needle aspiration of the lymph nodes. A raised serum ACE level may also indicate sarcoidosis. Cases of sarcoid uveitis would respond well to topical/systemic steroid therapy alone.
   (b) In cases of granulomatous anterior uveitis even if the systemic investigations are unrevealing, one could suspect tubercular aetiology if:
      (i) The patients do not show adequate response to topical/systemic steroids alone.
      (ii) There are frequent recurrences on stopping steroids.

Fig. 7.4 Anterior segment photographs of a 3-month-old infant showing broad-based anterior synechiae (*black arrows*) and a pupillary membrane (*white arrow*). The child had tubercular cranial nervous system involvement also

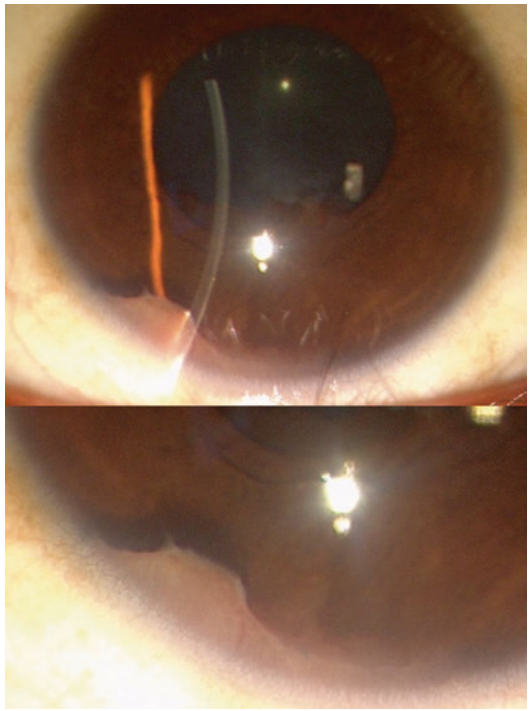

Fig. 7.5 Another anterior segment image showing broad-based synechiae

(c) Presence of a pigmented hypopyon could also suggest tuberculosis [20].
(d) Early neovascularisation of the iris or exudative membrane in the anterior chamber is another such indicator in our experience.

Such cases may be further investigated by performing a PCR of the aqueous to rule out tuberculosis. A therapeutic trial of anti-tubercular drugs may also be warranted in non-responding cases where suspicion is high.

2. Anterior uveitis (granulomatous or non-granulomatous) developing secondarily in a patient known to have systemic tuberculosis. The anterior uveitis of such a patient would be attributed to tuberculosis provided:
   (a) The patient is not known to have anterior uveitis prior to developing tuberculosis.
   (b) Other common associations of anterior uveitis such as ankylosing spondylitis have been excluded.

   The pathogenesis of such a uveitis could be active tubercular ocular infection or even an immune-mediated process, especially if it is non-granulomatous.
3. We generally do not suspect tuberculosis as the aetiology in cases of non-granulomatous anterior uveitis without any systemic evidence of systemic tuberculosis.

Investigations

A high index of suspicion based on the principles mentioned above would help in correctly diagnosing cases of tubercular aetiology. Additional tests which may add value to diagnosis are Mantoux test and Quantiferon TB-Gold test. However due to a high positive rate of these tests in areas endemic for tuberculosis, the specificity of these tests for diagnosing active tubercular infection is low. Importance of contrast-enhanced CT scan of the chest has already been enumerated above.

PCR of aqueous to detect tubercular DNA can also be performed where there is a high degree of suspicion [24].

Management

Standard anti-tubercular therapy (ATT) must be given to patients suspected of having tubercular anterior uveitis. The exact duration of such a therapy is not well defined. However, a minimum of 6 months of therapy must be given, and in some cases the duration may even be extended to 9 months. Additionally topical steroids guided by the anterior chamber reaction and mydriatics/cycloplegics should be given. A careful watch must be kept on the intraocular pressure in such cases.

Intermediate Uveitis

Presence of vitritis or significant amount of cells in the vitreous with or without evidence of snowbanking along the pars plana region with some spill over anterior uveitis in the absence of

chorioretinitis (posterior uveitis) is considered as intermediate uveitis. There may be some associated peripheral vasculitis. According to the International Uveitis Study Group, cases of inflammation predominantly involving the vitreous and peripheral retina only should be classified as having intermediate uveitis [25]. Intermediate uveitis can account for around 15% of cases of uveitis at large uveitis referral centres [22]. According to one study, the average age of patients developing intermediate uveitis is 31 [26]. In our practice we generally find patients developing intermediate uveitis from second to sixth decade of life. In a majority of patients, intermediate uveitis may be bilateral to begin with. Out of those who initially have a unilateral involvement, around 1/3 go on to later develop a bilateral disease [22]. The most common symptoms of intermediate uveitis are floaters and blurred vision. The floaters are due to vitreous cells and the diminution in vision is commonly due to development of cystoid macular oedema and cataract. The patients generally do not have pain and photophobia as seen in cases of anterior uveitis. Intermediate uveitis may be idiopathic or associated with some other systemic disorder. In western literature the most common systemic associations are sarcoidosis and multiple sclerosis [27]. Tuberculosis may also be one of the diseases associated with intermediate uveitis, especially in areas where it is endemic. Intraocular tuberculosis can present with chronic, smouldering vitritis with snowball opacities and peripheral snowbanking of exudates over the pars plana. This may be associated with peripheral vascular sheathing and peripheral retinochoroidal granuloma [28, 29]. There are no definite clinical indicators in cases of intermediate uveitis to suggest a tubercular aetiology. We found one article which indicates that early peripheral retinal neovascularisation may be seen in case of tubercular aetiology [30].

Systemic investigations to rule out tuberculosis should be carried out in all cases of intermediate uveitis in endemic areas. The most commonly suggested investigation for this is a contrast-enhanced CT scan of the chest. This also helps in ruling out or diagnosing sarcoidosis. A case of unilateral snowbanking with vitritis with mediastinal lymphadenopathy which showed caseous necrosis on fine needle aspiration cytology and thus was proved to be of tubercular aetiology has been described in literature [31]. Positive Mantoux test or interferon gamma assays are suggestive of exposure to tuberculosis. However, in countries where tuberculosis is endemic, it is difficult to diagnose tuberculosis only on the basis of these tests. Perhaps tests like ultrasound biomicroscopy and anterior segment optical coherence tomography (OCT) may shed more light regarding morphology of cases of intermediate uveitis with suspected tubercular aetiology.

Glaucoma can be seen in around 8% of cases of intermediate uveitis [32]. Other than cataract and cystoid macular oedema mentioned earlier, epiretinal membrane formation can also be seen. Some cases of traction-related secondary rhegmatogenous retinal detachments and non-rhegmatogenous detachments associated with choroidal detachments have also been reported in patients of intermediate uveitis [33]. Thus it is imperative to establish an aetiological diagnosis in these cases wherever possible and treat accordingly.

The therapy of suspected cases of tuberculosis is standard anti-tubercular therapy for 6–9 months along with tapering doses of systemic steroids.

Posterior Uveitis

Mycobacterium tuberculosis is an obligate aerobic, non-spore-forming, Gram-positive bacterium [34]. High oxygen concentration is required for its proliferation. This is the reason why tubercular lesions are seen at the lung apices, which have a very high oxygen tension. The uveal tissue [especially choroid and ciliary body] being a highly vascular structure provides a good environment for growth of tubercle bacilli. However, tuberculosis bacillus can persist even in hypoxia, which induces ‘nonreplicating persistence’ of the tubercle bacilli [35]. These differential growth capabilities of the bacilli may be responsible for its varied ocular manifestations.

Ocular posterior segment tuberculosis does seem to be part of disseminated tuberculosis, where the infective organism enters the eye through haematogenous dissemination. This may be multibacillary or paucibacillary dissemination. A patient is said to have multibacillary tuberculosis when the bacilli load is high. Multibacillary pulmonary tuberculosis patients are found to have bacilli even on a smear examination, whereas the paucibacillary cases are usually smear negative and might be only confirmed by culture [36]. Due to difficulty in obtaining ocular tissue for smear and culture, we lack definite evidence regarding the type of infection in the eye. However the ocular manifestations of tuberculosis can be quite varied, and thus we presume that the infection may also vary from a multibacillary to a paucibacillary type. Some manifestations presumed to be due to tuberculosis might be secondary to hypersensitivity to certain tuberculoproteins [34].

In our experience, a significant number of cases of tuberculosis of the posterior segment which are due to active mycobacterial infection and proliferation also have an evidence of active systemic tuberculosis elsewhere in the body. However, reported incidence of ocular involvement in active systemic tuberculosis is relatively low. A study by Biswas J and Badrinath SS from South India showed that only 1.39% patients of 1005 active systemic tuberculosis (pulmonary and extrapulmonary) patients had an ocular morbidity [8].

Clinical Manifestations of Posterior Segment Tuberculosis

Clinical manifestations of posterior segment tuberculosis may be due to direct invasion by the microorganism (active mycobacterial infection and proliferation) or due to a hypersensitivity to the microorganism. The posterior segment involvement includes choroidal tubercle, tuberculoma, tubercular subretinal abscess, serpiginous-like choroiditis, vitritis, choroidal vasculitis, optic neuritis, neuroretinitis, optic disc granuloma, ciliary body granuloma, retinitis, multifocal choroiditis, retinal vasculitis, panuveitis and endophthalmitis with or without panophthalmitis [37]. Amongst these, vitritis and retinal vasculitis are thought to be due to immune reaction to tubercular antigen [34]. Choroidal tubercle, tuberculoma, endophthalmitis and panophthalmitis are due to tissue invasion by the tubercle bacillus. Cyclitis, choroiditis, chorioretinitis and multifocal choroiditis may occur due to both tissue invasion and immune reaction [34].

Choroidal Tubercles

Choroidal tubercles are the most common presentation of tubercular posterior uveitis [37]. The clinical appearance of choroidal tubercles was first described by Edward Von Jaeger in 1855 [9]. Investigators have demonstrated that they are similar to tubercular granulomas seen elsewhere in the body [38]. Choroidal tubercle-like lesions have also been reproduced in an animal model by injecting guinea pigs with tubercular bacilli [38]. These appear as creamy to yellow coloured, flat to slightly raised deep nodules well under the retinal vasculature. Usually there are less than 5 tubercles in each eye, though multiple miliary choroidal tubercles may be seen which may be up to 50–60 in number [37]. Being deep lesions, their borders may not clinically appear very sharp but are still well defined. They are generally seen in the posterior fundus (Figs. 7.6 and 7.7) [37]. Since most of these lesions do not involve the macula, the patient may not have any ocular symptoms. Even subfoveal tubercles may not present with visual loss if the ellipsoid zone remains intact, and there is absence of subretinal fluid. The best way to visualise these lesions is by a dilated indirect ophthalmoscopic examination of the fundus. The size of these lesions can vary from 1/5th disc diameter to less than one disc diameter in size [37]. These may be bilateral or unilateral. In cases with only choroidal tubercles, the anterior chamber may be quiet with no cells and minimal flare. The vitreous is generally clear. Occasionally, choroidal tubercles may present with granulomatous anterior uveitis with varying degree of vitritis and media haze. Sometimes the

detection of these lesions may help in the diagnosis of systemic tuberculosis. Thus in cases of suspected systemic tuberculosis, especially pulmonary, meningeal or disseminated, it is a good idea to get a dilated indirect ophthalmoscopic examination of the fundus done as the presence of these lesions may aid in an early diagnosis of tuberculosis. Illingworth and Wright noted choroidal tubercles in 60% cases (25 of 42 cases) of miliary tuberculosis with or without meningitis [39]. However, only 1 out of 18 patients with meningitis without miliary tuberculosis revealed choroidal tubercles [39]. Choroidal tubercles suggest haematogenous dissemination of tubercle bacillus. In a study on ten proven cases of mycobacterial sepsis from India, six eyes (60%) had ocular involvement of which five cases had choroidal tubercles and one case had retinal vasculitis [40]. After treatment with antitubercular therapy, the choroidal tubercles fade, leaving flat hypopigmented patches with variable pigmentation (Fig. 7.8).

Ultrasound B-scan of the fundus may not pick up these lesions as they are not too large and not very thick. Recently optical coherence tomography (OCT) with enhanced depth imaging has been used to better characterise these lesion. On OCT they may appear as well-defined hyporeflective

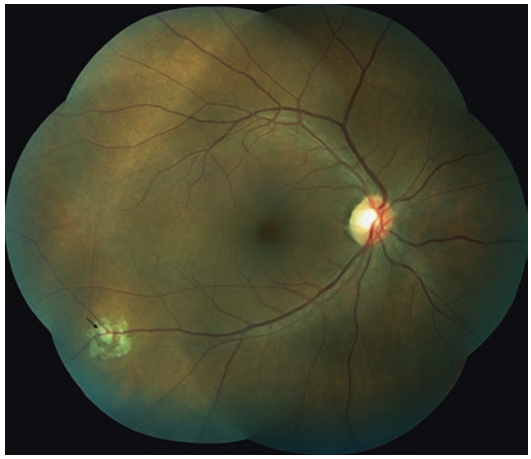

Fig. 7.6 Fundus montage showing a solitary choroidal tubercle (*black arrow*)

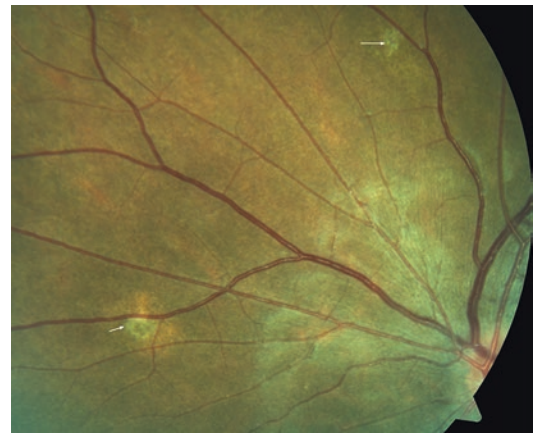

Fig. 7.8 Resolving choroidal tubercles (*white arrows*). Flat fading hypopigmented lesions with variable pigmentation

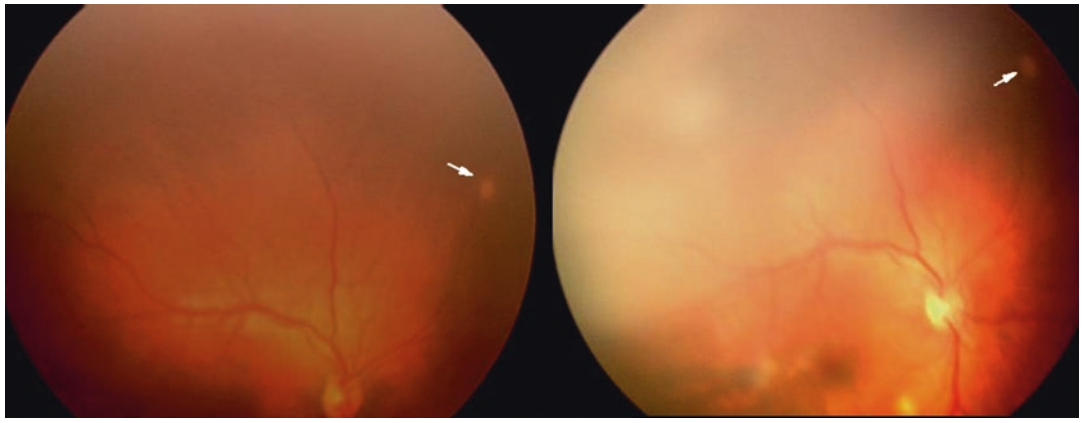

Fig. 7.7 Fundus images of a 3-year-old infant showing choroidal tubercles (*white arrows*). The child also suffered from central nervous system tuberculosis

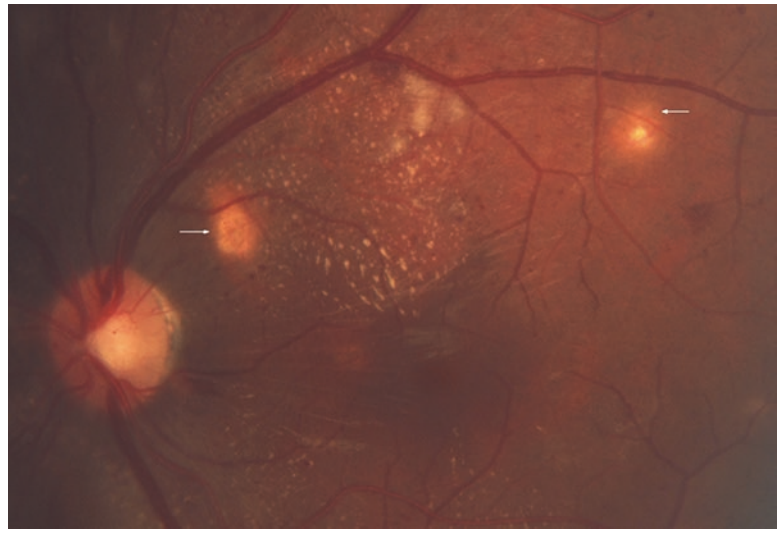

Fig. 7.9 Choroidal tubercles (*white arrows*) in a case of diabetic retinopathy

areas in the choroid obscuring the normal choroidal vasculature.

Choroidal tubercles may be associated with overlying subretinal fluid. We have also seen a patient with diabetes and miliary tuberculosis having multiple choroidal tubercles and proliferative diabetic retinopathy with macular oedema (Fig. 7.9). The patient was simultaneously treated with anti-tubercular therapy (ATT), pan-retinal photocoagulation and anti-VEGF therapy with bevacizumab. This treatment regimen targeted all the pathologies evident in the fundus. We found a good response of this treatment regimen on both the choroidal tubercles and the diabetic retinopathy component (Fig. 7.10). The tubercles usually heal in 3–4 months after ATT [37]. The healing is denoted by decreasing size, depressed scar, well-defined margins and a ring of peripheral pigmentation.

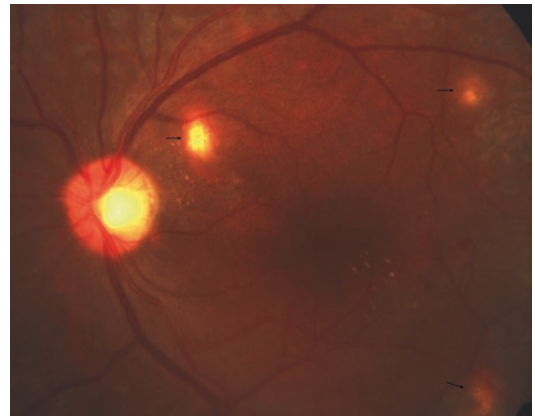

Fig. 7.10 Resolution of choroidal tubercles (*black arrows*) and diabetic retinopathy following anti-tubercular therapy, intravitreal bevacizumab injection and pan-retinal photocoagulation

Choroidal Tuberculomas

These are larger areas of granulomatous infiltration of the choroid with tubercular bacilli forming a subretinal mass lesion. These may be seen with or without the presence of adjacent choroidal tubercles. These are again best seen using an indirect ophthalmoscope. They appear as large creamy to yellow mounds elevating the retinochoroidal layers (Figs. 7.11 and 7.12). The margins may not be very well defined. There may be associated retinal haemorrhages or retinal folds adjacent to the lesions [37]. They may cause much more inflammation in the eye. Thus patients with these lesions may have associated cells in the anterior chamber with cells in the vitreous. The associated intense inflammation in the choroid can also leads to an exudative retinal detachment (Fig. 7.13). There may also be associated cystoid macular oedema. Sometimes these can also be complicated by formation of secondary choroidal neovascular membranes [41]. Such

patients may present to an ophthalmologist with loss of vision due to proximity of these lesions to the macula or optic disc or associated exudative detachment or cystoid macular oedema. If left untreated we have seen these lesions to progress significantly with involvement of adjacent ocular coats. Involvement of sclera may cause pain and presence of fluid in the subtenon space which may be detectable on ultrasound B-scan. Ultimately it may result in panophthalmitis. We have earlier reported one such case of tubercular panophthalmitis [42]. Fluorescein angiography of such lesions reveals an early hypofluorescence in the area of the lesion followed by late hyperfluorescence which may be diffuse or granular in appearance. However fluorescein angiography is not diagnostic of a tuberculoma as other inflammatory choroidal granulomas may also have a similar appearance. Ultrawide field imaging (UWFI) of the fundus might be helpful in detecting granulomas in the periphery and in patients with small pupils. Ultrasound B-scan generally shows a choroidal mound with variable (mild to moderate) internal reflectivity as opposed to a haemangioma which shows very uniform moderate internal reflectivity. Other differential diagnosis

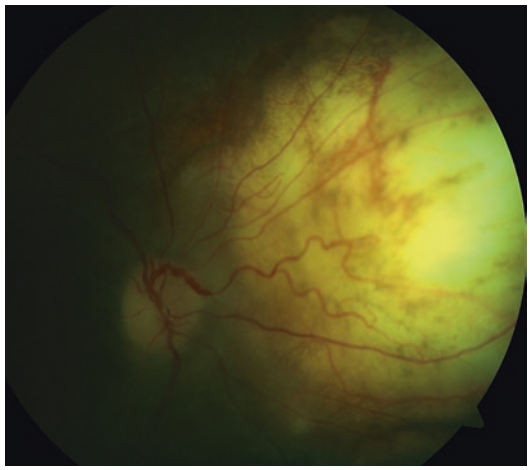

Fig. 7.11 A large choroidal tuberculoma seen in the nasal half of the fundus

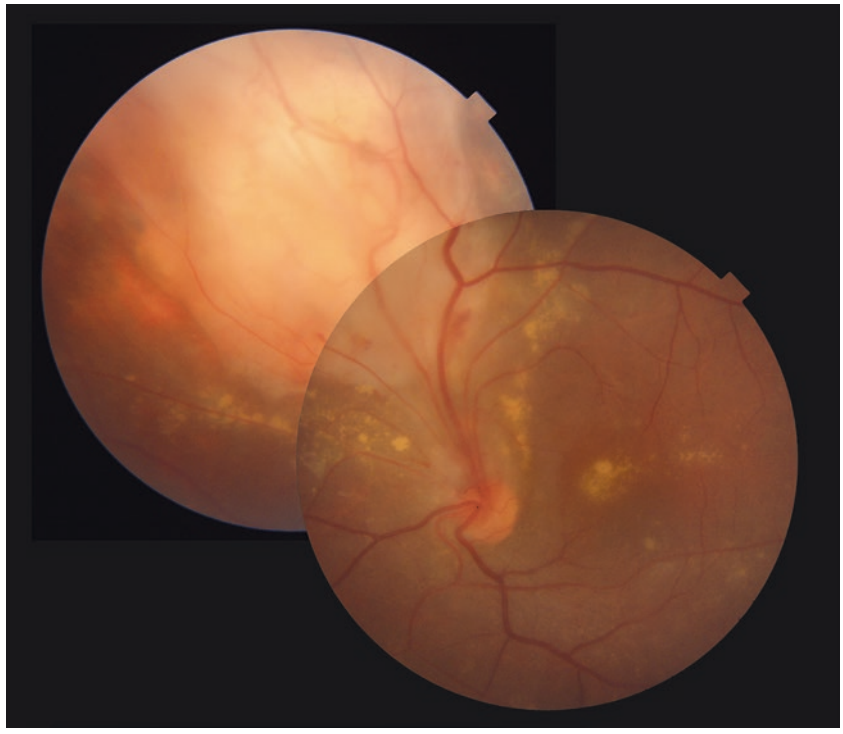

Fig. 7.12 Fundus montage showing another large tuberculoma superonasal to the optic disc with perilesional and macular exudates

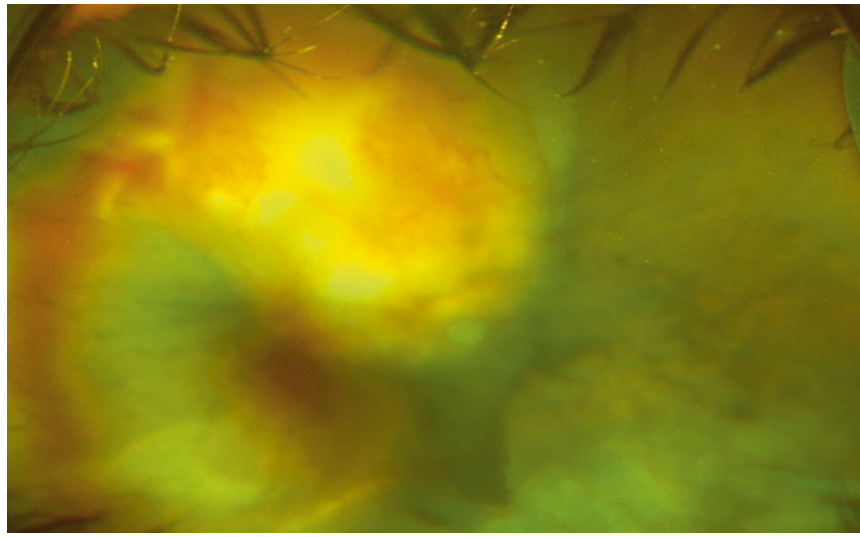

Fig. 7.13 A wide-field Optos fundus image showing a large tubercular granuloma in the upper half of the fundus with associated exudative detachment

may include choroidal metastasis, sarcoid granuloma and amelanotic melanoma. In cases of tuberculomas with internal caseous necrosis and abscess formation, the ultrasound B-scan may reveal an anechoic area within the choroidal mound. Choroidal melanomas typically show an initial high reflective spike followed by low internal reflectivity (high angle kappa) and choroidal excavation.

Lesions closely simulating choroidal tubercles/tuberculomas may also be seen in sarcoidosis, and sometimes it may be difficult to establish the correct aetiology despite ocular and systemic investigations. Systemic investigations such as contrast-enhanced high-resolution chest tomography, Mantoux test, interferon gamma release assays (IGRA) and serum ACE levels may aid in such differentiation. However, 'there is insufficient data and low quality evidence on the performance of IGRAs in low- and middle-income countries, typically those with a high TB and/or HIV burden' [43]. Polymerase chain reaction-based molecular assays of vitreous fluid are new techniques which may be used to confirm a diagnosis where the systemic investigations are unrewarding and a clinical suspicion of tuberculosis is high. Other differentials to be ruled out are systemic metastasis and ocular tumours such as a haemangioma or amelanotic melanoma. These can be ruled out by correlating the clinical setting with investigations like ocular ultrasound B-scan, MRI of the orbits and a whole-body PET scan. Rarely one may have to resort to fine needle aspiration from the choroidal mass itself.

Treatment includes anti-tubercular therapy (ATT) and systemic steroids to control the inflammatory component. The steroids are generally started 2–3 days after starting ATT. There might be an initial worsening of the ocular lesions on starting ATT due to a Jarisch–Herxheimer type of reaction [37]. This may require a step up of the anti-inflammatory medication. The duration of therapy is not well defined. There are studies which report treatment duration ranging from 6 to 12 months in such cases [44, 45]. Treatment duration in cases of central nervous system tubercular abscesses is guided by the radiological response. Thus we recommend that response to therapy be assessed by response documented by various ocular imaging modalities such as UWFI or fundus imaging (Fig. 7.14a, b), ultrasound B-scan and OCT. The 6-month ATT therapy used in pulmonary tuberculosis is mostly empirical with a rationale of rapid reduction of the bacteriological load in first 2 months followed by clearance of remnant bacteria over the next 4 months.

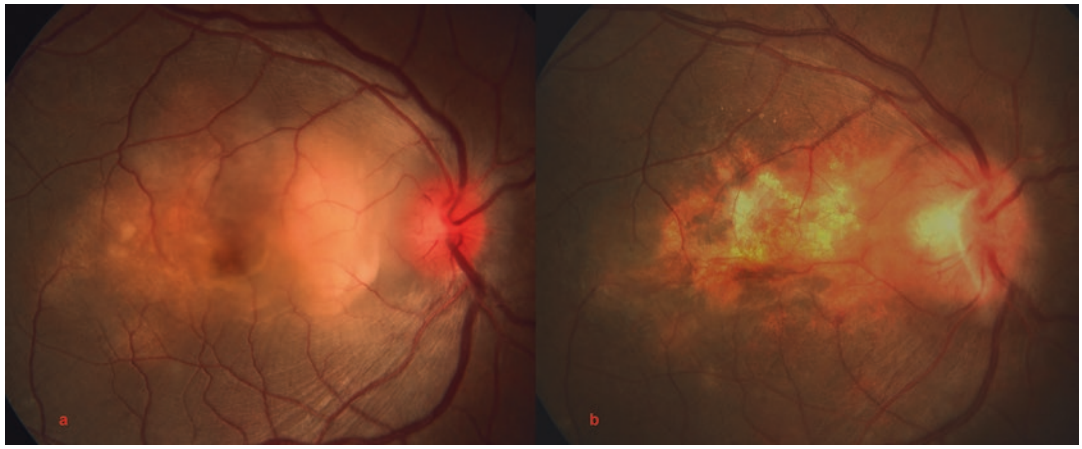

Fig. 7.14 (**a**) Active tuberculoma with surround neurosensory detachment at the posterior pole. (**b**) Following anti-tubercular therapy, serial follow-up fundus image showing reduction in height of the tuberculoma with development of pigmentary changes at the posterior pole and resolution of the neurosensory detachment

Thus, it might be prudent to extend ocular therapy with ATT for 3–4 months more than full macroscopic clinical resolution.

Paradoxical response to ATT is well known, especially in CNS TB [46–49] and is characterised by worsening of pre-existing tubercular foci or appearance or new lesions, either clinically or radiologically following initial improvement with treatment. These usually occur after 2 weeks of ATT and have been reported to occur within 2 weeks to 18 months of initiation of treatment. This response does not follow the natural history of the disease. This has been contributed to the improvement in host immune response following treatment and thus increased inflammatory reaction to the organism, especially in patients on HAART. Paradoxical response to ATT for ocular tuberculosis has been well described irrespective of the immune status of the patient [50–53]. Various risk factors and mechanism for the paradoxical response have been described including extrapulmonary tuberculosis, low lymphocyte count at baseline, inadequate immunosuppressive therapy at initiation of ATT or rifampicin-induced increased clearance of steroids, etc. [54, 55] Paradoxical reaction to ATT in ocular TB manifests in numerous forms like optic neuritis [47, 56], choroiditis [57], progressive ocular inflammation [58] (especially in eyes with serpiginous-like choroiditis) [53], etc. Interestingly there is a case report on treatment with bevacizumab of a serous detachment considered to be due to tuberculosis-associated immune reconstitution inflammatory syndrome [59].

Optical coherence tomography might be useful in early detection of associated secondary choroidal neovascularisation. Bevacizumab may be used to treat the secondary choroidal neovascularisation as well as to enhance resolution of these lesions [60–62]. Post resolution these lesions leave large areas of chorioretinal atrophy with variable pigmentation (Figs. 7.15 and 7.16). Some element of subretinal fibrosis may also be seen.

Serpiginous Choroiditis

The term ‘serpiginous choroiditis’ has been coined to describe a pattern of choroidal inflammation characterised by a creeping active border, which on healing appears like the borders of a continent. The classically described serpiginous choroiditis pattern is:

(a) Active choroidal inflammation, appearing as greyish yellow discolouration extending from the juxtapapillary area

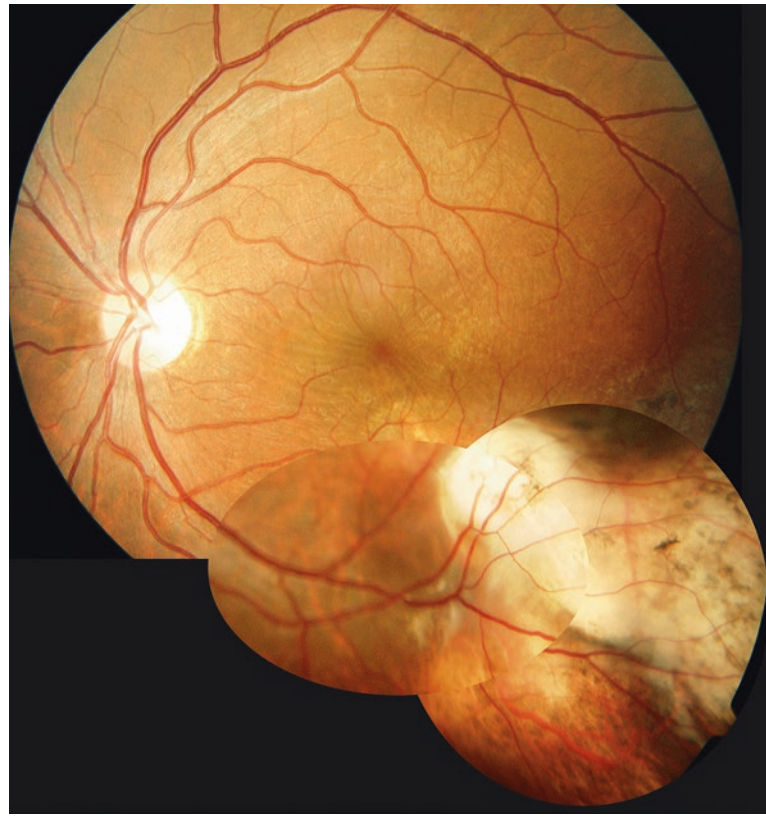

Fig. 7.15 Montage fundus image of the left eye of a patient showing large areas of chorioretinal atrophy in the inferotemporal part of the image following resolution of a choroidal tuberculoma

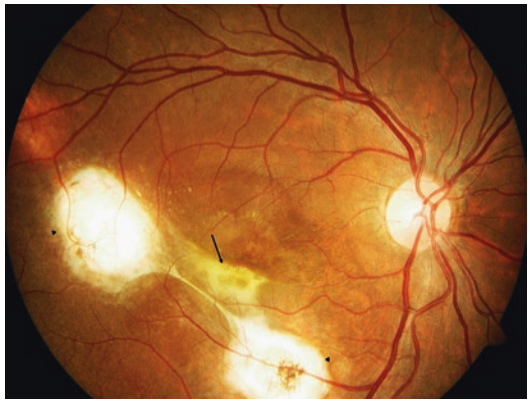

Fig. 7.16 Fundus image of the right eye of the same patient as in Fig. 7.15. Two resolved choroidal tuberculomas are seen temporal and inferior to the fovea (*black arrowheads*). Subretinal scarring following resolution of a choroidal neovascular membrane is also seen at the fovea (*black arrow*). The tuberculomas responded to antitubercular therapy, whereas bevacizumab was injected to treat the choroidal neovascular membrane

(b) Minimal to no inflammatory cellular infiltration in the vitreous
(c) Recurrences of the lesions at the margins of the healed scars

The exact aetiology of such a choroiditis has not been established as yet. There is a debate amongst ophthalmologists regarding its aetiology. Some authors consider it to be an autoimmune process [63] whereas others consider it as having as infective aetiology. One of the possible organisms postulated to cause serpiginous choroiditis is *Mycobacterium* tuberculosis [64]. Another possible aetiological agent is herpes virus [65]. Serpiginous-like choroiditis has also been described in a case of toxoplasma chorioretinitis [66].

In a comprehensive analysis, Nazari KH and Rao N have discussed points in favour and

against an autoimmune or a tubercular aetiology for cases with the morphological pattern of serpiginous choroiditis [63]. A summary of these points with few additional inputs from our experience is given below.

Points Favouring an Autoimmune Aetiology

1. Most patients with typical presentation lack any positive investigations for infectious diseases.
2. Association of serpiginous choroiditis with HLA-B7 and HLA-A2, HLA-B8 and HLA-Dw3 has been demonstrated.
3. Adequate immunosuppression alone controls the uveitis in most cases.
4. Some reports of association with other autoimmune diseases (celiac disease, Crohn's disease, polyarteritis nodosa, autoimmune thrombotic thrombocytopenic purpura) are present.
5. Available histopathology reports do not look similar to tubercular inflammation, and acid-fast bacilli have never been demonstrated in such lesions.

Points Against Autoimmune Aetiology

1. Only a few patients show further development of any systemic autoimmune disease.

Points Favouring Tubercular Aetiology

1. Serpiginous-like lesions can be seen in patients with latent/systemic tuberculosis (however, could be an autoimmune phenomenon).
2. Serpiginous-like features have been seen in patients with PCR evidence for *Mycobacterium tuberculosis*.
3. Anti-tubercular therapy is said to reduce number of relapses according to one study [37].

Points Against Tubercular Aetiology

1. Standard immunosuppressive treatment does not lead to worsening of ocular disease. Typical choroidal granuloma/abscess formation not seen in this disease with or without immunosuppressive agents.
2. Standard immunosuppressive treatment of serpiginous ocular disease does not lead to flaring up of the tubercular infection and further manifesting as systemic tuberculosis.
3. Response of serpiginous choroiditis to immunosuppressive agents alone.
4. Anti-tubercular therapy (ATT) alone does not cure the disease. In most studies ATT has been given in conjunction with steroids to treat this disease. The administration of steroids is a significant confounding factor.

Some ophthalmologists consider tubercular serpiginous choroiditis to have a different morphology from the typically described pattern of serpiginous choroiditis mentioned above. The features suggestive of tubercular aetiology mentioned by these authors are:

1. Unilateral disease (more commonly).
2. Multifocal, irregular, serpiginous lesions involving the posterior pole, mid-periphery and periphery, but usually sparing the juxtapapillary area. However, peripapillary choroid may be involved in advanced cases of multifocal serpiginous choroiditis.
3. Prominent inflammatory cellular reaction in the vitreous, usually with a cellular reaction in the anterior chamber.
4. Pigment clumping usually at the centre of lesions.

The subset of patients of serpiginous choroiditis with the above clinical features have been referred to as multifocal serpiginous choroiditis or serpiginous-like choroiditis [23, 64, 67–69].

Few articles advocate using immunosuppressive agents for serpiginous choroiditis. Some articles comment on progression of serpiginous choroiditis despite ATT and increased need of

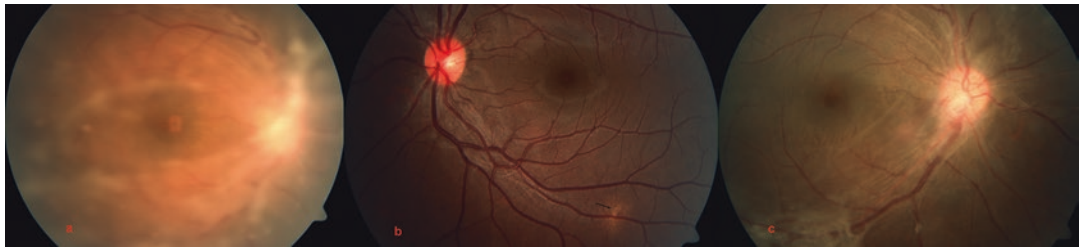

Fig. 7.17 (**a**) Right eye image of a patient of panuveitis at presentation showing hazy media with vitritis. (**b**) Left eye image of same patient at presentation showing a choroidal lesion suggestive of a choroidal tubercle (*black arrow*). (**c**) Post-vitrectomy and post anti-tubercular therapy image of right eye showing significant clearing of media

immunosuppression, thus questioning whether the pathology is solely an infective process or an immunological one or indicative of Jarisch–Herxheimer reaction [55, 58, 70–72].

Investigations like Quantiferon TB-Gold test have been used to establish a tubercular aetiology in cases of serpiginous choroiditis [73]. However, the authors of this study themselves write in the conclusions that despite Quantiferon TB-Gold test positivity, 'Whether bacterial activity or secondary immunologic processes are causative remains a matter of speculation' [73]. In tuberculosis endemic countries, establishing a diagnosis of active tuberculosis just on the basis of Quantiferon TB-Gold test is all the more difficult [74].

Perhaps at this juncture we do not have a definite answer to the exact aetiology of serpiginous or multifocal serpiginous-like choroiditis. Use of ATT in such cases is left to the discretion of the treating ophthalmologist. Results of ocular and systemic ancillary investigations, systemic evidence of tuberculosis, history of contact to a case of tuberculosis and lack of adequate response to steroids can aid in taking this decision.

There is another chapter on serpiginous choroiditis in this text with viewpoints of other authors regarding this entity. Other posterior segment manifestations such as retinitis and vasculitis are also dealt with in detail in separate sections of this book.

Tubercular Endophthalmitis and Panophthalmitis

Occasionally, tubercular infection may present with an acute onset, severe intraocular inflammation with corneal infiltration, severe anterior chamber reaction and a hypopyon. Intense posterior segment inflammation may be associated with a large subretinal abscess, which may invade the retina and vitreous. The subretinal abscess may burst into the vitreous cavity leading to endophthalmitis or may involve sclera leading to panophthalmitis [75–81]. These are rare manifestations of tuberculosis, especially seen in immunocompromised patients, drug users or children. We have also described one such case of tubercular panophthalmitis in a child [42]. Recently, another case of tubercular panophthalmitis with lymphadenitis and central nervous system tuberculomas has been reported [82].

Cases of tubercular panuveitis if left untreated may progress to an endophthalmitis-like picture. In areas endemic for tuberculosis, it is essential to rule it out in cases of panuveitis, especially if the examination findings do not suggest other well-described entities such as Vogt–Koyanagi–Harada's disease, acute retinal necrosis, cytomegalovirus retinitis, etc. Presentation and response to therapy of two of our cases of panuveitis who were also found to have systemic evidence of tuberculosis on CECT chest are shown in Figs. 7.17, 7.18, and 7.19.

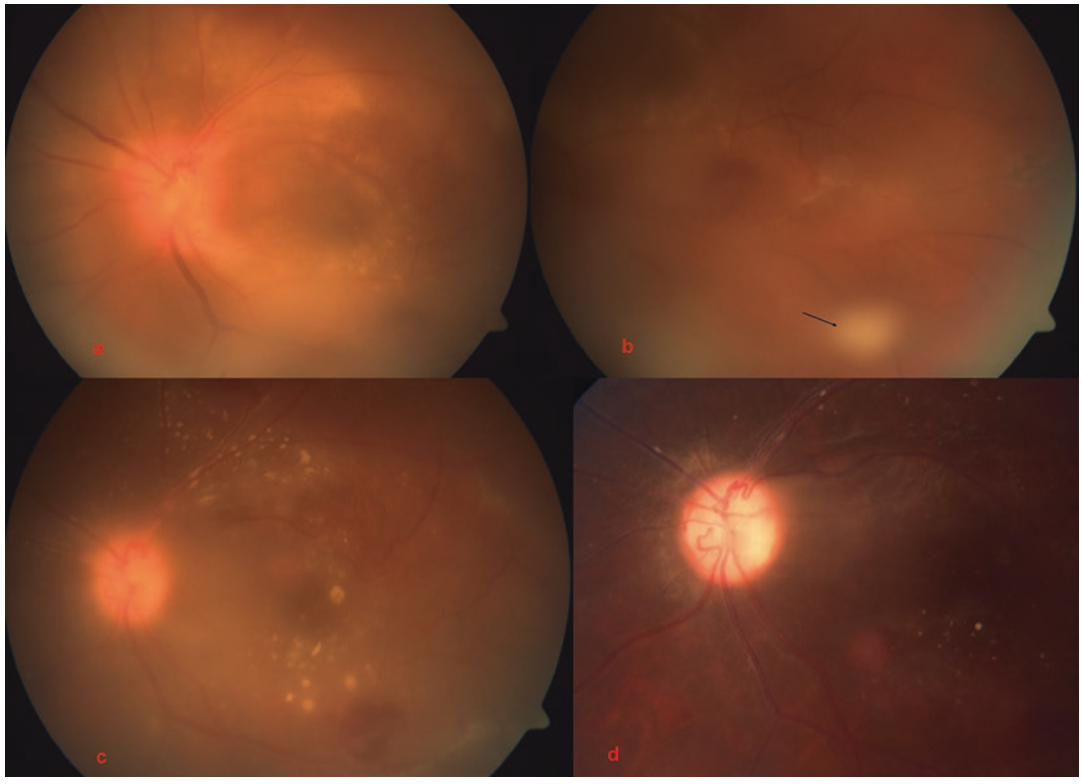

Fig. 7.18 (**a**) Left eye of a patient of panuveitis at initial presentation showing hazy media with disc oedema and diffuse chorioretinal infiltration. (**b**) A focal patch of retinitis is also seen (*black arrow*) in the left eye through the hazy media along with some areas of perivenular pigmentation. (**c**) Following anti-tubercular therapy, the media is seen to start clearing with resolution of the chorioretinitis. Preretinal clumps are seen in the posterior hyaloid. (**d**) One month following therapy, the chorioretinitis is seen to completely resolve with evolution of disc pallor. The clumps in the vitreous are also seen to be reducing

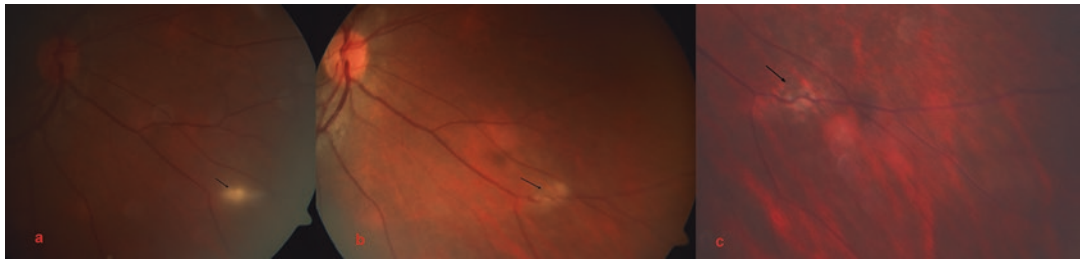

Fig. 7.19 (**a**) A focal patch of perivenular chorioretinitis (*black arrow*) in seen in the right eye of the patient described in Fig. 7.18. (**b**) The focal patch is seen to start resolving following anti-tubercular therapy (*black arrow*). (**c**) The focal patch resolves leaving a perivenular pigmented scar

Compliance with Ethical Requirements Atul Kumar, Rohan Chawla, Raghav Ravani and Koushik Tripathy declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

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Tubercular Multifocal Serpiginoid Choroiditis

8

Sahil Jain, Aniruddha Agarwal, Kanika Aggarwal, and Vishali Gupta

Introduction

Tuberculosis (TB) is one of the most common infectious diseases affecting a large number of individuals especially in developing countries. TB can present as pulmonary or extrapulmonary disease resulting in severe morbidity and mortality. Ocular TB is a rare form of extrapulmonary TB which may present with protean manifestations [1, 2]. The most common clinical presentation of ocular TB is posterior uveitis [2]. As described in preceding chapters, various forms of posterior uveitis associated with TB have been described in the literature. Thus, recognition of ocular TB and its management is an important aspect of uveitis practice especially in developing countries such as India.

The choroid is the most common site of ocular TB since it caters to the high oxygen demand of *Mycobacterium tuberculosis*. TB-related posterior uveitis can present as choroidal tubercles, choroidal granulomas/subretinal abscesses, serpiginous-like choroiditis (also known as multifocal serpiginoid choroiditis), retinal vasculitis, neuroretinitis, endophthalmitis, and panophthalmitis [2–6].

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Multifocal serpiginoid choroiditis (MSC) is a unique posterior segment manifestation of ocular TB [5]. MSC possibly results from a hypersensitivity reaction to the tubercular bacilli sequestered in the retinal pigment epithelium (RPE). This entity presents with well-defined choroidal lesions that grow in a serpentine manner with an active advancing edge and healing center. It is differentiated from the classic serpiginous choroiditis which is thought to be autoimmune in etiology [5].

The index chapter focusses on the epidemiology, pathology, and clinical and imaging features of patients with tubercular MSC. In addition, the treatment and complications such as paradoxical worsening of TB MSC have been highlighted.

Multifocal Serpiginoid Choroiditis

TB MSC usually presents as bilateral, chronic, recurrent inflammation of choriocapillaris, choroid, and the RPE [5]. These patients are expected to have positive laboratory evidence of active or latent TB, in contrast to patients with autoimmune serpiginous choroiditis.

Epidemiology

Prevalence of ocular TB and TB MSC is reported differently in worldwide literature. In developed

A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_8

countries, the incidence rate is low (approximately 1.4%) compared to developing counties where incidence rate is reported as high as 18% in patients with systemic TB. In South India, the incidence of ocular TB has been reported to be 1.39% and 0.39% in two different studies from one center. On the other hand, a study from a tertiary eye care center in North India reports 30% incidence of ocular TB.

TB MSC is seen more commonly in males. This condition typically affects young to middle-aged adults from TB-endemic areas [4, 5]. Unlike the classic autoimmune serpiginous choroiditis, TB MSC occurs at a younger age, associated with mild vitritis, and is bilateral in majority of the cases [7].

Pathophysiology

Classic serpiginous choroidopathy is believed to be autoimmune in nature. This condition responds well to immunosuppressive therapy and systemic corticosteroids. On the other hand, TB MSC is usually treated with a combination of ATT as well as oral corticosteroids with or without immunosuppressive therapy in order to control the inflammation and limit the recurrences.

TB MSC is believed to represent an immune-mediated hypersensitivity reaction to the acid-fast bacilli sequestrated in the RPE. The exact role of various cytokines and interleukins involved in the pathogenesis of TB MSC is yet to be elucidated in the literature.

Clinical Features

Patients with TB MSC most commonly present with complaints of blurred vision, metamorphopsia, floaters, paracentral scotomas, and/or visual field defects. The posterior segment manifestations of TB MSC may be classified based on the morphological appearance of the lesions on fundus examination. Broadly, there are three main patterns of choroiditis among patients with TB MSC:

1. Placoid chorioretinitis: In this subtype of choroiditis, a diffuse plaque-like lesion is observed which has a characteristic amoeboid pattern and active edge. The borders of the lesions are yellowish white and elevated, whereas the center of the lesion is less elevated with pigmentary changes suggestive of a healing process in the center of the lesion (Figs. 8.1 and 8.2).
2. Multifocal choroiditis: This phenotype presents with discrete lesions, yellowish white in color, and measuring about ¼–1 disc diameter (DD) in size with well-defined margins and slightly raised edges. The edges of these lesions are noncontiguous initially and show a wavelike progression over a period of 1–4 weeks and gradually become confluent (Fig. 8.3).
3. Mixed pattern: These lesions present with overlapping features of both multifocal and placoid chorioretinitis.

Imaging Features

Fundus Photography, Autofluorescence, and Wide-Field Fundus Imaging

In order to accurately study the morphology of the chorioretinal involvement in TB MSC, it is important to obtain color fundus photography at regular intervals. This greatly aids in the analysis of the fundus lesions and provides an objective assessment of change in the lesions over an extended period of time. Serial fundus photography (from acute stage to the stage of healing) is very useful in assessment of morphological evolution of the lesions [5]. In addition, color fundus photography can enable detection of other features such as vitreous haze among patients with intraocular TB. Careful analysis of fundus photographs may also help in the detection of complications such as development of choroidal neovascular membranes.

Studies have shown that fundus autofluorescence (FAF) is a very useful noninvasive imaging modality in the management of TB MSC. Using FAF, the lesions can be assessed as they evolve from the acute stage to the stage of healing. Lesions of TB MSC can be staged using FAF imaging to determine the response of therapy as well as

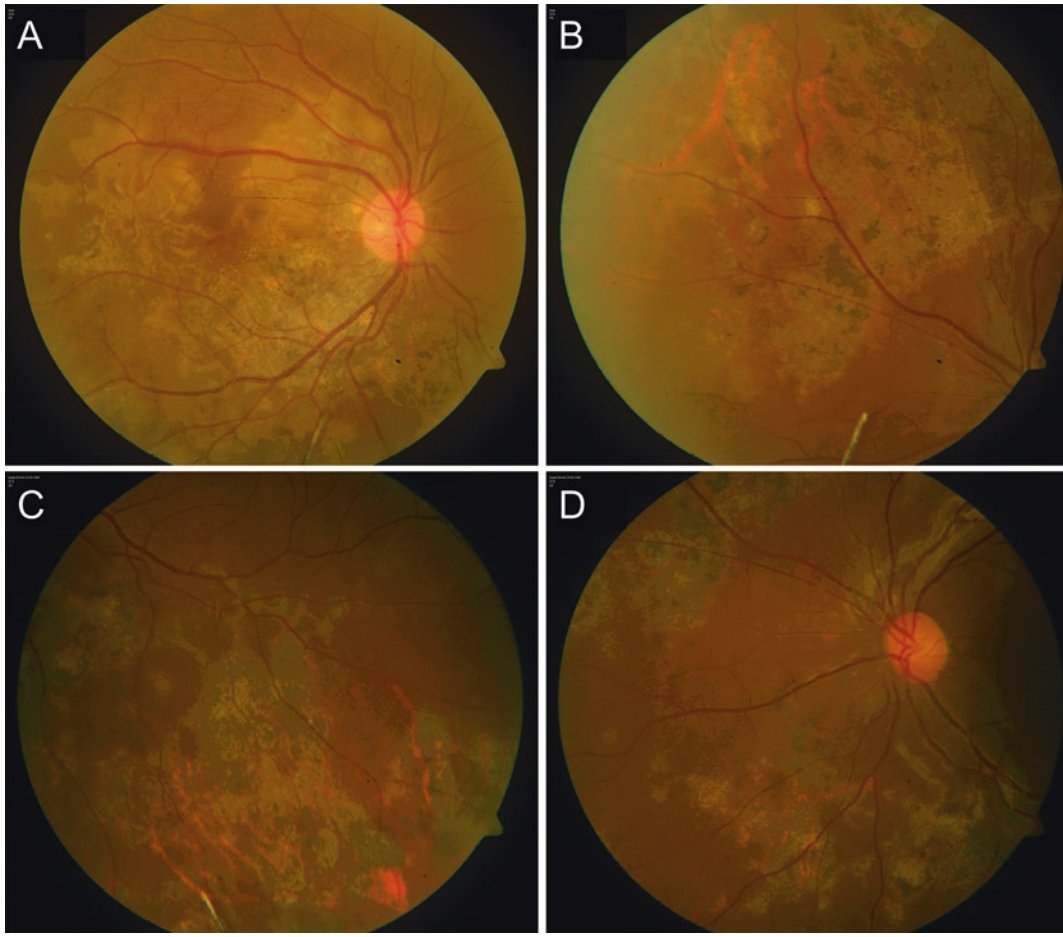

Fig. 8.1 Color fundus photography of a 34-year-old female diagnosed with tubercular multifocal serpiginoid choroiditis (TB MSC). The lesion appears confluent and *yellowish white* and is involving the posterior pole (**a**) and mid-periphery of the retina. Peripheral frames (**b**–**d**) show presence of perivascular choroiditis lesions that are classically observed in patients with TB MSC. This subtype of TB MSC with large confluent lesions is termed as placoid type of chorioretinitis

determine the natural course of the lesions (Fig. 8.3) [8]. Active lesions demonstrate ill-defined hyper-autofluorescence throughout the lesions. Thus, the lesions have a diffuse, amorphous appearance (Stage 1). In the stage of early healing (Stage 2), a thin rim of hypo-autofluorescence is seen surrounding the lesion which remains predominantly hyper-autofluorescent with a stippled pattern. With further healing, the lesion becomes predominantly hypo-autofluorescent (Stage 3) on FAF imaging. On complete healing, the lesions become uniformly hypo-autofluorescent without hyper-autofluorescent areas (Stage 4) [8].

Ultrawide-field fundus imaging is a recent addition in the imaging modalities used for the assessment of various chorioretinal pathologies (Fig. 8.3). Compared to conventional imaging (fundus photography and fluorescein angiography), ultrawide-field imaging systems aid in detection of additional features such as perivascular choroiditis, retinal vasculitis, and retinal neovascularization [9]. This imaging technology can be very useful in the management of TB MSC with modalities such as laser photocoagulation in areas of non-perfusion as well as to monitor the overall response to treatment on successive visits.

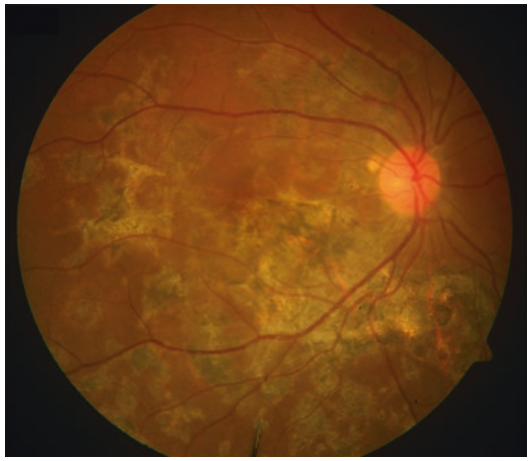

Fig. 8.2 Color fundus photograph of the same patient depicted in Fig. 8.1 shows healing of the tubercular multifocal serpiginoid choroiditis lesion 8 weeks after initiation of antitubercular therapy and oral corticosteroids. The lesions appear pigmented and have a sharper border compared to the baseline images. The posterior pole does not show presence of any new lesion at this visit

In addition, ultrawide-field imaging may be superior to conventional imaging in identifying changes such as *peripheral paradoxical worsening* (worsening of the primary disease upon initiation of anti-TB therapy due to possible release of antigens from the mycobacteria; ocular *Jarisch-Herxheimer reaction*) which may be otherwise missed on conventional imaging [9].

Fluorescein Angiography

Fluorescein angiography (FA) is a very useful modality in the diagnosis and follow-up of patients with TB MSC. The active lesions of TB MSC appear hypofluorescent in the early phase and show hyperfluorescence in the late phase. In the natural history of the disease (without any therapy), the lesions may progress to become confluent, and the advancing edge shows early hypofluorescence with late hyperfluorescence. Due to retinal pigment epithelial damage and choriocapillaris atrophy, the areas of healing may demonstrate window defects on FA [5]. Thus, FA is very helpful in demonstrating the activity of the lesions of TB MSC. In addition, complications of the disease such as inflammatory choroidal neovascularization may be detected using FA, though it may be very challenging in the absence of high index of suspicion [10].

Ultrawide-field FA is very useful in the management of intraocular TB. In comparison with conventional FA, ultrawide-field imaging can reveal additional information such as peripheral capillary non-perfusion areas, retinal neovascularization, and retinal vascular leakage. Such findings may alter treatment decisions such as the need for scatter laser photocoagulation [9]. In the recent times, ultrawide-field FA is being increasingly used in the management of TB MSC.

Indocyanine Green Angiography

The proper evaluation of TB MSC is incomplete without performing ICGA. Active lesions of TB SLC remain hypofluorescence from early to late phase on ICGA. ICGA is very useful in detecting choriocapillaritis and presence of choriocapillaris hypoperfusion among patients with TB MSC. Other changes of tubercular uveitis include presence of numerous hyperfluorescent spots, fuzzy appearance of choroidal vessels in the intermediate phase, and late choroidal hyperfluorescence due to dye leakage which tends to regress after completion of treatment with antitubercular therapy and corticosteroids. The ICGA changes are usually reversible and may be used to monitor the response to therapy [11–13]. The lesions of TB MSC may heal and result in development of choriocapillaris atrophy, which presents with early hypocyanescence followed by iso-cyanescens in the late phase.

Optical Coherence Tomography

Spectral-domain OCT has provided numerous insights into the pathogenesis of TB MSC. Various manifestations of chorioretinal involvement in TB MSC include peripapillary retinal atrophy, disruption of the photoreceptor and other outer retinal layers, thinning of retinal pigment epithelium, mild cystic changes as well as subretinal fibrosis in area of old choroidal neovascularization, and marked attenuation of the interdigitation zone in the outer retina [14, 15]. Lesions of TB MSC may also result in alteration of the ellipsoid and the myoid zones in the outer retina along with choriocapillaris thinning. In the

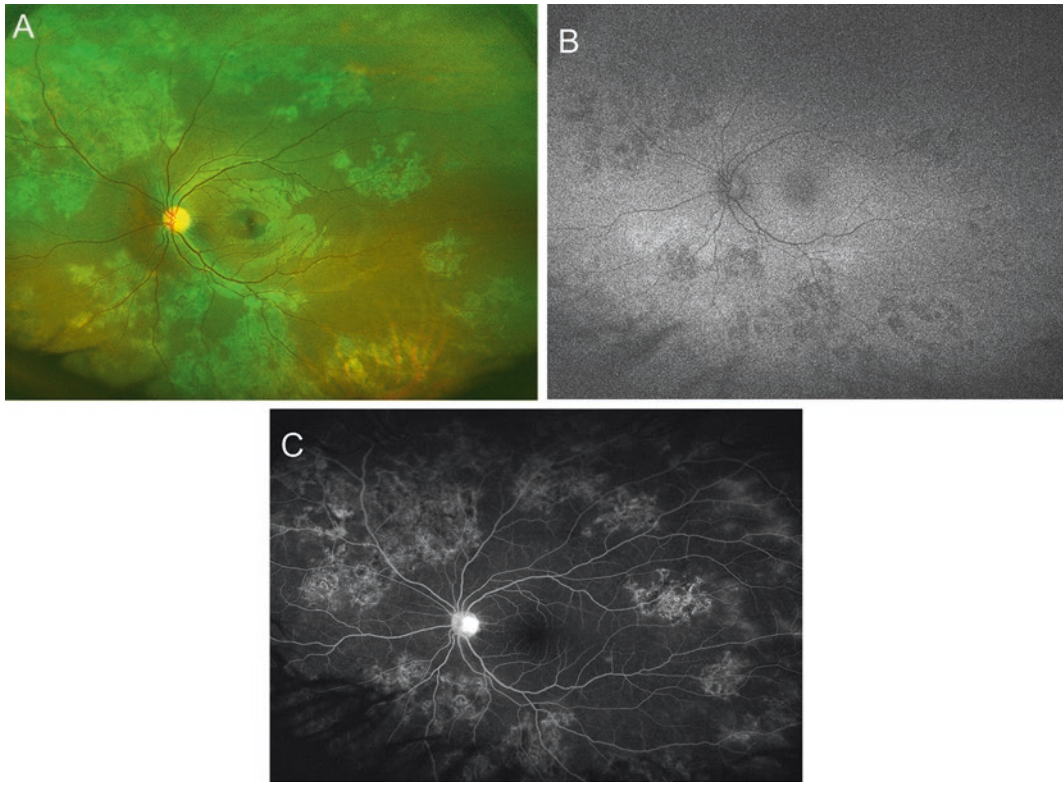

Fig. 8.3 Ultrawide-field fundus photography, autofluorescence, and fluorescein angiography of a 23-year-old male diagnosed with tubercular multifocal serpiginoid choroiditis (TB MSC). (**a**) Color fundus photography shows presence of multifocal yellowish-white perivascular choroiditis lesions involving the posterior pole and the periphery. (**b**) Ultrawide-field fundus autofluorescence shows hypo-autofluorescence with active edges that appear hyper-autofluorescent. Fluorescein angiography (**c**) shows hyperfluorescent active edges in the late phase of the dye transit. Central healed areas appear hypofluorescent on fluorescein angiography

acute stage of TB MSC, active edges of the lesions show localized, fuzzy area of hyper-reflectivity in the outer retinal layers involving the retinal pigment epithelium, photoreceptor outer segment tips, external limiting membrane, and the outer nuclear layer without increased backscattering from the inner choroid. As the lesions begin to heal from the center, the hyper-reflective fuzzy areas begin to disappear and are replaced by irregular, hyper-reflective knobbly elevations of the outer retinal layers. There is an increased reflectance from the choroidal layers due to attenuation of the retinal pigment epithelium-photoreceptor complex. As the lesions continue to heal further, there is loss of retinal pigment epithelium and outer retinal layers and persistent increased reflectance from the choroid on OCT. [16]

Introduction of enhanced-depth imaging (EDI)-OCT helps in detection of deeper choroidal involvement in various vitreoretinal conditions including TB MSC. Using EDI-OCT, choroidal infiltration, elevation of the retinal pigment epithelium-Bruch's membrane complex, and focal increase in choroidal thickness have been observed along lesions of TB MSC. The most characteristic change on EDI-OCT is the development of choriocapillaris ischemia along active lesions of TB MSC [13]. Figure 8.4 represents various chorioretinal findings observed on OCT in TB MSC lesions.

Optical Coherence Tomography Angiography

The technology of optical coherence tomography angiography (OCTA) has recently revolutionized

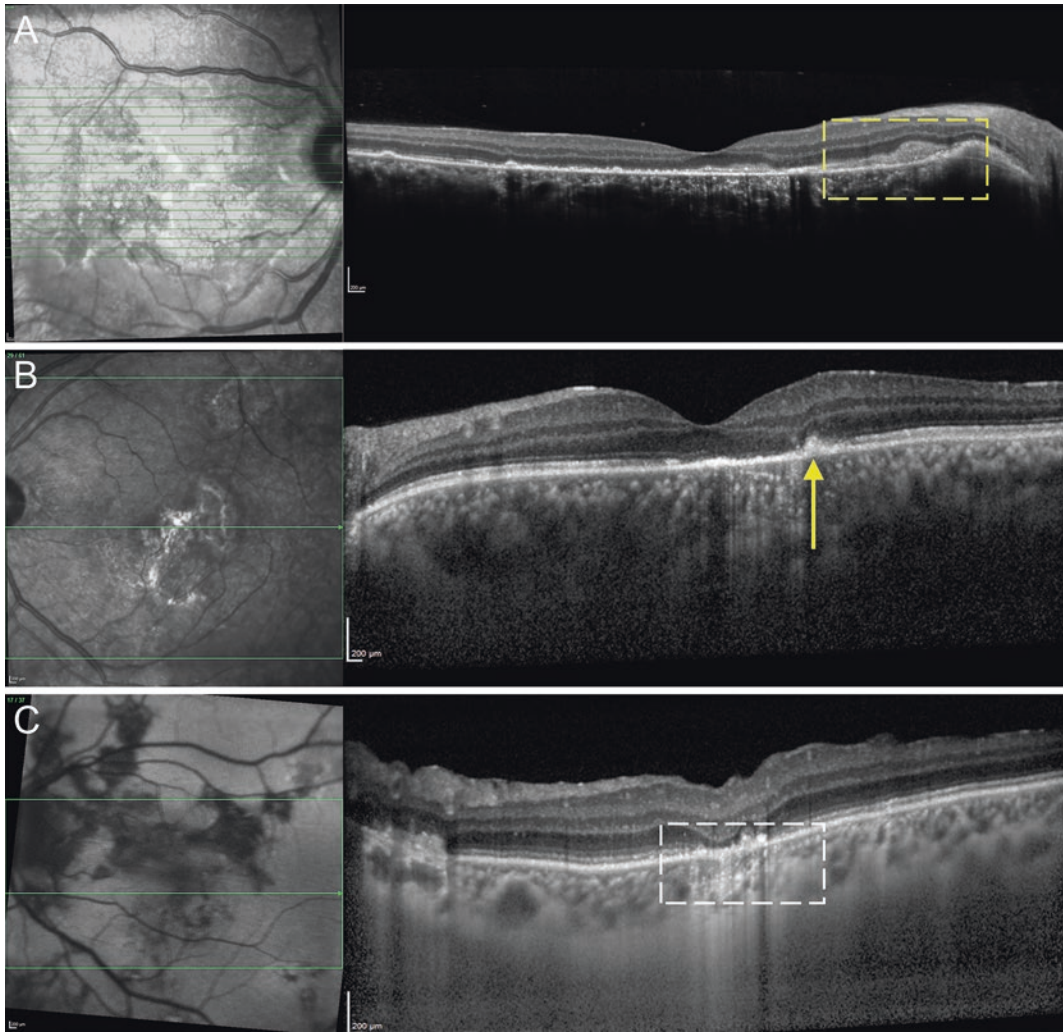

Fig. 8.4 Enhanced-depth imaging optical coherence tomography (EDI-OCT) of three patients (**a**–**c**) with tubercular multifocal serpiginoid choroiditis (TB MSC). Case no. 1 (**a**) shows a patient with active TB MSC lesions with irregular retinal pigment epithelial (RPE) elevations and subretinal hyper-reflective material (*yellow dashed square*). Case no. 2 (**b**) shows presence of knobbly elevations of the RPE (*yellow arrow*), indistinct outer retinal layers with discontinuous external limiting membrane, and ellipsoid/myoid zones in the active stage of the disease. There is presence of inner choroidal thickening. Case no. 3 (**c**) represents a patient with healed TB MSC showing irregular RPE, atrophy of the outer retinal layers, choriocapillaris attenuation, and thinning of the choroid (*white dashed square*) in the area of the previous TB MSC lesions

our thinking and understanding of the pathophysiology of chorioretinal vascular involvement in various uveitic entities. OCTA is being increasingly used in the management of patients with uveitis to provide further insights into the natural history of the disease and detection of early complications such as choroidal neovascularization [17].

Among patients with TB MSC, OCTA may demonstrate presence of choriocapillaris hypoperfusion as flow void areas on en face images [18]. These findings may be correlated with other imaging modalities such as ICGA. Thus, noninvasive tools such as OCTA may enable detailed evaluation of the retinochoroidal vasculature

among patients with intraocular TB [19]. In a recent report, choroidal neovascularization was detected using OCTA in a patient with tubercular choroiditis [20]. Thus, further advances in imaging may enhance our knowledge of pathogenesis of intraocular TB.

Treatment of Tubercular Multifocal Serpiginoid Choroiditis

Treatment of systemic TB consists of multidrug therapy (MDT). The first-line MDT therapy for systemic TB includes isoniazid, rifampin, ethambutol, and pyrazinamide. Second-line agents are used in the presence of mycobacterial resistance. These agents include levofloxacin, streptomycin, and amikacin/kanamycin, among others. The duration and dosing regimen depend on the organ system involved, severity of disease, and the history of prior anti-TB therapy. Recently, rifampin resistance has been demonstrated in ocular TB [21]. Thus, it is important to obtain the sensitivity profile of the mycobacteria since resistance of this organism is increasing. Failure of response to therapy due to resistance may result in diagnostic and therapeutic challenges.

The treatment of TB MSC consists of standard four-drug regimen of isoniazid (5 mg/kg/day), rifampicin (10 mg/kg/day), ethambutol (15 mg/kg/day), and pyrazinamide (20–25 mg/kg/day) along with pyridoxine (vitamin B6). Following the initial phase, ethambutol and pyrazinamide are stopped after a period of 2 months, while isoniazid and rifampin are usually continued for 12 months. Anti-TB therapy is usually given in combination with systemic steroids (oral prednisolone 1 mg/kg/day) which is tapered off over the next 6–12 weeks depending upon the level of inflammation seen clinically and on imaging such as FAF and fluorescein angiography. Topical steroids may be employed in cases with anterior segment cells and flare. In the presence of continuous progression of the lesions or recurrence of the disease, long-term immunosuppression may have to be added. Thus, systemic immunosuppressants such as azathioprine, cyclosporine, or mycophenolate mofetil may be added as and when required [1]. A subset of patients treated with anti-TB therapy may develop paradoxical worsening of ocular disease (*ocular Jarisch-Herxheimer reaction*) [22]. As described previously, this condition must be differentiated from progression of the lesions since it is treated with increasing systemic immunosuppression. The role of anti-TB therapy in intraocular TB is to reduce the antigen load by eliminating the bacilli, which may prevent recurrence of the disease.

Complications of TB MSC such as inflammatory choroidal neovascularization or macular edema may be treated with the use of intravitreal anti-vascular endothelial growth factor (anti-VEGF) injections.

Compliance with Ethical Requirements Sahil Jain, MS, Aniruddha Agarwal, MS, and Vishali Gupta, MS, declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

Financial Support The authors have no financial disclosure/proprietary interest. No conflicting relationship exists for any author.

This work was partly supported by a grant from Department of Science and Technology, India, for the development of Centre of Excellence at the Advanced Eye Centre, PGIMER Chandigarh.

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Tubercular Retinitis and Retinal Vasculitis

9

Soumyava Basu and Taraprasad Das

Introduction

Tuberculosis (TB) has traditionally been considered a disease of the uveal layers, especially the choroid. However, retinal involvement, typically retinal vasculitis, affects a large subgroup of patients presenting with ocular TB. Though recognized more than a century ago [1], it remains poorly defined and therefore poses a diagnostic and therapeutic challenge. In this chapter, we will present historical and recent data to outline the clinical features, diagnostic criteria, and management options in TB retinitis and retinal vasculitis.

The association between TB and retinal vasculitis was first suggested by Axenfeld and Stock in 1911 [1]. Gilbert (1935) first demonstrated tubercle bacilli around a retinal vein in an eye with retinal periphlebitis [2]. Since then, several studies (outlined below) have tried to examine the association between TB and retinal periphlebitis.

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Pathogenesis

The pathogenesis of tubercular retinal vasculitis and retinitis has been subjected to much debate [3] and is therefore discussed in detail. Herein, we have attempted to derive a hypothesis from historical data and clinical characteristics of retinal TB.

Both experimental and clinical evidences point to active *Mycobacterium tuberculosis* infection in eyes with retinal TB. Finnoff's (1924) and Ohmart's (1933) experiments showed the development of perivasculitis in rabbit eyes following injection of TB bacilli into the common carotid artery and ciliary body, respectively [4, 5]. Verhoeff and Simpson (1940) demonstrated tuberculous granuloma within the central retinal vein in human eyes [6]. Since then, several cases of isolated retinal TB, both in the presence and absence of systemic TB, have been reported in published literature [7]. More recently, an intraretinal granuloma was demonstrated histologically and immunohistochemically, in an eye with retinal vasculitis [7]. Similar to this case, several other series of clinically suspected TB retinal vasculitis have been reported positive for *M. tuberculosis*, by polymerase chain reaction (PCR) [8, 9]. This observation has been validated in other patients by optical coherence tomography (OCT) as well [10]. Finally, in TB-endemic populations, presence of focal chorioretinal

A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_9

lesions overlying blood vessels has been statistically proven to characterize tubercular etiology in the eyes with retinal vasculitis [11]. Most of these patients developed recurrent inflammation, unless treated with anti-TB therapy.

Despite such strong evidence in favor of direct role of *M. tuberculosis* in pathogenesis of retinal TB, there are significant pointers toward an indirect role too. Finnoff (1924) showed that heat-killed bacilli could produce retinal perivasculitis in rabbits, just as live organisms [12]. Retinal and vitreous hemorrhages, along with vasculitis, were also seen after tuberculin skin testing [13]. Interestingly, peripheral blood T cells from a patient who developed anterior uveitis following BCG treatment for bladder cancer showed immune reactivity for retina-specific antigens [14]. This raised the possibility of molecular mimicry between BCG and retinal antigens as an initiating factor for ocular TB. Finally, the resolution of TB-associated retinal vasculitis with corticosteroids (without any anti-TB therapy) too suggests an indirect role of *M. tuberculosis* in pathogenesis of retinal TB [15].

Taken together, current evidence strongly suggests a direct causative role of the bacilli in pathogenesis of retinal TB. Yet several phenomena such as retinal inflammation by dead *M. tuberculosis* or resolution without anti-TB therapy remain unexplained. Ongoing and future research should be able to resolve these issues.

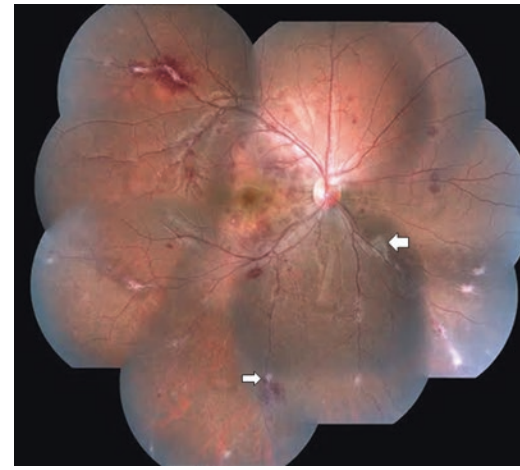

Fig. 9.1 Color montage photograph of the right eye showing active periphlebitis in all four quadrants and healed chorioretinitis lesions (*arrows*) overlying blood vessels

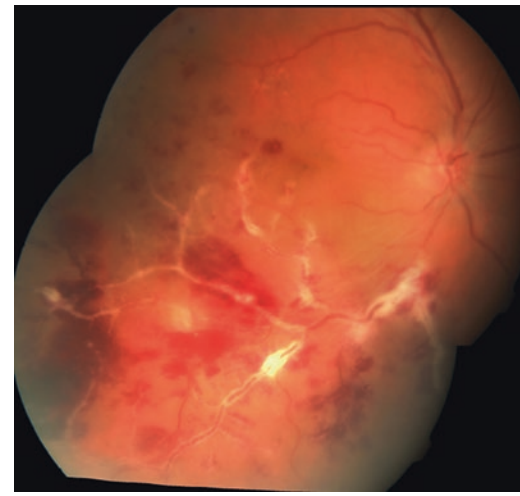

Fig. 9.2 Color photograph of the right eye showing active retinal periphlebitis in inferotemporal quadrant but no focal lesions overlying blood vessels

Clinical Presentations

Clinical presentations of isolated retinal TB can be divided into the following subgroups:

I. Retinal periphlebitis with or without focal chorioretinal lesions overlying blood vessels: The presence of healed or active focal chorioretinal lesions overlying blood vessels, in association with periphlebitis, is highly suggestive of TB in endemic countries (Fig. 9.1) [11]. These are intraretinal granuloma, as observed histologically and on OCT [7, 10]. However, PCR-proven TB retinal vasculitis is known to occur even in the absence of focal chorioretinal lesions (Fig. 9.2). These are relatively easy to diagnose if there is coexisting pulmonary TB (healed or active) but remain a diagnostic challenge in the absence of supportive evidence for TB. Such cases must be thoroughly investigated for alternative etiology, such as sarcoidosis or Behçet's disease, even in TB-endemic countries.

II. Retinal periphlebitis in association with other forms of ocular TB: These include coexisting multifocal serpigenoid choroiditis (Fig. 9.3) [16], neuroretinitis, or intermediate uveitis and help in establishing a TB etiology for the disease process.
III. Isolated retinitis lesions without periphlebitis: These occur typically as neuroretinitis (Fig. 9.4), but rarely focal retinitis lesions can be seen in the peripheral fundus that must be distinguished from other infectious and noninfectious etiologies, through detailed clinical and laboratory evaluation.
IV. The Eales' disease conundrum: Henry Eales described idiopathic retinal vasculitis with recurrent vitreous hemorrhage in 1880, in young men from poor socioeconomic backgrounds [17]. Since then, the term has established itself in ophthalmological lexicon, even though advances in modern medicine should lead us to overcoming our deficiencies in etiological diagnosis. Indeed Eales' disease has been associated with several causative factors, most prominently *M. tuberculosis* [18]. But regardless of its association with TB, the term Eales' disease is best avoided since it puts an unwarranted diagnostic label on a patient, preventing us from exploring potentially serious etiological conditions such as TB, anterior retinal necrosis (ARN), sarcoidosis or, Behçet's disease.

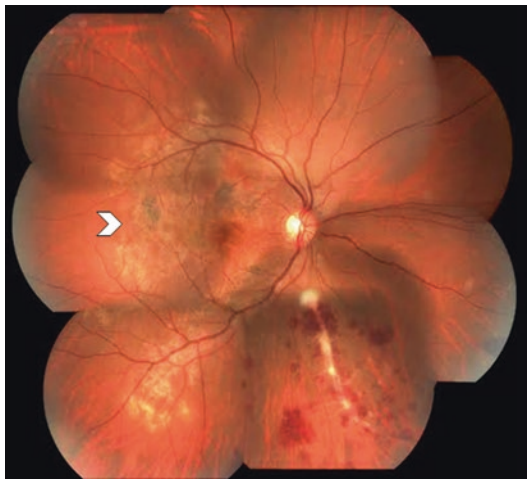

Fig. 9.3 Color montage photograph of the right eye showing active periphlebitis in infero-nasal quadrant and multifocal serpigenoid choroiditis at macula

Imaging

Imaging has a crucial role in determining etiological diagnosis in retinal TB, as also in identification of its complications and sequelae.

I. *Fluorescein angiography (FA)* is probably the most vital investigation for etiological diagnosis, since it reveals capillary non-perfusion

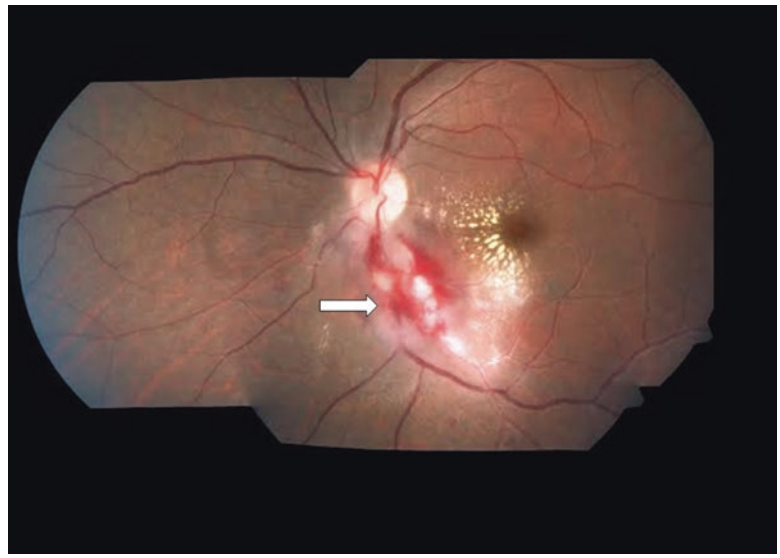

Fig. 9.4 Color montage photograph of the left eye showing full-thickness retinitis along the inferotemporal arcade, associated with a partial macular star

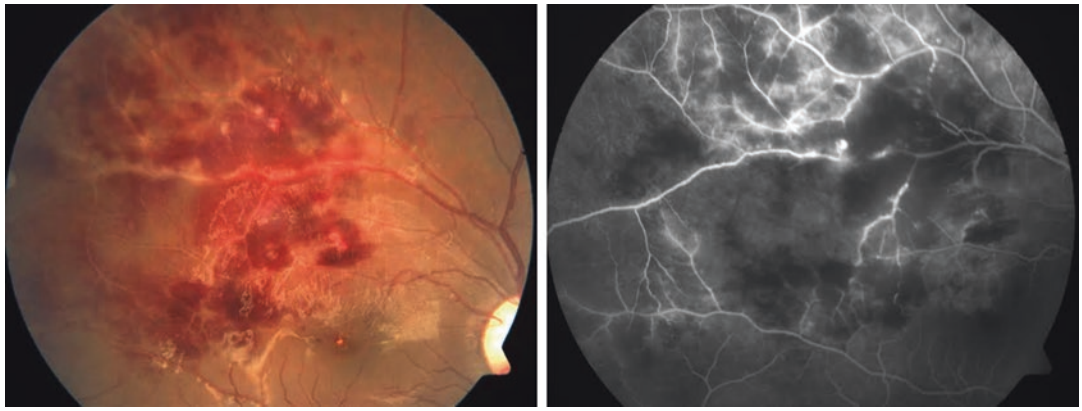

Fig. 9.5 Color photograph of the right eye showing active periphlebitis and retinal hemorrhages along supero-temporal quadrant with corresponding mid-phase fluorescein angiogram showing extensive capillary non-perfusion

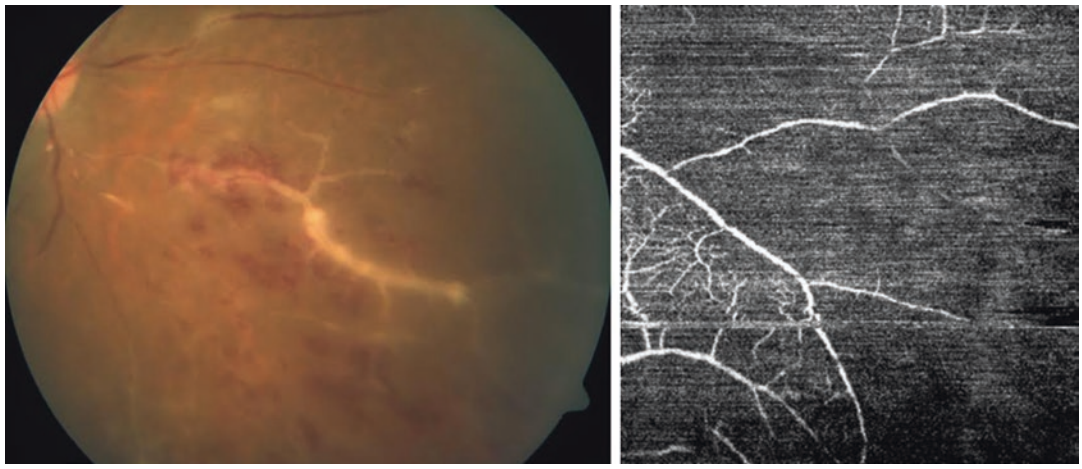

Fig. 9.6 Color photograph of infero-nasal quadrant of the right eye showing active periphlebitis and corresponding OCT angiogram showing flow void areas in the deep retinal capillary plexus

(CNP) in the quadrants affected by retinal periphlebitis (Fig. 9.5). While it is also seen in certain other conditions such as Behçet's disease, the presence of CNP areas in association with retinal periphlebitis and corroborative evidence of TB helps in distinguishing TB from several other conditions such as sarcoidosis. Apart from CNP areas, FA also helps in identification of retinal and disc neovascularization and cystoid macular edema (CME).

II. *Optical coherence tomography (OCT)* helps in noninvasive identification of CME and other macular complications, such as epiretinal membrane and full-thickness macular hole. In addition, high-resolution OCT can also help distinguish a primarily retinal lesion from a choroidal one.

III. *OCT angiography* is a recently introduced noninvasive tool for mapping retinal and choroidal vasculatures. It can also help in etiological diagnosis by identifying CNP areas without the need for fluorescein dye (Fig. 9.6). However, it cannot reveal active processes such as dye leakage.

Diagnosis

The diagnosis of retinal TB is largely based on clinical and imaging characteristics, outlined above. In TB-endemic regions, these include retinal periphlebitis associated with focal chorioretinal lesions overlying blood vessels and presence of CNP areas on FA/OCT angiography. It is crucial to recognize past exposure to open pulmonary TB patients. The role of ancillary tests such as tuberculin skin test, interferon-gamma release assay, and chest radiography is overemphasized in diagnosis of ocular TB in general. While they provide useful supportive evidence, neither their presence confirms the diagnosis nor their absence excludes ocular TB. A detailed clinical evaluation to rule out other etiology is more valuable in establishing the association with TB. In recent years, PCR has been used to provide definitive evidence of *M. tuberculosis* in aqueous or vitreous samples from eyes with retinal TB. Although it provides a more direct evidence as compared to the ancillary tests, it is still fraught with the possibility of both false-positive and false-negative results [9]. Quantitative real-time PCR can be useful in overcoming these weaknesses and providing more accurate results.

Management

The management of retinal TB depends on the specific clinical presentation and involves medical, surgical, or combined approaches (Table 9.1).

Medical: Since current evidence suggestive of *M. tuberculosis* is driven by inflammatory response, the treatment includes a combination of anti-TB therapy and corticosteroids [15]. Anti-TB therapy is generally of 6 months' duration with 2-month four-drug intensive phase and 4-month two-drug continuation phase. Corticosteroid therapy is generally systemic, supplemented by topical therapy for anterior uveitis and peri−/intraocular therapy for significant vitritis or CME. Since retinal TB is commonly associated with CNP and tissue hypoxia, there is a significant role of intravitreal anti-VEGF agents in treatment of CME or retinal/disc neovascularization.

Surgical: Surgery is commonly required for treatment of complications of retinal periphlebitis such as non-resolving vitreous hemorrhage, tractional retinal detachment, or epiretinal membranes. More recently, one of the authors (SB) has performed therapeutic vitrectomy in eyes with TB retinal vasculitis. This procedure not only provided vitreous samples for molecular diagnosis of TB but helped in faster resolution of inflammation (statistically compared to fellow eyes with active retinal periphlebitis, unpublished data). As evidence accumulates, this might emerge as first-line therapy for active retinal periphlebitis.

Table 9.1 Approaches to the management of retinal TB

Medical management	Surgical management
Anti-TB therapy	Pars plans vitrectomy for non-resolving vitreous hemorrhage, tractional retinal detachment, or epiretinal membrane
Corticosteroids Systemic Topical Peri−/intraocular	
Intravitreal anti-VEGF drugs	Therapeutic vitrectomy for active posterior segment inflammation

Summary

Retinal TB commonly presents as retinal periphlebitis associated with focal chorioretinal lesions overlying blood vessels and areas of CNP on FA. Occasionally, it may present with isolated retinal vasculitis or isolated retinitis lesions. The diagnosis is based on identification of clinical and imaging signs and careful exclusion of mimicking entities. Management is based on a combination of anti-TB and corticosteroid therapy with surgical intervention required for management of sequelae and complications.

Acknowledgments Krushna Gopal Panda, L V Prasad Eye Institute, Bhubaneswar for his fundus imaging.

Compliance with Ethical Requirements Soumyava Basu and Taraprasad Das declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

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Tuberculous Optic Neuropathy

10

Rohit Saxena and Divya Singh

Introduction

Tuberculosis is an infection caused by the bacterium *Mycobacterium tuberculosis* and is most commonly acquired by the inhalational route by which the infectious agent enters into the lungs and the primary infection is established. These infected individuals run a 10% risk of reactivation of the infection which can manifest as either pulmonary or extrapulmonary disease [1]. The hematogenous or lymphatic spread can result in involvement of the other sites. Ocular involvement is reported in 6.8% of patients with pulmonary tuberculosis [1, 2]. Till date, very less has been reported in the literature about the optic nerve involvement in tuberculosis. However, the advent of antimicrobial agents against *Mycobacterium tuberculosis* has led to marked improvement in the patient survival, and the reports of tuberculous optic neuropathy in the literature have been on rise since then. Tuberculous optic neuropathy entails a host of optic nerve involvements which may follow direct infection with the *Mycobacterium tuberculosis*, bacille Calmette-Guerin vaccination, or as a result of the hypersensitivity reaction. This bewildering array of manifestations of tuberculous optic neuropathy comprises of optic neuritis, retrobulbar neuritis, papillitis, neuroretinitis, papilledema, and optic nerve tubercle [3]. In this chapter, we try to describe the various types of tuberculous optic nerve involvement, clinical features, diagnostic and treatment modalities, and visual outcomes in these patients.

Clinical Manifestations

In our experience, a likely possibility of tuberculous optic neuropathy should be considered in the patients hailing from endemic areas. Other risk factors should be excluded such as past history or positive family history of tuberculosis and any history of immunocompromised state such as malignancy or diabetes mellitus. Patients usually present with unilateral, painless diminution of vision. The disease can have diverse manifestations, but the most common presentation was papillitis (Table 10.1). The previous reports also suggest that the most common manifestation of tuberculous optic neuropathy is papillitis (51.6%), followed by neuroretinitis (14.5%) and the optic nerve tubercle (11.3%) [3–10].

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A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_10

Moreover, patients with central nervous system tuberculosis can present with varied neuro-ophthalmic manifestations such as cranial nerve palsies (Fig. 10.1), gaze palsies, internuclear or total ophthalmoplegia, or one-and-a-half syndrome (Fig. 10.2) [11–16].

Visual field defects could also be of various types, but the most common defects noted were the enlargement of the blind spot and central scotoma. The visual recovery is generally good if the diagnosis is established early and the treatment is instituted. However, there is often a delay in diagnosis due to the late presentation of the patient and lack of definitive diagnostic tools to establish the tubercular etiology. The recovery is usually full or partial with permanent visual field defects. It can also result in optic atrophy in some patients [3].

Table 10.1 Clinical manifestations of tuberculous optic neuropathy [3]

Optic nerve involvements	Number of eyes (n = 62)	Percentage involved (%)
Papillitis	32	51.6
Neuroretinitis	9	14.5
Optic nerve tubercle	7	11.3
Compressive optic neuropathy	5	8.1
Retrobulbar neuritis	5	8.1
Optic neuritis	5	8.1
Anterior ischemic optic neuropathy	2	3.2
Papilledema	0	0

Establishing the Diagnosis

It is very difficult to reach at a specific diagnosis of the tuberculous optic neuropathy as there are no specific diagnostic criteria available [17]. This is due to the limitations of the available tests and difficulty in obtaining the biopsy of the intraocular tissues [3, 18, 19]. Though the situation has improved over past few years with the availability of the polymerase chain reaction for ocular fluid analysis, the limitations relate to the low

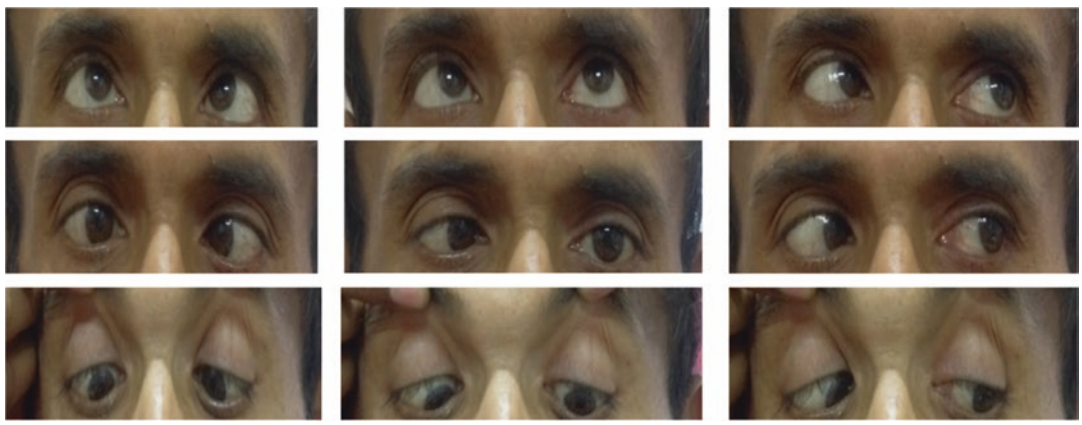

Fig. 10.1 Sixth cranial nerve palsy

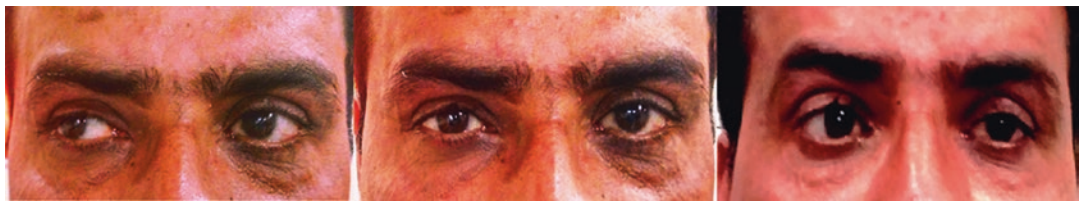

Fig. 10.2 One-and-a-half syndrome

Table 10.2 Criteria for diagnosis of intraocular tuberculosis [3]

Consistent ocular signs
Positive response to antituberculosis treatment
Positive Mantoux reaction
Positive IFN-gamma release assay
Active or old lesion(s) consistent with pulmonary tuberculosis on chest imaging
Identification of acid-fast bacilli by microscopy or culture
Positive *M. tuberculosis* PCR from ocular fluid

sensitivity and specificity of this test [20–23]. Gupta et al. [24] established a set of recommendations for the successful diagnosis of the disease. These can be summarized as follows: consistent clinical signs and positive results of ocular investigations or positive results of systemic investigations or therapeutic response to antituberculosis treatment [24]. Using this set of criteria, patients can be classified as either "presumed" or "confirmed" cases [24]. These recommendations were later modified to include the interferon-gamma (IFN-γ) release assay [25–27]. Thus, the modified criteria include consistent ocular signs, active or old tuberculous lesion on chest imaging, positive Mantoux reaction or IFN-γ assay, detection of *Mycobacterium tuberculosis* DNA in ocular fluid samples on polymerase chain reaction (PCR), positive microscopy or culture of acid-fast bacilli, and/or positive response to antituberculosis treatment [3] (Table 10.2). It is also mandated to exclude other etiologies for optic neuropathy by necessary investigations including the imaging studies for the optic nerve and brain.

Treatment

Previously, different treatment regimens have been discussed for the management of ocular tuberculosis [24, 28, 29]. A systematic review and meta-analysis recommended a four-drug regimen including isoniazid, rifampicin, pyrazinamide, and ethambutol for the treatment of intraocular tuberculosis for a total duration of 6–9 months [30]. Previously, the role of corticosteroids in improving the final visual outcome in tuberculous optic neuropathy was being debated, but no useful role has so far been elicited [3]. It is extremely important to work in unison with an infectious disease physician and develop the antituberculosis schedule in managing such cases for better visual outcomes [3, 18, 24, 31].

Another concern while treating the patients on antitubercular regimen is the medication-induced optic neuropathy especially with the use of isoniazid and ethambutol [32–35]. It usually occurs as a progressive, painless, bilaterally symmetrical visual disturbance with temporal pallor of the disc [36]. The toxicity is duration and dose dependent, and the symptoms may appear after the patient has been on the drug for a substantial duration of time [36]. Since the patients already have a compromised optic nerve status, it is imperative to monitor closely for any further optic nerve dysfunction with the use of these medications by evaluating the color vision, contrast sensitivity, and visual fields. An initial improvement in these parameters followed by deterioration after starting medications increases the likelihood of patient suffering from drug-induced toxicity. These cases usually show the red-green color defects, but other defects might also be seen, and the characteristic visual field defect in such cases is the central or centrocecal scotoma with preservation of the peripheral visual field [36]. Retinal nerve fiber layer thickness analysis using optical coherence tomography and visual evoked responses (VER) might have a role in early diagnosis of drug toxicity [37]. In a previous study done by us, we found out that macular fibers were most sensitive to the toxic insult by the antitubercular drugs which was reflected as the significant loss of the thickness of temporal RNFL [38]. Also, in cases of subclinical toxicity, the latency was found to be delayed on pattern VER test [38].

As a preventive measure, pyridoxine is often combined with isoniazid to reduce the risk of drug-induced peripheral neuropathy. On the other hand, complete cessation of the ethambutol intake is warranted if the toxicity is noted due to this drug.

Lastly, it is extremely important to rule out systemic involvement as a large set of patients presenting with tuberculous optic neuropathy has been found to have systemic manifestations [3, 39].

Compliance with Ethical Requirements Rohit Saxena and Divya Singh declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

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Ocular Tuberculosis in Immunocompromised Patients

11

Pukhraj Rishi, Ekta Rishi, Sridevi Nair, S. Sudharshan, and Sharanya Abraham

Introduction

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* (MTB). It can present in a myriad of ways, with pulmonary involvement being the most common. It is responsible for causing significant morbidity worldwide and is the most common cause of death in patients suffering from HIV. Tuberculosis (TB), along with HIV, is a leading cause of mortality worldwide [1]. About 30% of the world population is estimated to have latent infection with *Mycobacterium tuberculosis*, only 10% of this manifest active disease. Patients with HIV have a much higher chance of converting to an active disease, by nearly 25 times more as compared to the global rate [2, 3]. WHO Global Report on TB estimated that there were around 9.6 million new cases of TB in 2014. More than half of these cases were from Southeast Asian and Western Pacific countries. Of the new cases, 1.2 million (about 12%) were HIV positive, majority of which were from the African region. The incidence of TB with HIV has declined as compared to the previous decade. It was at its highest in 2005 at 1.39 million. TB was responsible for the death of 1.5 million patients in 2014, of which 0.4 million were HIV positive. However, the prevalence of tuberculosis among these patients and the causative mortality has significantly declined since 1990, mostly due to advances in antiretroviral treatment [4]. Though TB has since long been an endemic infection in the developing world, its recent re-emergence in the developed countries has been attributed to factors like migration, the epidemic of HIV and other immunocompromised conditions, and antitubercular drug resistance. These factors have led to a second peak in the incidence of TB in these countries [5, 6, 7]. Indeed, the majority of newly diagnosed cases in the USA were seen among the migrant population [8].

Ocular Tuberculosis

Lung is the most common site of tubercular infection. Up to one-fifth of the cases among immunocompetent patients have extra-pulmonary tuberculosis [9]. Extra-pulmonary tuberculosis can affect a number of sites including the lymph nodes, meninges, pleura, eye, gut, genitourinary tract, bone, and adrenals. It should be noted that extra-pulmonary tuberculosis may be seen in the absence of pulmonary tuberculosis in more than half of the cases [10]. The recent rise

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A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_11

in the incidence of extra-pulmonary tuberculosis has been attributed to the increase in immunodeficient conditions such as AIDS. In fact, in one study more than half of the AIDS patients with tuberculosis had at least one site of extra-pulmonary involvement [11]. There have also been reports of non-tubercular mycobacterial infections in AIDS patients [12].

The disease spectrum of ocular tuberculosis includes the infection of the ocular surface, periocular adnexa, and intraocular tissue by MTB and its related species [13]. The reported incidence of ocular tuberculosis is highly variable among different parts of the world. While the Western world reports an incidence varying from 1.34% to 18%, the incidence from the Indian scenario, where tuberculosis is an endemic disease, varies from 0.39% to 1.39% [14, 15, 16, 17]. More recently, the Philippines, a country with one of the highest number of tuberculosis cases in Asia reported an incidence of 6.8% of ocular tuberculosis [18].

Ocular Tuberculosis in Immunocompromised Patients

Patients with AIDS and other immunodeficient conditions are at a much higher risk of developing systemic tuberculosis infection. Tuberculosis is also the most common co-morbidity and the most common cause of mortality in AIDS patients [19–21]. In India, where TB is endemic, up to half of the patients with HIV have been reported to be infected with tuberculosis [22].

Ocular opportunistic infections in HIV including tuberculosis and CMV retinitis have shown a decline since the introduction of HAART in the mid-1990s [23]. Ocular tuberculosis in HIV patients has been found to be relatively rare. Some studies which evaluated the ocular manifestation in HIV patients in the pre-HAART era failed to find cases of ocular tuberculosis among them [24, 25]. Studies from post-HAART era without ocular tuberculosis have also been reported [26, 27]. Most studies describing ocular tuberculosis in HIV-positive patients are from the post-HAART era. A recent study from India analysed 1000 HIV patients and reported nearly two-thirds of them showing HIV-related ocular involvement. Ocular tuberculosis was seen in 3.8% of patients with ocular involvement and was the third most common infectious opportunistic infection after CMV retinitis and toxoplasmosis [28]. Babu et al. retrospectively studied a large (n = 766) sample of HIV patients in a South Indian setting and found nearly 2% of them to have ocular tuberculosis [29]. Another study from India evaluating HIV patients reported ocular tuberculosis in 23% of the systemic tuberculosis patients [30].

Although most studies report CMV retinitis as the most common ocular opportunistic infection in HIV patients, a study from Tehran found *Mycobacterium tuberculosis* to be the most common pathogen responsible for HIV-related ocular involvement among these patients (3 of 15 patients with ocular involvement) [31]. Mehta et al. studied a cohort of patients coinfected with HIV and MDR-TB, and they found ocular tuberculosis to be the most common cause of ocular inflammatory disease (i.e. in 10% of the patients) [32]. The authors attributed this to the general higher prevalence and endemicity of tuberculosis in the developing world. The increased prevalence of ocular tuberculosis was also attributed to antitubercular drug resistance among the patient group. Beare et al. reported an incidence of 3.9% of ocular tuberculosis among HIV patients. They associated the presence of disseminated tuberculosis to a higher risk of ocular infection [33]. Mehta et al. found 60% of the patients with culture-positive disseminated tuberculosis to have ocular tuberculosis [30]. Thus, disseminated infection shows a higher risk of ocular involvement. Few other studies from Africa and Southeast Asia reported an incidence of 5–6% of ocular tuberculosis in HIV-positive patients with disseminated tuberculosis [34, 35]. Among the pre-HAART era studies, one from Malawi reported 1% of HIV patients to have ocular tuberculosis [36], while Bouza et al. reported 11 of the 18 ocular tuberculosis patients from their study to be HIV positive [15].

Pathogenesis

Robert Koch was the first to stain and demonstrate MTB [37]. Jan-Maitre first described ocular tuberculosis in 1711 [38]. Choroidal tubercles were first

recognized by Gueneau de Mussy in 1830 [39]. First clinical description of choroidal tubercle was given by Edward von Jaeger in 1855 [40].

Mycobacterium tuberculosis is a slow-growing aerobic nonmotile bacterium. It is an airborne infection spread by droplet inhalation. The droplet size is very small (1–5 microns), and after inhalation, it reaches the alveoli where the organisms further divide inside the alveolar macrophages. The cell-mediated immunity gets activated within 2–12 weeks, which arrests the multiplication of the organism and leads to granuloma formation. A compromised cell-mediated immunity such as seen in the HIV-positive individuals predisposes them to a higher risk of acquiring infection and also developing an active disease. In immunocompetent individuals, cell-mediated immunity and granuloma formation limit the multiplication of organism, therefore never manifesting the disease in the majority, and thus the infection remains latent in them. Only 10% of them develop an active disease in which case we use the term tuberculosis to define the disease [41–43]. In HIV patients, coinfection with tuberculosis leads to activation of T cells and macrophages. This activation leads to further proliferation of the virus within these cells. This in turn leads to exacerbation of condition leading to increased morbidity [21, 30].

Ocular tuberculosis is referred to as primary infection when the bacteria invade the eye directly before any of the other organs. It is known as secondary infection when the bacteria invade the eye due to spread from another organ. This spread maybe via the haematogenous route or by direct contiguous invasion from a neighbouring tissue. The primary form is relatively rare [44, 45].

Uveal tissue of the eye has a rich vascular supply and is the most frequent site for spread of tubercular bacteria through bloodstream. There are primarily two mechanisms of ocular tissue damage. The first is direct bacterial invasion, which occurs through the haematogenous route or from the contiguous sites like the meninges and the sinuses. Ocular tissue damage may also occur due to immune hypersensitivity reaction to antigens present in another focus in addition to the direct invasion. In case of hypersensitivity reaction, the bacterium may not be found in the ocular tissue [46, 47].

Clinical Features

Ocular tuberculosis most commonly presents with uveal tissue inflammation. The proportion of cases of uveitis due to tuberculosis is quite varied depending on the geographical location of the reported study and endemicity of the disease there. It is relatively higher in the developing world [48–54]. Ocular tuberculosis can present with a myriad of manifestations involving the ocular adnexa, anterior segment, and the posterior segment. The eyelid and conjunctiva may be affected by the primary form of disease. There is direct inoculation of the bacteria onto the ocular surface tissue, and the lesions may resemble a conjunctival neoplasm [55]. Phlyctenules may form on the conjunctiva and are a result of the immune hypersensitivity reaction [56]. There have been a few reports of eyelid lesion in tuberculosis resembling a chalazion [57, 58]. Orbital tuberculosis may present in the form of a tuberculoma, which usually occurs due to haematogenous spread of the bacteria to the orbit. Other presentations include orbital bone periostitis and orbital infection due to direct extension from perinasal sinuses [59, 60]. Other manifestations include episcleritis; scleritis; keratitis; anterior, intermediate, or posterior uveitis (granulomatous or non-granulomatous); ciliary body granuloma; choroidal tubercles and tuberculoma; serpiginous choroiditis; retinal vasculitis; optic neuropathy; vitritis; endophthalmitis; and panophthalmitis. The manifestations like phlyctenulosis, vitritis, anterior uveitis, interstitial keratitis, serpiginous choroiditis, and retinal vasculitis are due to the immune hypersensitivity reaction, while endophthalmitis, choroidal mass, and nodular scleritis are due to the direct invasion of the organism [14, 61–66].

Choroidal tubercle or granuloma (Fig. 11.1) is a common ocular manifestation seen in HIV-positive patients with ocular tuberculosis. These patients may be often asymptomatic. This underlines the importance of a fundus examination in these patients even if they do not complain of vision loss. The choroidal lesion may not always be accompanied by vitreous inflammation. The tubercle occurs usually due to haematogenous spread of the bacterium and is an indicator of

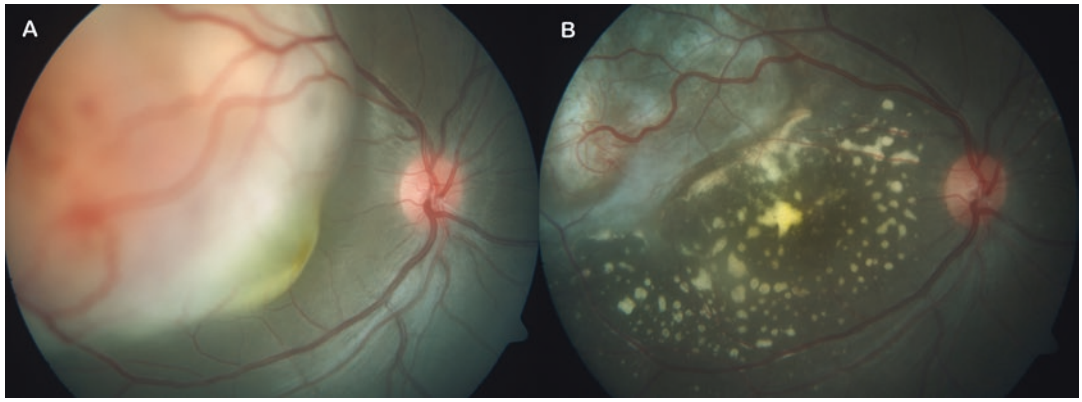

Fig. 11.1 Colour fundus photograph of the right eye (**a**) shows a subretinal abscess involving the macula. Fine needle aspiration biopsy revealed MTB. Post-treatment colour fundus photograph (**b**) of the same patient with significant regression after systemic antitubercular treatment

disseminated tuberculosis. The presence of a choroidal tuberculoma in an immunocompromised patient in a setting where tuberculosis is endemic is highly suggestive of disseminated tuberculosis [15, 29, 47, 62, 67–72]. Choroidal tubercles are the infectious foci appearing as small grey-yellow lesions with indistinct margins. They are less than one-fourth of the size of the optic disc found usually on the posterior pole. They usually present as fewer than five lesions. Less commonly, they may enlarge to form a tuberculoma, which presents as a solitary choroidal mass and may be accompanied by subretinal exudation [73, 74].

The manifestations of ocular tuberculosis in HIV patients may be more fulminant due to defective cell-mediated immunity in these patients. Authors from the Indian subcontinent have reported a number of ocular manifestations in these patients .In addition to choroidal tubercles, patients also may present with subretinal abscess, conjunctival mass, and panophthalmitis. AIDS patients show a higher propensity for progression to panophthalmitis due to a compromised immunity, which could often worsen rapidly. An interesting phenomenon may be seen in these patients due to immune reconstitution syndrome, wherein a worsening of the tubercular inflammation may be seen when HAART is started. This heightened inflammation itself may hasten the progression to panophthalmitis in these patients. Ocular tuberculosis in AIDS patients may not necessarily occur at very low CD4 counts or correlate with the counts, and it may even progress despite adequate systemic treatment. Thus, one should always look out for these lesions even if the CD4 counts are good [29]. Most patients with choroidal granuloma suggestive of ocular tuberculosis are asymptomatic [15, 28].

Choroidal tuberculoma and retinochoroiditis have also been reported in HIV patients with active pulmonary tuberculosis. There have been reports of a few cases with signs of active and healed anterior uveitis, in addition to chorioretinal lesions in patients with ocular tuberculosis and HIV [75, 30, 33]. The presence of CNS tuberculosis in AIDS patients increases the risk of ocular infection, and they may present with choroidal infiltrates [75]. A study from Iran described similar features of bilateral multiple and focal choroiditis along with vitritis and anterior chamber inflammation [31]. In HIV patients, ocular tuberculosis may present with manifestations of other opportunistic infections like CMV retinitis and toxoplasmosis. Thus, one must keep in mind the possibility of other concurrent infections [76].

Management

The diagnosis of ocular tuberculosis remains a challenge in the absence of a definitive diagnostic criterion, even in the immunocompetent patients. Ocular tuberculosis does not have a typical or

characteristic clinical picture with which it presents. Most other causes of uveitis may also present with similar clinical picture. Also, the definitive diagnosis of ocular tuberculosis requires microbiological isolation of the organism from the tissue or body fluid, which can be difficult and highly invasive in case of ocular disease [77]. Another point to note is that ocular tuberculosis may often exist without other systemic manifestations or foci of infection; thus, it is not possible to rule it out completely if systemic investigations like radiological imaging and sputum exam are normal [78].

Gupta et al. enumerated the following clinical signs as consistent with intraocular tuberculosis in the immunocompetent patients, namely, broad posterior synechiae, retinal perivasculitis with or without discrete choroiditis or scars, multifocal serpiginous choroiditis, single or multiple choroidal granuloma, optic disc granuloma, and optic neuropathy. Among these broad posterior synechiae, retinal vasculitis with or without choroiditis or scars and serpiginous-like choroiditis were shown to have the higher specificity for diagnosis. They have also proposed a classification system for intraocular tuberculosis (IOTB) which classifies the disease in confirmed, possible, and probable IOTB [79].

There is a lack of consensus on the guidelines to diagnose and treat ocular tuberculosis, including the use of immunosuppressive agents. However, with rise in the multidrug-resistant cases of tuberculosis, it has become imperative to make an accurate and early diagnosis of the condition to avoid inappropriate treatment [80–82]. Currently, diagnosis of ocular tuberculosis is made on the basis of ocular lesions, evaluation of intraocular fluid, evidence of tuberculosis elsewhere in the body, and response to antitubercular treatment. In immunocompromised patients, ocular lesions may precede other systemic findings, and hence, detecting them may be critical to early diagnosis of the disease and commencement of treatment [83]. Traditionally, systemic tuberculosis was diagnosed on the basis of tests like chest X-ray, Mantoux tuberculin skin sensitivity test, sputum examination, etc. However, these do not work well for ocular tuberculosis, especially in the immunocompromised. Tests like Mantoux test may be negative due to altered immune status, and chest X-ray may be normal since these present many times as extra-pulmonary tuberculosis. Also, being a paucibacillary infection, the ocular samples are rarely positive in microbial culture tests. Therefore, detection of the ocular lesions clinically becomes very crucial [62, 83–85].

The newer tests to diagnose tuberculosis include the immunological tests such as interferon gamma release assay (IGRA), a test which measures the IFN-gamma levels, and the polymerase chain reaction which detects the mycobacterial genomic material. IGRA, unlike tuberculin sensitivity test, is not affected by the BCG vaccine status. Commonly used IGRA tests include QuantiFERON-TB Gold (QFT-G) test and T-SPOT.TB test. QFT-G test has been found to be useful in detecting intraocular tuberculosis with good sensitivity and may also be helpful in deciding to start steroid therapy in uveitis patients. It also has the advantage of being able to detect latent tuberculosis in BCG-vaccinated patients with fewer false positives as compared to Mantoux tuberculin skin sensitivity test (TST). However, it has been noted to have a lower specificity in the immunocompromised as compared to the immunocompetent [86–89]. QFT-G test has a higher sensitivity and specificity for detection of ocular tuberculosis as compared to systemic disease [90]. In fact, QFT-G test may be diagnostically superior to tuberculin skin sensitivity test especially in the immunocompromised patients, though some claim the difference between the two to be only marginal [91–93].

However, there have been studies which have reported that QFT-G test may be indeterminate in patients with immunosuppression [94]. In these patients, the T-SPOT.TB test may show better sensitivity to detect the disease [95]. T-SPOT.TB test relies on quantitating the IFN-gamma-releasing T cells, rather than the cytokine levels directly [96]. The T-SPOT.TB test has been found to be a useful adjunct in the diagnosis of ocular tuberculosis in non-endemic areas [97]. Ariga et al. found IFN-gamma release to correlate with peripheral blood T cell population, which may be altered in an immunocompromised patient. They

also prescribed a lower cut-off value for the IFN-gamma levels for diagnosing these patients in the low endemic settings [98]. In fact, higher levels of interferon gamma on this test have been found to correlate with successful response to treatment [99]. Interferon gamma assay has been prescribed for aiding the diagnosis of ocular tuberculosis in conjunction with the clinical features and positive TST [100, 101]. Recent studies have shown QFT-G test to be superior to T-SPOT.TB test for diagnosing ocular tuberculosis [102].

PCR has been known to detect mycobacterial gene from aqueous and vitreous samples with good specificity [103]. Babu et al. used PCR to diagnose ocular tuberculosis successfully in HIV-positive patients [29]. The newer quantitative PCR which allows real-time assessment of the process and enables better quantification of genetic material has also been used to diagnose ocular tuberculosis [104, 105]. A newer nucleic acid amplification test called the loop-mediated isothermal amplification assay PCR (LAMP PCR) has also been found to have a very good sensitivity and specificity in detecting mycobacterial genome in uveitis patients and may be an alternative modality to the conventional PCR [106]. Recently, Rishi et al. reported the use of RT-PCR to demonstrate *Mycobacterium tuberculosis* RNA in patients with culture-positive tubercular endogenous endophthalmitis. They emphasized that in contrast to the microbial culture method which takes at least 2–3 weeks to provide results, RT-PCR can provide evidence of the microbe in a much shorter time [107].

Currently, most ophthalmologists treat ocular tuberculosis with a standard ATT regime of 9–12 months, depending on other systemic involvements. The use of steroids along with ATT has also been prescribed to control the inflammation especially in the acute phase, and it has been shown to be beneficial in reducing the damage due to immune hypersensitivity. The use of steroids is not advisable without concurrent ATT. However, in immunocompromised patients, a risk of worsening of the tubercular inflammation is seen when HAART and ATT are started together. This can often lead to panophthalmitis and thus the loss of the eye. To avoid this, it is suggested that the HAART be started a few weeks after initiating ATT [83, 108, 109]. Shorter duration of ATT and concurrent use of immunosuppressives have been associated with higher failure rates. Other factors like non-compliance and drug resistance affect the treatment outcomes in an adverse manner [80, 110]. The use of ATT for cases of tubercular uveitis has also been associated with a reduced rate of disease recurrence [111].

Conclusion

The diagnosis and management of ocular tuberculosis remains a clinical challenge in the absence of standardized criteria, even in the immunocompetent. In immunocompromised patients, the clinical ocular features are less typical and may deteriorate faster than the immunocompetent patients if early diagnosis is not made. Other factors like immune recovery uveitis may also lead to a rapid worsening of the disease. Diagnostic tests like TST and radiological imaging are often inconclusive in these patients making the diagnosis even more challenging. Thus, early diagnosis based on clinical features such as choroidal lesions may help in the timely diagnosis and appropriate treatment, thus preventing complications.

Compliance with Ethical Requirements Pukhraj Rishi, Ekta Rishi, Sridevi Nair, Sridharan Sudharshan, and Sharanya Abraham declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this article.

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Conjunctival and Corneal Tuberculosis

12

Namrata Sharma and Neelima Aron

Pathogenesis

Mycobacterium tuberculosis can affect the eye in two possible ways. Primary ocular TB affects any structure of the eye with or without concurrent systemic disease. Secondary ocular TB refers to either hematogenous seeding of the eye from a distant site of infection or from direct spread from adjacent structures. Various mechanisms in which the *M. tuberculosis* may cause TB are listed in Table 12.1. The most common mechanism of affliction of the anterior structures of the eye is by the hypersensitivity reaction to the tuberculous antigen with or without the presence of viable mycobacteria in the body. The presence of tubercle bacilli in the ocular system stimulates an immune-mediated delayed hypersensitivity Th1 (type 1 helper cells) reaction forming granulomas [3]. Actual invasion of the bacilli in the cornea or conjunctiva is rarely found. *M. tuberculosis* and other nontuberculous bacteria (most commonly *M. bovis*, *M. africanum*, and *M. microti*) can affect both the anterior segment and the posterior segment of the eye. The most common structure of the eye to be involved is the choroid [4]. The conjunctiva and cornea are the sites of primary ocular involvement. This chapter will focus on highlighting the tubercular afflictions of these two important structures of the eye.

Conjunctival Tuberculosis

M. tuberculosis may affect any structure of the eye or adnexa. Tuberculous affliction of the conjunctiva may present as an ulcer, subconjunctival nodule, pedunculated polyp, or tuberculoma. The symptomatology includes features of chronic conjunctivitis like itching, discomfort, redness, mucopurulent discharge, inflamed edematous lids, preauricular/cervical swelling, and rarely fever [5]. The initial diagnosis is often missed due to the nonspecific findings and similar presentations with other diseases affecting the eye. This often leads to delayed diagnosis and incorrect treatment administered to the patient thereby increasing ocular morbidity and prolonging therapy [6].

Phlyctenular Keratoconjunctivitis

Phlyctenular keratoconjunctivitis (PKC) is seen due to a variety of distinct conditions with TB

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A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_12

being the commonest in India. In the Western world, this has been supplanted by *Staphylococcus aureus* as the most common causative antigen [7]. Phlycten is derived from the Greek word, phlyctaena, which means blister. The name is a misnomer because the lesion is actually a solid nodule instead of a fluid-filled bubble that can be single or multiple [8]. These nodules are referred to as phlyctenules and represent a localized hypersensitivity reaction to the mycobacterial antigens [9].

Table 12.1 Mechanisms involved in conjunctival and corneal tuberculosis

Mechanism	Clinical manifestation
Immune reaction to tubercular antigens	Phlyctenulosis Interstitial keratitis
Tissue invasion by *Mycobacterium tuberculosis*	Nodular scleritis

Table 12.2 Clinical presentations of phlyctenular keratoconjunctivitis

Type	Clinical features
Simple	Most common Isolated limbal nodule
Necrotizing	Large phlycten with necrosis and ulceration
Miliary	Multiple phlyctens arranged linearly at limbus

Clinical Presentation

Phlyctenules are usually localized to the limbus in the exposed interpalpebral region and occur more commonly in children [10]. Conjunctival lesions may cause only mild to moderate irritation of the eye or may be asymptomatic in many cases, while the corneal lesions may be associated with severe pain, photophobia, and blepharospasm [10]. It has also been seen that the nodules due to TB may have more light sensitivity than those associated with staphylococcus [11].

Phlyctenular conjunctivitis can present in three forms: simple, necrotizing, and military (Table 12.2). The usual presentation is a localized, elevated, gelatinous pinkish-gray nodular limbal lesion with a soft necrotic center and marked injection of the surrounding conjunctival vessels (Fig. 12.1). With progression, the lesions may show some degree of ulceration and staining with fluorescein but later on get epithelized. In few cases, there may be a very large phlycten associated with necrosis and ulceration which fails to epithelize and may lead to severe conjunctivitis. In some cases, multiple nodules may be present along the corneal limbus in a disorganized manner or may be arranged linearly along the limbus in the form of a ring.

Corneal phlyctenules also begin at the limbus, and unlike conjunctival phlyctenules, they frequently ulcerate and develop neovascularization. In some instances, the phlyctenule will migrate across the corneal surface due to recurrent

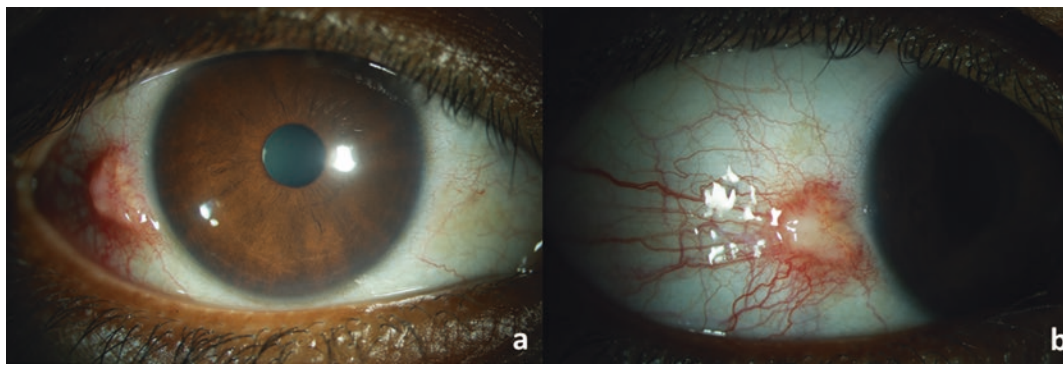

Fig. 12.1 Clinical presentation of phlyctenular conjunctivitis. (**a**) Limbal location of a phlyctenule. (**b**) Presence of a localized, elevated, gelatinous pinkish-gray nodule with a soft necrotic center and marked injection of the surrounding conjunctival vessels

episodes of inflammation and be associated with cervical lymphadenopathy. These "marching phlyctenules" demonstrate an elevated leading edge with a trailing leash of vessels. Corneal phlyctenulosis may leave corneal scars upon healing leading to permanent visual loss. In very rare instances, corneal perforation may occur [12].

Diagnosis

The diagnosis of PKC is mainly clinical. One should have a strong suspicion for PKC especially in recurrent episodes and failure of remission. Chest radiographs, purified protein derivative skin testing, or QuantiFERON Gold testing should be done for patients with a history of travel to endemic regions or symptoms suggestive of tuberculosis infection. Active multiplying bacilli are not found in these cases since it is a hypersensitivity reaction, and hence an excision biopsy to isolate the offending microorganism is of no use.

Histologically, scrapings can be taken from the affected eye which show predominantly helper T cells, cytotoxic T lymphocytes, monocytes, and Langerhans cells. The presence of antigen-presenting cells, monocytes, and T cells and conspicuously absence of bacilli support the rationale that PKC is likely due to a delayed cell-mediated reaction [13].

Differential Diagnosis

The nodules of phlyctenular conjunctivitis may be confused with other causes of nodules on the ocular surface such as nodular episcleritis, Salzmann's nodular degeneration, and inflamed pinguecula or pterygium. Long-standing recurrent episodes of conjunctivitis may be similar to that seen in acne rosacea keratitis, trachoma, and vernal keratoconjunctivitis. Cases where ulceration of the phlycten is seen may be misdiagnosed as infectious corneal ulcer, ulcer associated with spring catarrh, and peripheral ulcerative keratitis due to other causes.

Treatment

The rationale of management for PKC is the reduction of inflammatory response, and hence the mainstay of treatment is topical steroids. Surface-acting steroids such as fluorometholone may be used in mild cases. However, severe cases require topical prednisolone acetate 1% eye drops or dexamethasone/betamethasone for achieving remission. In eyes with multiple recurrences or those developing steroid dependence, topical cyclosporine A is added, and steroids are tapered off [14]. The retinal examination, slit lamp examination, and intraocular pressure measurement should be done periodically to rule out steroid-induced glaucoma and cataract in view of prolonged use of steroids.

In cases with corneal ulceration, topical fourth-generation fluoroquinolones are added along with cycloplegics in the form of atropine 1% eye drops twice a day. Corneal scrapings should be taken to rule out secondary superadded infection.

In addition to treating the inflammatory response, it is important to treat the underlying etiology, that is, to decrease the source of antigens responsible for the inflammation. In patients with suspected TB on chest radiography, tuberculin skin test, or PCR, full-dose antitubercular treatment (ATT) is given to eliminate the focus of antigenic load [15]. Close contacts should also be evaluated and treated accordingly.

In rare instances of corneal perforation, surgical treatment in the form of corneal gluing, amniotic membrane grafting, or corneal patch grafts may be required.

Other Forms of Tubercular Conjunctivitis

Based on the morphological characteristics, the other manifestations of TB-related conjunctivitis that can be seen are hypertrophic, granulomatous, and pedunculated mass and tuberculomas. Upper palpebral conjunctiva is the most common site of involvement followed by bulbar conjunctiva and fornix. Unilateral presentations are more common than bilateral. These cases may have presence of live mycobacteria in the ocular tissues. The definitive diagnosis can be made by demonstration of bacilli in the histopathology specimens [16]. However, they may be

missed on small biopsy tissues available after excision. Further, the chances of detection of mycobacteria on microscopic examination are less than on cultures. These bacteria show a slow growth on the Lowenstein-Jensen media and should be examined periodically for a minimum of 8 weeks before reporting negative results. The presence of granulomatous inflammation with caseation in the biopsied specimen strongly suggests the diagnosis of conjunctival TB. In case of negative results, nested PCR may be performed which shows amplification of the *Mycobacterium tuberculosis* genome and increases the detection rates [17].

Thus, eyes with chronic/recurrent unilateral conjunctivitis which fulfill one of the following criteria should be treated as tubercular conjunctivitis: [5]

1. A positive smear/culture or positive PCR for *M. tuberculosis*
2. Histopathological findings of caseating granulomas or epithelioid giant cells in biopsy samples with or without isolation of acid-fast bacilli on Ziehl-Neelsen staining
3. Response to ATT and/or presence of systemic signs of TB

Corneal Tuberculosis

Corneal tuberculosis is a rare ophthalmic manifestation of TB. It may present in two forms: phlyctenular keratitis and interstitial keratitis. The manifestations are almost always thought to be related to the hypersensitivity of the tubercular protein rather than the direct effect of active disease. Corneal involvement in phlyctenular keratitis has been described above and almost always accompanies phlyctenular conjunctivitis.

Interstitial keratitis may be an isolated finding or associated with scleritis or uveitis. This may possibly be due to the presence of tubercular antigen in the aqueous humor. Interstitial keratitis is typically unilateral and presents as a sectoral, peripheral, stromal infiltrate with vascularization. It can be differentiated from syphilitic keratitis in being more anterior and having more frequent recurrences [18]. The mainstay of treatment includes topical steroid eye drops to suppress the hypersensitivity reaction, topical antibiotics, and topical cycloplegics such as atropine 1%. Oral ATT should be administered to suppress the antigenic load and remove the stimulus causing hypersensitivity.

Case reports in literature show varied presentations of corneal TB. As mentioned before, corneal manifestations are usually unilateral. Bilateral central interstitial keratitis [19] and bilateral disciform keratitis [20] are the atypical corneal involvements which have been reported. Bayraktutar et al. reported a case with unilateral chronic, insidious, progressive stromal melting unresponsive to treatment which was later found out to be tubercular in origin [21]. Arora et al. described a case of peripheral ulcerative keratitis with chronic malabsorption syndrome and underlying military TB [22]. Multiple small peripheral stromal melts were present in various stages of healing associated with nodular scleritis. Axillary lymphadenitis on biopsy was suggestive of caseating granulomas, and hence a diagnosis of TB was made. Oral ATT along with the treatment of malabsorption led to a quick favorable response in the ocular condition with resolution of symptoms. Sclerokeratitis is another manifestation of ocular TB with involvement of both cornea and adjacent sclera. Focal necrotizing scleritis may be present in isolation [23]. Diffuse involvement of sclera is rare. Cases of posterior scleritis [24] and scleral perforation have also been noted.

Treatment

As mentioned, conjunctival and corneal TB are manifestations of hypersensitivity reactions to tubercular proteins. Thus, the diagnosis is based on presumptive grounds. Oral antitubercular treatment (ATT) has been found to play an important role in the resolution of symptoms [25]. Currently, WHO recommends the treatment of ocular TB on the similar lines as active pulmonary and extrapulmonary TB. A minimum of 6 months of therapy is advised with an intensive phase of 2 months consisting of daily administration of isoniazid, rifampicin, pyrazinamide, and ethambutol as per body weight. This is followed by 4 months of continuation-phase treatment of isoniazid and rifampicin. Till date, there have been no published randomized control clinical trials to optimize the

therapy for ocular TB. The response to therapy can usually be monitored by clinical examination and resolution of inflammation.

Conjunctival and corneal TB are rare presentations of ocular TB with often missed or delayed diagnosis. A high index of suspicion with systemic evaluation can help us in early diagnosis thereby reducing ocular morbidity.

Compliance with Ethical Requirements Namrata Sharma and Neelima Aron declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

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Tubercular Scleritis

13

Mi Fang Helen, Rupesh Agrawal, Vishali Gupta, and Carlos Pavesio

Introduction

Scleritis is a severe painful inflammatory process involving the outer coat (sclera) of the eye, resulting in disabling ocular pain and a wide range of symptoms, depending on the location and intensity of the inflammatory process.

Scleritis may be harbinger of other systemic diseases, and it is important to exclude multisystem disease. Different etiologies of scleritis exist, varying from idiopathic to autoimmune to infectious. Infectious scleritis is a rare but important cause of scleritis, occurring in around 5–10% of patients [1]. Differentiation between noninfectious and infectious etiologies is crucial, as treatment regimens differ greatly.

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A vast variety of microorganisms can infect the sclera. Men and women appear to be equally affected. Infectious scleritis can also occur after ocular surgery, especially in pterygium surgery where mitomycin C is utilized, scleral buckle surgery, and pars plana vitrectomy [2]. Trauma should also be excluded, as infectious scleritis can be a result of penetrating injury [3]. Table 13.1 shows a non-exhaustive list of organisms that can be causative agents of scleritis.

Tubercular scleritis is a rare and unique form of extrapulmonary tuberculosis. The causative organism is the *Mycobacterium tuberculosis*. Infrequently, it occurs in the absence of active pulmonary tuberculosis [4]. Although more common in the immunocompromised, it can also be seen in immunocompetent patients. Both anterior scleritis and posterior scleritis associated with tuberculosis (TB) have been reported [5].

The *Mycobacterium* itself can cause an immune-mediated inflammatory microangiopathy and may indirectly lead to an inflammatory scleritis [1]. As such, tuberculous scleritis may result from either a direct invasion of the sclera by the bacterium or an immune reaction to circulating antigens [6].

Mycobacterial infections other than tuberculosis (MOTT) have a less common causative organism in immunocompetent patients, but can present in a disseminated form in immunocompromised patients. *M. chelonae* is one of the types of these MOTT species shown to cause scleritis [7].

A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_13

Table 13.1 Common causative organisms of scleritis

Bacterial
Pseudomonas aeruginosa
Actinomyces species
Nocardia species
Mycobacterium species
Fungal
Fusarium species
Aspergillus species
Viral
Herpes simplex virus
Varicella-zoster virus

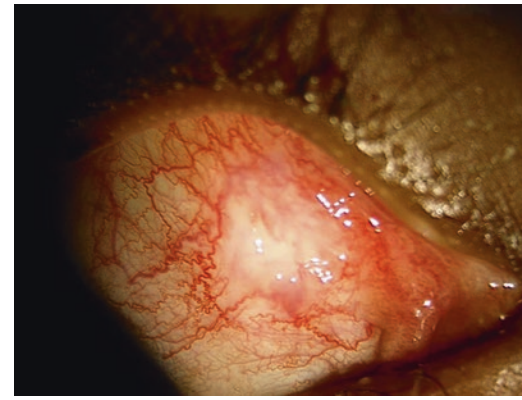

Fig. 13.1 Infectious scleral abscess with inflamed sclera positive for tubercular bacilli on biopsy

Clinical Features

The commonest presentation of tubercular scleritis is similar to that of other infectious scleritis, with pain, eye redness, and blurring of vision. Patients can complain of severe boring ocular pain, which may be referred to other regions of the head or face. The globe is often tender to touch.

As with other types of scleritis, the sclera may assume a violaceous hue, better seen in natural ambient sunlight. Inflamed episcleral vessels can have a crisscross pattern (in patients with episcleritis). Clinically, the blood vessels are adherent to the sclera and will not be able to be moved with an applicator. Scleral edema can be noted by slit lamp examination. Edges of the scleritis can be more yellowish white as compared to the noninfectious forms, which will be whitish and more avascular (Fig. 13.1).

Tubercular scleritis is usually anterior, with painful nodular lesions with localized slight elevation of the sclera. The lesions can be nonnecrotizing or necrotizing (which can result in scleromalacia). The sclera usually appears necrotic, thin, and avascular. Inflammation may be seen at the edges. Scleral perforation can occur if disease is severe. Diffuse scleritis is less common than nodular scleritis in patients with TB [8]. Posterior scleritis resulting from TB is extremely rare, and it may present as an isolated posterior scleritis or posterior scleral tuberculoma [5, 9]. Unilateral optic disc swelling may present secondary to tubercular posterior scleritis [10]. It has also been reported that tubercular scleritis can present with subretinal abscess [11].

Scleritis in TB may be isolated (Fig. 13.1) or can occur together with corneal or iris involvement. This will result in sclerokeratitis and uveitis, respectively. Anterior granulomatous uveitis can occur together with scleritis, and posterior synechiae are often seen [12]. Tuberculous sclerouveitis can rarely masquerade as an ocular tumor and can be associated with necrotizing scleritis [13].

Investigations and Work-Up

Standard work-up of scleritis should be performed, with a complete physical examination, paying particular attention to the respiratory system, skin, and musculoskeletal system.

Other etiologies of scleritis should also be considered. Baseline laboratory investigations should include a complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), treponemal serology, tuberculin skin test (refer below), and immune markers such as rheumatoid factor, antinuclear antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA).

Further investigation and work-up should depend on demographics of the patient. If the patient resides in a non-endemic country where the incidence of TB is low, laboratory

investigations should be done on a case-by-case basis. A failure of the inflammation to improve on the corticosteroid therapy (topical or systemic) should raise the index of suspicion for infectious scleritis, and tubercular scleritis should be a differential. However, in a TB-endemic country, index of suspicion should be much higher, and laboratory investigations for TB should be considered much earlier on [14].

Tuberculin skin test can be done using the *Mantoux* method, which is an intradermal injection of 0.1 mL (two tuberculin units) purified protein derivative and the resultant induration after 72 h measured by an independent observer [15]. Interferon-gamma release assays (IRGAs) and polymerase chain reaction (PCR) for detection of TB DNA can also be done if clinically indicated. Chest radiograph should also be obtained to look for any pulmonary manifestation of TB or latent TB.

Cultures of the involved area, including the base and edge of the lesion, can be obtained if there is an indication. Clinicians can consider a lamellar scleral biopsy if clinical suspicion is high or the scleritis worsens with anti-inflammation therapy alone [16].

Treatment

Usual scleritis management with nonsteroidal anti-inflammatory drugs (NSAIDs) should still be commenced, if there are no contraindications.

Antituberculosis therapy (ATT) should be initiated upon diagnosis of tubercular scleritis. Typically, a four-drug regimen is started, namely, rifampicin, isoniazid, pyrazinamide, and either ethambutol or streptomycin. The exact treatment regimen and side effects should be comanaged with a physician.

Treatment with ATT should be continued for 4 weeks to 6 months after full resolution of clinical signs (Fig. 13.2). However, the exact time of treatment has not been established [7]. In the event of coexisting systemic manifestations of TB, the treatment duration and regime may differ based on the extent of the disease.

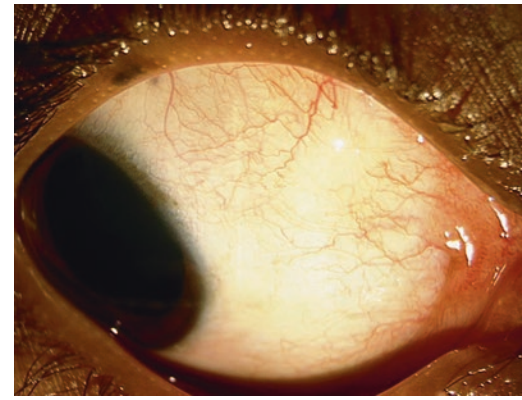

Fig. 13.2 Resolution of scleral abscess and inflammatory signs post antitubercular therapy

The organisms may be difficult to eradicate completely, and prolonged course of treatment may be necessary. MOTT organisms are known to be resistant to typical antituberculous drugs, and close clinical monitoring is required.

In the event that medical therapy alone is not adequate, surgical debridement may be required [17]. Cryotherapy and lamellar or penetrating corneoscleral grafts in addition to intensive medical therapy may be required in tubercular scleritis patients [17, 18]. In the event of severe thinning from the disease or post-debridement, scleral patch grafting may be required [1, 19].

Prevention of postoperative infective scleritis is also important, and avoidance of excessive cautery during surgical procedures may spare the episcleral blood flow, hence allowing better wound healing and less susceptibility to infection [20].

Corticosteroids should be given cautiously, and close monitoring is required in view of the infectious etiology. Topical corticosteroids are usually initiated and should be given concurrently with ATT.

Symptomatic management with analgesics for pain control can also be considered.

Complications of Disease

Inadequate treatment of tubercular scleritis can result in disease recurrence. Extension into the cornea results in sclerokeratitis. Corneal changes

include segmental anesthesia, acute stromal infiltrates, sclerosing keratitis, limbal guttering, and keratolysis.

Glaucoma can also occur secondary to tubercular scleritis, especially in cases with limbitis. Posterior scleritis can be complicated with exudative retinal detachment, optic nerve head swelling, and macular edema. Cataracts can also occur.

Clinicians should also monitor closely for globe perforation in view of the scleral wall thinning, although the incidence is rare. Intraocular extension can result in endophthalmitis [21].

Prognosis of Disease

Poor prognostic factors include a presenting vision worse than 20/200, concomitant keratitis, and concomitant endophthalmitis [17]. Studies have shown that the final visual outcome does not correlate significantly with time from presentation to diagnosis. There is also no significant correlation between visual outcome and any specific inciting factor (such as trauma or surgery) [17].

Upon resolution of the scleritis, patients will still require monitoring to watch for recurrence or possible reactivation of latent TB.

Conclusion

Tubercular scleritis can present with a variety of clinical features. Tuberculosis must be considered as one of the differentials in the evaluation of a patient presenting with scleritis, especially if not responding well to usual corticosteroid therapy. A combination of antituberculosis and corticosteroid therapy is usually given, with close monitoring. Treatment should be tailored to the patient and monitored clinically for resolution or recurrence.

Compliance with Ethical Requirements Authors declare that we have no conflict of interest. No animal or human studies were carried out by the authors for this article.

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Orbital and Periorbital Tuberculosis

14

Neelam Pushker and Amar Pujari

Introduction

Extrapulmonary form of tuberculosis is seen in 15–25% of all cases of tuberculosis [1, 2]. Lymph node tuberculosis is the commonest form of extrapulmonary tuberculosis. Ocular tuberculosis has been described in 2–30% of extrapulmonary cases, choroid involvement being the commonest and orbital/periorbital tuberculosis constituting a very small fraction of these cases [2]. Systemic association may be found in 12–75% of patients with extrapulmonary tuberculosis.

Tuberculosis of the orbital and periorbital structures is an extrapulmonary form of tuberculosis with varied presentations. The disease is usually seen in children and young adults and is slow growing, chronic, and unilateral. The duration of symptoms might range from few weeks to years [3]. In most of the cases, the infection is acquired by hematogenous or lymphatic spread or rarely by direct inoculation as in the infection of the skin or paranasal sinuses. Common forms of periorbital and orbital tuberculosis are:

1. Orbital tuberculosis
2. Lacrimal gland and sac tuberculosis
3. Eyelid tuberculosis
4. Periorbital cutaneous tuberculosis
5. Spread from paranasal sinuses
6. Orbital tuberculosis in immunocompromised patients and coexisting with fungal infections

Orbital Tuberculosis

Orbital tuberculosis is an uncommon form of extrapulmonary tuberculosis. These bacilli gain access to the orbital cavity through hematogenous route or direct spread from paranasal sinuses. In a major review, authors described five forms of orbital tuberculosis: classical periostitis; orbital soft tissue tuberculoma or cold abscess, with/ or without bone involvement; spread from paranasal sinuses; and tubercular dacryoadenitis. The commonest form of presentation was classical periostitis followed by orbital tuberculoma or abscess with or without bone involvement. In their review, authors also found that more than 50% of cases of orbital tuberculosis were reported from India, mostly in males with mean age of 19 years (range, 2–76 years); 39% cases had associated systemic tuberculosis [3]. In a

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A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9_14

case series of nine cases, found over a period of 10 years, three cases were of cutaneous tuberculosis, two cases had dacryocystitis, and four cases had diffuse orbital tuberculosis. All these patients were from either Asia or African subcontinent with three patients having previous history of tuberculosis [4]. In another series of six patients from South India, the presentations observed were tubercular dacryoadenitis in two cases, classical periostitis in two cases, orbital tuberculosis with bone involvement in one case, and ocular adnexal tuberculosis in one case; systemic involvement was present in only one case [5]. In a different series of 14 patients, 5 of the cases had proptosis and 9 had a discharging sinus. Primary focus of infection in lungs was found in eight cases, and all of them had erosion of the orbital bones [6].

The classical periostitis presents with chronic discharging sinus which might be recurrent usually along the orbital rim [3]. The surrounding skin usually gets pigmented, swollen, or scarred in chronic cases. The discharge varies from serosanguinous to purulent. Associated severe ectropion may be found because of the tethering of tissues to underlying bone. Imaging shows irregularities, sclerosis, or destruction of orbital bone with minimal soft tissue inflammation.

In patients with orbital tuberculoma or cold abscess, proptosis is a predominant clinical feature with edema, induration of soft tissues which is felt as a mass, with or without cold abscess. Associated ophthalmoplegia, diplopia, and reduced vision may be seen. Destruction of bone due to osteomyelitis can be picked up on imaging. The infection of zygomatic bone is seen commonly because of its high vascularity. Orbital abscess/tuberculoma might extend into adjacent spaces such as the extradural space/brain, sinuses, or temporal fossa depending on the location of infection. Delay in diagnosis or an initial manifestation of tuberculosis may also present as orbital apex syndrome. In a retrospective study, seven patients with orbital apex syndrome were attributable to tuberculosis [7]. Tuberculosis can also rarely present as sclerosing lesion with enophthalmos [8].

High index of suspicion should be kept in all cases of inflammatory mass/abscess, granulomatous or non-granulomatous, which are chronic, recurrent with cold signs and symptoms, and not responding to conventional treatment. Rarely orbital tuberculosis can present as enophthalmos [8] or masquerade pseudotumor [9] or optic nerve glioma [10].

Orbital tuberculosis affecting pediatric population is not that uncommon (Figs. 14.1a, b, 14.2a, and 14.3). However, only few studies are available on orbital tuberculosis in the pediatric population. In a study from our center, authors reported eight cases of tuberculosis in the age range of 3–16 years (median 10 years). The clinical presentation was similar to adult population as four cases had classical periostitis, three cases with discharging sinus in upper lid, three with a cystic mass, and two with lid necrosis. Underlying bony changes were found in five patients [11]. In another report from India, authors reported seven children between the ages of 6 months and 9 years who presented with preseptal cellulitis/abscess. Orbital tuberculosis may also present as eyelid swelling/abscess. As proper imaging was not done in most of these cases, it is difficult to comment on the posterior extent of the involvement. In this report, X-ray orbit did not reveal any bony erosion. Evidence of an underlying active or healed systemic focus of tuberculosis which included the bone, lungs, or lymph node was present in all the cases. Clinically, systemic examination was normal in all these patients except one, and the diagnosis was established on investigations [12]. Associated intracranial involvement has also been reported in another report [13].

Eyelid Tuberculosis

Primary eyelid involvement may present as redness, swollen eyelid, chronic conjunctivitis, chalazion, preseptal cellulitis, tarsal necrosis, or a surgical complication following blepharoplasty surgery [14–16]. It can also be the initial presentation of orbital, adnexal, or cutaneous tuberculosis [17]. In a case report, authors

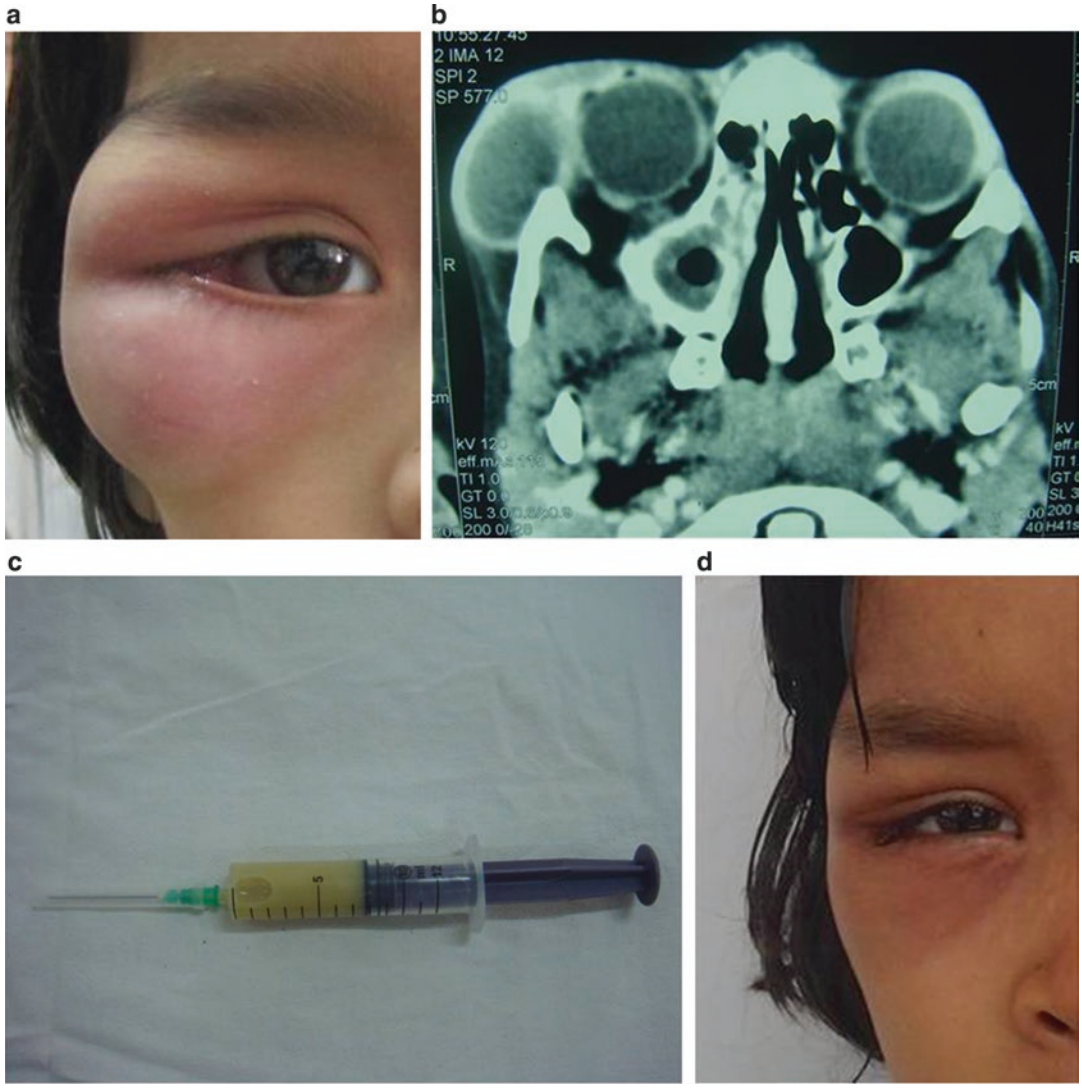

Fig. 14.1 (**a**) Clinical picture of a patient (case 1) with a swelling along the right orbital rim and erythema of the skin. (**b**) CECT orbits (axial cut) of case 1, suggestive of a well-defined cystic lesion with uniform peripheral enhancement along the lateral orbital rim with no bony changes. (**c**) Picture shows (case 1) pus aspirate from the cystic lesion. (**d**) Clinical picture of case 1 shows partial resolution of the lesion at 2 months of follow-up

reported a patient of tuberculosis presenting simultaneously with eyelid swelling and thyroid enlargement [18].

Lacrimal Gland and Sac Tuberculosis

Involvement of the lacrimal gland is rare and lacrimal sac is even rarer. The former was first described by Abadie (1881), and since then many cases have been reported [19]. Over a period of 20 years, 14 cases of tuberculosis involving the orbit and lacrimal gland have been described in a case series [20]. Patients present with abaxial proptosis with a mass in the region of the lacrimal gland, ptosis, and limitation of ocular movements. Lacrimal gland involvement usually occurs in association with periostitis/osteomyelitis which usually affects the lateral orbital wall or with involvement of the orbital soft tissue/abscess [21, 22]. Isolated lacrimal gland involvement has

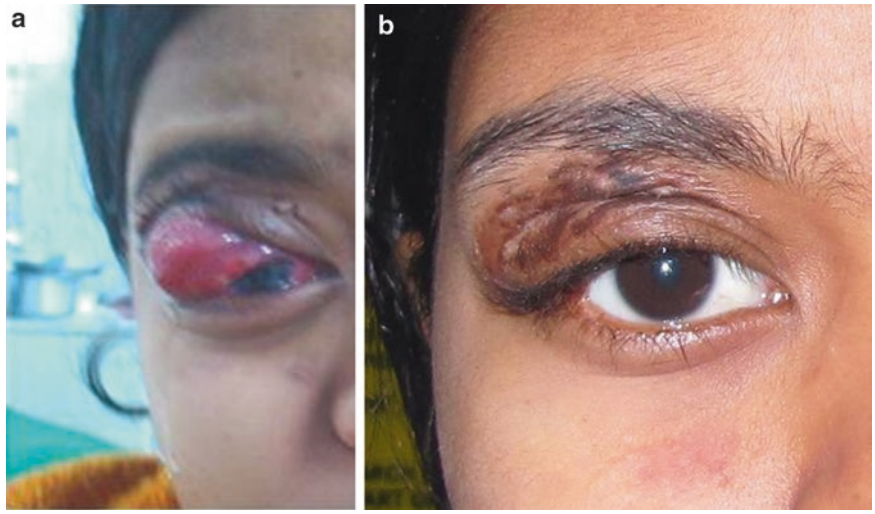

Fig. 14.2 (**a**) Clinical picture of a patient (case 2) shows severe ectropion of the upper eyelid with discharging sinus and inflammatory signs. (**b**) Clinical picture of case 2, posttreatment, correction of right upper eyelid ectropion using skin grafting procedure

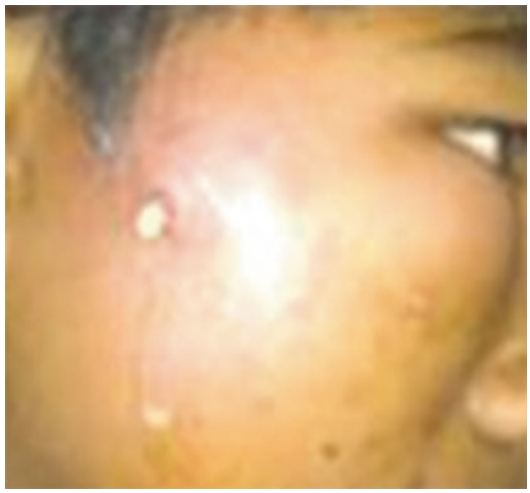

Fig. 14.3 Clinical picture of a patient with right discharging sinus with periorbital swelling due to zygomatic bone tuberculosis

also been reported. According to the author, the isolated form is usually of the sclerotic type and rarely of the caseous type [19, 20].

Tubercular infection of the lacrimal drainage system (sac and nasolacrimal duct) is very rare [4, 23]. The sac infection usually occurs secondary to nasolacrimal duct infection [24–26]. The latter commonly presents with epiphora because of which the diagnosis might get delayed resulting in spread of infection to adjacent structures like sac, conjunctiva, nasal cavity, sinuses with or without its destruction, or overlying skin infection (lupus vulgaris) [23, 27]. Rarely, extensive involvement of the conjunctiva, skin, eyelid, and cheek heals with significant facial deformity and ocular surface damage. Systemic involvement has also been reported [28].

Spread from Paranasal Sinuses

The maxillary sinus is most commonly involved. Patients generally present with proptosis and/or discharging fistula in the sinus region, palpable mass, epistaxis, etc [3].

Periorbital Cutaneous Tuberculosis

An estimated 1–2% of all tuberculosis cases have skin involvement. The lesion typically occurs around the nose followed by the arms, legs, and trunk. The periorbital skin lesions can involve the eyelid skin and conjunctiva and may also present with cicatricial ectropion or bony involvement. Lupus vulgaris is the commonest form of cutaneous tuberculosis seen in India, followed by tuberculosis verrucosa cutis and scrofuloderma.

The former is characterized by slowly enlarging plaque with slightly elevated borders and central atrophy.

Other presentations are preseptal cellulitis, ulcerated skin nodule, erythematous plaque, or pigmented nodular lesion mimicking basal cell carcinoma [17, 28, 29]. Alternate differential diagnoses for skin tuberculosis are mucocutaneous leishmaniasis, pyogenic granuloma, fungal infection, treponematosis of the skin, sarcoidosis, neoplastic ulcer, Wegener's granulomatosis, and midline granuloma [28]. Because it masquerades many skin lesions, the diagnosis may not be established until the disease is biopsied or the patient presents with a full-blown picture.

Orbital Tuberculosis in Immunocompromised Patients and Coexisting Fungal Infections

There is an increase in prevalence of pulmonary as well as extrapulmonary tuberculosis due to an epidemic of human immunodeficiency virus (HIV) infection and the greater use of different types of immunosuppressive therapies [2, 30]. In human immunodeficiency virus (HIV)-positive patients, extrapulmonary tuberculosis accounts for up to 53–62% cases of tuberculosis [2]. These patients are at markedly increased risk for primary or reactivation tuberculosis and for second episode of tuberculosis from exogenous reinfection. Among adult patients with HIV, the incidence of ocular involvement is high, varying from 50% to 90%. Tuberculosis of orbit in such patients is extremely rare. Authors reported a case with proptosis because of tuberculosis as the initial manifestation in a HIV-positive patient [31].

Common fungal infections are zygomycetes which have two orders of organisms that infect humans, *Mucorales* and *Entomophthorales*. *Mucorales* include *Rhizopusa* and *Mucor*, which are angioinvasive and lead to acute infection in immunocompromised patients, while *Entomophthorales* include *Basidiobolus ranarum*, *Conidiobolus incongruus*, and *Conidiobolus coronatus*; these are not angioinvasive but invade subcutaneous tissue and cause chronic infection in immunocompetent patients. Presence of secondary infection in a tubercular lesion is seen in the pulmonary site, but its coexistence with fungal lesion is a rare entity. Orbital tuberculosis with coexisting fungal infection is extremely rare and leads to a diagnostic dilemma. Such infections are seen in immunocompromised patients such as diabetics, blood malignancies, neutropenia, AIDS, malnutrition, or anemic patients. A case of coinfection in the skull base and orbit by *Mycobacterium tuberculosis* and *Aspergillus flavus*, in a poorly controlled diabetes mellitus patient, was reported for the first time in 2014 [32]. In another case study, authors reported a case of disseminated tuberculosis with *Conidiobolus coronatus* infection presenting as orbital cellulitis in an adolescent [33].

Investigations

Patients presenting with orbital and periorbital manifestations of tuberculosis may have symptoms of active tuberculosis elsewhere. Detailed local and systemic examination is a must for the diagnosis in all suspicious/atypical cases as well as cases not responding to conventional treatment. CT scan of the head and orbit is done to know the extent of lesion, bony, and intracranial involvement. Blood examination for raised ESR values and lymphocytosis should be done. Mantoux test helps to know the hypersensitivity to tubercular protein and is considered to be significantly raised if induration is more than 15 mm and borderline if it is between 10 and 15 mm. However, Mantoux test has a limited value in adults in endemic countries like India. In a study, a positive Mantoux test was found in 67–90% of healthy individuals [34]. However, it may be of use in children aged 5 years and below.

As orbital disease is essentially a paucibacillary condition, so in all cases, biopsy specimen for histopathological and/or microbiological examination is mandatory. Open or fine needle aspiration biopsy is done in most of the cases (Fig. 14.1c). Demonstration of tubercle bacilli on Ziehl-Neelsen staining is the most rapid way of detection of infection. However, according to a review, bacilli were seen only in 18 out of 59

cases of orbital tuberculosis [3]. Histopathologically, it is a granulomatous inflammation (epithelioid granulomas with Langerhans giant cells) with caseation necrosis. Immunohistochemical staining using mycobacterial antigen MPT64 may provide supportive evidence. Polymerase chain reaction is a rapid, nucleic acid amplification technique for the diagnosis. It has high specificity (>90%) for pulmonary and extrapulmonary disease with variable sensitivity [35, 36]. Culture of mycobacteria is considered the gold standard for confirmation of infection. In paucibacillary form of tuberculosis, such as orbital tuberculosis, limited studies are available on culture sensitivity and specificity, but according to a major review on orbital tuberculosis, 19 out of 79 cases yielded a positive culture [3]. In pulmonary tuberculosis, the sensitivity of culture technique is 80–85% with a specificity of 98% [35]. Chest X-ray and/or chest CT scan in many cases shows features of active or healed tubercular lesions. In a review on orbital tuberculosis, chest radiographs were consistent with pulmonary disease in 53% cases [3]. Sputum examination is required in cases with clinical suspicion of chest infection. Immunoglobulin release assay (IGRA), fluorescence quantitation PCR (FQ-PCR), and colloidal gold assay are the newer tests which help in the confirmation of diagnosis.

Generally more than one test is necessary for the confirmation of diagnosis. In a case series reported from our center, drainage and curettage was done for five patients, needle drainage of fluid was done in one patient, and in two patients local debridement was done. Polymerase chain reaction for tuberculosis was positive in four cases, and acid-fast bacilli (AFB) were isolated on culture in three cases. On histopathology, six cases had granulomatous inflammation with caseating necrosis in one, though AFB could not be found [11]. In another report from our country, in all seven patients with tubercular preseptal cellulitis, an evidence of underlying active and healed focus was present. In addition to this, a strongly positive Mantoux test with necrosis reaction in one case, acid-fast bacilli from the discharging pus in one case, positive family history in one case, and smear positive for AFB in one case helped in establishing the diagnosis [12]. In a separate case series of six patients, all patients had chronic granulomatous inflammation with caseation necrosis, polymerase chain reaction was positive in two patients, acid-fast bacilli were found in two patients, culture was negative in all, and chest radiograph was normal in all the patients [5].

Definitive diagnosis of tuberculosis by demonstration of bacilli and/or positive culture is not possible in all the cases. Histopathology, PCR, and ancillary investigations along with positive family history, evidence of systemic focus, and/or strong clinico-radiological features help in the diagnosis. Also response to treatment is often taken as confirmation of etiology in patients with presumptive diagnosis of tuberculosis.

Treatment

In orbital and periorbital tuberculosis, antitubercular drugs are the mainstay of treatment. Tissue biopsy and/or drainage of pus is recommended for the diagnosis. Extensive debridement is usually not required. In the absence of a definitive evidence, a presumptive diagnosis is made based on strong clinical suspicion and/or histopathology. For new cases, the treatment consists of an intensive phase which consists of 2 months of isoniazid, rifampicin, pyrazinamide, and rifampicin (HRZE) followed by a continuation phase in which only pyrazinamide is stopped and the rest of the three drugs (HRE) are given for 4 months. The continuation phase may be extended in certain forms of tuberculosis like CNS, skeletal, disseminated, etc. During treatment, associated ocular problems need to be tackled. In some patients with corneal exposure, a tarsorrhaphy should be done along with lubricants. A definitive procedure for the deformity can be done after complete healing.

Prompt diagnosis and complete treatment course lead to a favorable response in most of the cases. Tuberculosis being a destructive disease results in facial deformity and ocular morbidity. Depending on the location of infection, patient can present with cicatricial ectropion and retraction

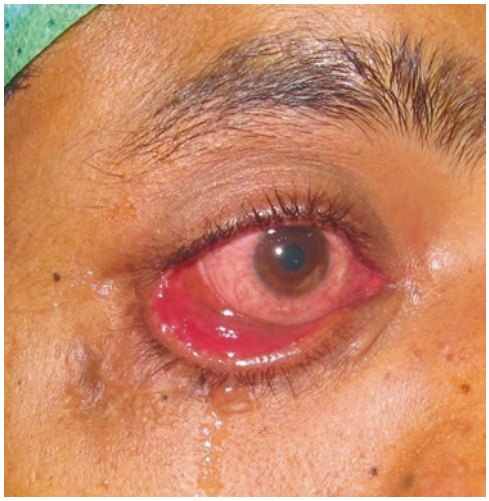

Fig. 14.4 Clinical picture of a patient with right lower eyelid cicatricial ectropion as a sequel of zygomatic bone tuberculosis

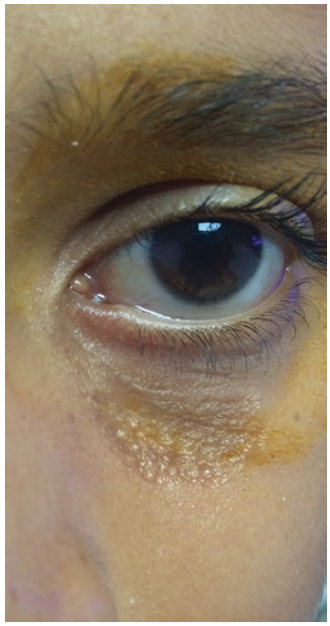

Fig. 14.5 Clinical picture of a patient with left-side mild cicatricial retraction of the lower eyelid with scarring of skin as a sequel of periorbital cutaneous tuberculosis

and corneal opacity because of exposure and/or infection, residual proptosis, pigmentation or atrophy of the skin, lacrimal drainage obstruction, loss of eyeball, etc. (Figs. 14.1d, 14.2b, 14.4, and 14.5) [3, 11]. Depending on the disfigurement, some of these problems can be addressed.

As a paucibacillary form of tuberculosis, orbital tuberculosis is not usually infectious unless associated with smear-positive pulmonary tuberculosis. Mortality is extremely rare. According to a major review, only 2 out of 79 cases died, both due to the spread of infection to the brain [3].

Differential Diagnosis

Heterogeneous group of diseases of various causes can present with inflammatory, ill-defined mass lesions in the orbit. Some granulomatous diseases of the orbit are Wegener's granulomatosis, sarcoidosis, foreign body granuloma, ruptured dermoid cyst, etc. Ruptured dermoid cyst is generally painful with recurrent episodes of inflammation because of leakage of contents. Imaging is usually helpful as it can detect the presence of fat which is suggestive of a dermoid. Wegener's granulomatosis is described as limited or generalized (involving kidney and/or lungs). The orbital disease is painful and infiltrative and usually involves muscles, sclera, coats, and sinuses. Sarcoidosis of the orbit usually involves lacrimal glands and presents as subacute or chronic, painless mass effect lesion. Foreign body granuloma usually presents as recurrent orbital inflammation with or without fistula formation. Presence of trauma or surgery is present in these cases with retained wooden foreign body, bone wax, silicone, etc., reported [37].

To conclude, orbital and periorbital tuberculosis is difficult to diagnose because of varied clinical manifestations which lead to a delay in diagnosis. Definitive diagnosis is not possible in all cases. In certain cases, based on a strong clinical suspicion along with supportive investigations, a presumptive diagnosis is made. The use of a complete course of ATT is of paramount importance for the disease management. The patient and their family members need to be counseled about the associated public health issue of tuberculosis.

Compliance with Ethical Requirements Neelam Pushker and Amar Pujari declare that they have no conflict of interest. No human or animal studies were carried out by the authors for this chapter.

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A. Kumar et al. (eds.), *Ocular Tuberculosis*, Essentials in Ophthalmology,
DOI 10.1007/978-3-319-57520-9