**Clinical Cases in Dermatology**
*Series Editor:* Robert A. Norman

Jashin J. Wu *Editor*

# Clinical Cases in Psoriasis

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# Clinical Cases in Dermatology

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# Clinical Cases in Psoriasis

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# Contents

# Chapter 1
# 12-Year-Old with Scaly, Itchy Scalp

**Daniel J. No, Mina Amin, and Jashin J. Wu**

A 12-year-old male presents with a 2-month history of a pruritic and scaly scalp. The patient was referred to dermatology by his pediatrician after failed empiric treatment with griseofulvin for presumptive tinea capitis. Since the initial examination performed by his pediatrician, the patient also developed erythematous, pruritic, scaly papules and plaques on bilateral arms, legs, and postauricular folds. His pediatrician prescribed low- to mid-potency topical corticosteroids, and he experienced mild improvement. Upon further questioning, the patient admitted to frequent self-scratching with subsequent development of lesions in the areas of irritation.

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He denied joint stiffness or pain. He denied a family history of psoriasis. With the exception of obesity and impaired fasting glucose, the patient was otherwise healthy and denied recent illness, sore throat, or sick contacts.

On physical examination, the scalp showed multiple areas of erythematous papules with overlying silvery scale coalescing to plaques on the right parietal-temporal scalp. The lesion spanned approximately 5 inches. No alopecia was appreciated. Bilateral posterior auricular folds had approximately 1-inch area of erythema with a thick white scale. The back and bilateral lower extremities had multiple areas of indurated pink plaques with loose micaceous scale. The left inguinal crease had a well-defined bright red erythematous patch without an overlying scale. Nail pitting was evident on the right second digit nail plate. There was no evidence of dactylitis or joint inflammation. Approximately 4% of the body surface area was affected.

Based on the clinical case description, what is the most likely diagnosis?

1. Tinea capitis
2. Atopic dermatitis
3. Plaque psoriasis
4. Seborrheic dermatitis
5. Contact dermatitis

## Diagnosis

Plaque psoriasis

## Discussion

Pediatric psoriasis accounts for about one-third of all cases of psoriasis (Tollefson et al. 2010). The clinical presentation and course vary, but the most frequently observed variant is plaque-type psoriasis, followed by guttate psoriasis. Erythrodermic psoriasis and pustular psoriasis are rare but

life-threatening forms of psoriasis that have been observed in the pediatric population. Interestingly, the distribution of lesions tends to differ in comparison to psoriasis in adulthood. Most children present with lesions localized to the scalp, face, extensor regions, postauricular area, and intertriginous areas. Additionally, there appears to be a stronger genetic component to pediatric psoriasis in comparison to adult-onset psoriasis (Raychaudhuri and Gross 2000).

The increased prevalence of childhood obesity is of particular concern because studies reveal that children affected by psoriasis tend to have excess adiposity. In fact, data suggests a stronger correlation between obesity and psoriasis with the pediatric population in comparison to adults affected by psoriasis (Paller et al. 2013). The increased body mass indices, waist circumference percentiles, and waist to height ratios place these children at an increased risk of developing conditions such as hypertension, metabolic syndrome, hyperlipidemia, and diabetes mellitus. This underscores the importance of early diagnosis and intervention with a particular focus on healthy lifestyle modification.

## Treatment

Topical medications remain the mainstay of therapy in the management of psoriasis in the pediatric population. Corticosteroids are the most frequently used agents and are considered the first-line treatment. Mid-potency topical corticosteroids (class 2–4) are reserved for the trunk, scalp, and extremities. Their use should be avoided in sensitive areas such as the face and intertriginous areas. Such areas are at a higher risk of skin atrophy, erythema, depigmentation, and irritation. Therefore, the use of low-potency topical corticosteroids (class 5–7) is recommended for sensitive sites. Recalcitrant lesions on the trunk, scalp, and extremities may have an improved response with high-potency corticosteroids. However, high-potency corticosteroids should be used with great caution, especially when a large body surface area

is affected. Continuous use of high-potency corticosteroids should not exceed 2 weeks. Treatment can resume after a steroid-free period of at least 2 weeks. Of note, percutaneous absorption is also enhanced in children, which puts them at a higher risk of developing cutaneous and systemic side effects (Silverberg 2010). As in the case for our patient, the vehicle is of particular importance when treating scalp psoriasis. Alcohol based solutions, gels, and foams are cosmetically more elegant for patients with fine hair. Ointments may be more appropriate for patients with oily hairstyles.

Topical vitamin D analogs, calcipotriene and calcitriol, are also considered first-line medications in the management of psoriatic lesions in children. They can be used as monotherapy or in conjunction with topical steroids to minimize extended steroid exposure. Additionally, they serve as an excellent alternative to topical steroids for sensitive regions such as the face and intertriginous areas. Calcipotriene and calcitriol have similar efficacy; however, when applied to sensitive areas of the skin, the latter appears to be less irritating and better tolerated (Ortonne et al. 2010). Due to their slow onset of action, they require about 8 weeks of application, twice daily for maximal effect.

Tacrolimus ointment is an effective and safe therapeutic option for short-term treatment of pediatric psoriasis affecting the face and intertriginous sites (Brune et al. 2007). However, tacrolimus may not be as effective on areas where thicker plaques are found, such as on the trunk or extremities. Twice daily application has shown modest clearance after 2–30 days of treatment (de Jager et al. 2010). Ideally, treat with a topical corticosteroid twice daily for 2 weeks, followed by a topical vitamin D analog or tacrolimus ointment twice daily for 2 weeks, and then repeat this cycle as needed.

Treatment of pediatric patients with biologic medications is reserved for moderate-to-severe and recalcitrant cases that are widespread (greater than 10% BSA). Currently, no biologic agents are FDA approved for the treatment of psoriasis in pediatric patients, and treatment is commonly based on clinical trials, case reports, guidelines for adult psoriasis, and anecdotal experiences. However, etanercept was demonstrated

to be highly efficacious and safe for use in pediatric patients in a randomized control study (Paller et al. 2008). The majority of reported adverse events were upper respiratory tract infections, headache, and nasopharyngitis. There were no reports of opportunistic infections, demyelinating diseases, malignancies, or deaths. Additionally, the conclusion of the 5-year open-label extension study confirmed the high safety profile and long-term efficacy in the management of childhood plaque psoriasis (Paller et al. 2016).

Ustekinumab is another biologic agent used for the treatment of moderate-to-severe plaque psoriasis. The CADMUS study exhibited the high efficacy and safety profile of ustekinumab for use in adolescent patients (Landells et al. 2015). As expected, the most common adverse effect observed was nasopharyngitis. There were no reports of opportunistic infections, malignancies, anaphylactic reactions, or deaths related to treatment.

Our patient was treated with fluocinonide ointment applied twice daily to lesions on the legs and back for 2 weeks, followed by a 2-week break, and then repeated as needed. Fluocinonide gel was applied twice daily to the scalp and posterior auricular folds for 2 weeks, followed by a 2-week break, and then repeated as needed. Desonide topical cream was applied twice daily for the inguinal crease for 2 weeks, followed by a 2-week break, and then repeated as needed.

## Key Points

- Pediatric psoriasis plaques tend to be localized to the scalp, face, postauricular area, extensor regions, and intertriginous areas.
- Topical medications remain the mainstay of management. Utilize low-potency topical steroids, vitamin D analogs, and calcineurin inhibitors for sensitive areas of skin.
- Although not FDA approved yet, clinical trials demonstrate that biologics are efficacious and safe for severe pediatric psoriasis.

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# Chapter 2
# A 54-Year-Old with Diffuse Red, Scaly Spots on Entire Body

**Daniel J. No, Mina Amin, and Jashin J. Wu**

A 54-year-old man presented with a 7-year history of poorly controlled erythematous, scaly papules, and plaques on his entire body. The patient came seeking an alternative treatment after multiple years of topical corticosteroid use with suboptimal results and difficulty applying the ointment on his entire body. The patient has a family history of psoriasis. He did not complain of joint tenderness, swelling, or stiffness.

On physical examination, small, teardrop-like and round, erythematous papules and plaques with a thin overlying fine scale were found diffusely scattered on the face, neck, chest, abdomen, back, and upper and lower extremities (Fig. 2.1). The affected body surface area was 15%.

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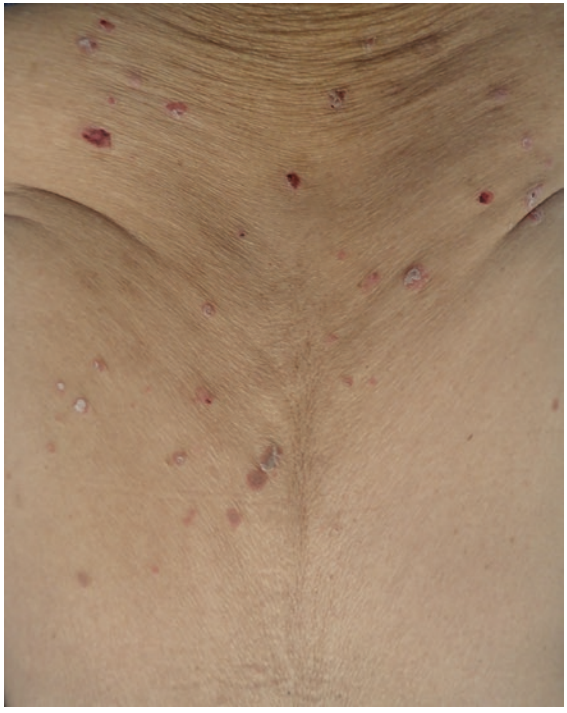

FIGURE 2.1 Small, discrete, well-demarcated papules with overlying scale

Based on the clinical case description, what is the most likely diagnosis?

1. Pityriasis rosea
2. Pemphigus foliaceus
3. Guttate psoriasis
4. Small plaque parapsoriasis
5. Tinea corporis

## Diagnosis

Guttate psoriasis

## Discussion

Guttate psoriasis most commonly presents in children and young adults, classically appearing 2–3 weeks after a group A streptococcal pharyngitis infection (Menter et al. 2009). Other less commonly associated triggers include viral infections and medications (Fry and Baker 2007). Guttate psoriasis may arise as an initial manifestation or acute exacerbation in chronic plaque psoriasis. The guttate lesions are frequently described as small, teardrop-shaped erythematous, scaly, sharply demarcated papules. Most commonly they are numerous and diffusely distributed along the trunk and proximal extremities. The differential diagnosis can include small plaque parapsoriasis, pityriasis rosea, pityriasis lichenoides chronica, secondary syphilis, tinea corporis, and pemphigus foliaceus.

Fortunately, guttate psoriasis tends to have a good prognosis with complete resolution and low rates of recurrence. Several small-scale retrospective studies have investigated the long-term outcomes of patients who developed guttate psoriasis. Of the patients with a single manifestation of guttate psoriasis, 25–39% of patients progressed to a chronic form of psoriasis (Ko et al. 2010; Pfingstler et al. 2016). The role of antistreptococcal antibiotics is unclear; however, studies do not advocate the empiric use of antibiotics (Dogan et al. 2008). Tonsillectomy has also been reported to improve outcomes for recurrent and recalcitrant cases; however, direct evidence is lacking (Owen et al. 2000).

## Treatment

Ultraviolet B (UVB) phototherapy is indicated as a first-line treatment of generalized guttate psoriasis. Narrowband UVB (NB-UVB) is the phototherapy of choice due to its superior efficacy and minimal side effects compared to other modalities

such as broadband UVB and ultraviolet A phototherapy (Barbagallo et al. 2001). Additionally, the lack of systemic toxicity makes phototherapy a more appealing management option when compared to systemic treatments. Recalcitrant lesions may demonstrate better response with the concomitant use of topical corticosteroids or vitamin D analogs. However, patients with more widespread skin involvement may find the use of topical treatments challenging and cumbersome.

Methotrexate is a well-established medication in the management of various forms of psoriasis and is also considered to be a first-line agent in the treatment of guttate psoriasis. The most common reported side effects are nausea, dyspepsia, anorexia, and headache. Gastrointestinal side effects can be minimized with folic acid supplementation without decreasing therapeutic efficacy (Shea et al. 2013). Due to the possibility of developing serious side effects such as bone marrow suppression and hepatic fibrosis or cirrhosis, pretreatment laboratory studies are recommended. Testing should place an emphasis on blood cell count, hepatic, and kidney function. In the case of our patient, pre-therapy laboratory studies revealed mild transaminitis. Although mildly abnormal liver function tests are not considered to be an absolute contraindication, we felt that the potential risks outweighed the benefits of therapy, especially with other modalities such as NB-UVB phototherapy as an excellent and safe alternative.

Apremilast is a new oral agent that acts by inhibiting phosphodiesterase 4, thereby diminishing the production of key cytokines involved in the pathogenesis of psoriasis. An indirect comparison study showed similar efficacy between methotrexate and apremilast (Armstrong et al. 2016). However, the slow onset of action of apremilast calls into question the practicality of its use in the management of guttate psoriasis. Likewise, acitretin monotherapy has a limited role in the management of guttate psoriasis due to its slow onset of action (Lee and Koo 2005).

Cyclosporine is considered to be a second-line agent in the management of guttate psoriasis. Its use is limited to only short-term and intermittent use due to its undesirable side

effect profile. However, because most cases of guttate psoriasis are short-lived, the application of cyclosporine in this setting is very appropriate. Cyclosporine is highly efficacious, and its rapid onset of action makes it advantageous (Menter et al. 2009).

Despite the advancements and increasing utilization of biologic medications in the treatment of plaque psoriasis, their role in guttate psoriasis is not as clearly defined and should be considered as a third-line agent. Currently, their use in guttate psoriasis is based on anecdotal experiences. The transient and self-limited nature of most guttate psoriasis cases further questions its application. Biologic agents are also extremely costly, and the financial burden placed upon the patient is an important consideration. Furthermore, intermittent therapy with biologic medications during psoriasis flares can increase the likelihood of the patient to develop neutralizing antibodies. The presence of neutralizing antibodies has been correlated with diminished efficacy of biologic medications, an undesirable circumstance if the patient developed chronic psoriasis later in the future (Levin et al. 2014).

As previously mentioned, our patient was not treated with methotrexate due to mild transaminitis. As an alternative, the patient was treated with NB-UVB phototherapy with concurrent topical fluocinonide and calcipotriene. Moderate improvement was noted after 23 phototherapy sessions.

## Key Points

- Guttate psoriasis typically presents acutely with widespread skin involvement after an inciting factor such as streptococcal pharyngitis.
- The majority of guttate psoriasis cases have an excellent prognosis with no episodes of recurrence or progression to chronic psoriasis.
- Narrowband UVB phototherapy and methotrexate are both considered to be first-line medications in the management of guttate psoriasis.

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# Chapter 3
# Red Rash on Scalp

**Stacey Pun, Daniel J. No, Mina Amin, and Jashin J. Wu**

## 45-Year-Old with Red Rash on Scalp

A 45-year-old female presented with red, scaly plaques on the scalp for 2 years (Fig. 3.1). The patient complained of occasional pruritus at lesional sites, however denies of any joint stiffness or nail changes. She had a positive family history of psoriasis. The patient was otherwise healthy.

On physical examination, there were red scaly indurated plaques on the scalp with a body surface area of 4%.

Based on the case description, what is your diagnosis?

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Figure 3.1 Mildly erythematous patches and plaques with fine overlying scale were present along the anterior hairline

1. Scalp psoriasis
2. Seborrheic dermatitis
3. Tinea capitis
4. Atopic dermatitis
5. Discoid lupus erythematous

## Diagnosis

Scalp psoriasis

## Discussion

The scalp is among the most commonly involved body regions and is frequently one of the first sites affected in patients with psoriasis. The particular vulnerability of the scalp to psoriasis may be due to multiple factors including lack of UV penetration to the skin, Malassezia proliferation caused by high sebum production, and koebnerization due to frequent brushing and styling of the hair. These same factors that predispose the scalp to the development of psoriatic plaques also make it especially difficult to treat (Kircik and Kumar 2010).

Psoriatic scalp lesions have variable morphology and distribution. Classically, they present as asymmetric, sharply demarcated plaques with overlying silver-white scale. These plaques can extend beyond hair margins to include the forehead, posterior neck, ear, and retroauricular skin (Crowley 2010). Patients often complain of scale shedding and pruritus. Most patients also report significant social and psychological distress, primarily due to pruritus and the appearance of these lesions, especially when they extend onto the face (Kircik and Kumar 2010).

Of note, mild scalp psoriasis may show only minimal scaling and can be difficult to diagnose (Johnson and Armstrong 2013). While scalp psoriasis and seborrheic dermatitis are both common and present with scaling, there are features that distinguish these disease entities. Psoriatic plaques are well defined and the scale is silver-white. In contrast, the scaly patches of seborrheic dermatitis are greasy, yellow, ill-defined, and more diffusely distributed on the scalp. Seborrheic dermatitis is more often seen on the central face of patients who complain of combination oily and dry skin. Autoimmune conditions that involve the scalp can also mimic psoriasis. While localized alopecia can be seen in psoriatic plaques on the scalp, it is non-scarring, and hair growth typically resumes when lesions improve. In contrast, discoid lupus erythematous (DLE), which may also present with scaly

plaques on the scalp, causes a scarring alopecia. Dermatomyositis may also present with scaly, pink, pruritic patches on the scalp. Furthermore, involvement of the extensor surfaces of the knuckles, elbows, and knees may resemble psoriasis. However, scalp patches are usually more prominent posteriorly than anteriorly (Bolognia et al. 2014). It is important to consider atopic dermatitis and tinea capitis in a child with a scalp rash because both of these conditions are much more common than psoriasis in childhood.

Ultrapotent topical corticosteroids are first-line therapy for scalp psoriasis. They act rapidly, resulting in marked improvement often within 2 weeks of treatment initiation (Crowley 2010). Based on available evidence, clobetasol propionate and betamethasone dipropionate have the largest treatment effect of the steroids in these classes when used as monotherapies. Theoretical side effects of long-term use include local skin atrophy, folliculitis, and telangiectasia. These side effects were not observed in 2–4 week studies, although evidence is insufficient to draw conclusions about the safety of topical corticosteroids for greater than 8 weeks. These agents are best given as foams, gels, or solutions, as ointments and creams can be greasy, more difficult to apply, and thus unappealing to patients (Mason et al. 2013; Van de Kerkhof et al. 1998).

Topical calcipotriol can be used as an alternative first-line treatment. Side effects include burning, redness, dryness, and itching (Crowley 2010). They also have a slow onset of action compared to corticosteroids, which may make them unappealing to patients. While calcipotriol binds the vitamin D3 receptor and can alter bone and calcium metabolism, there are few reports of clinically significant alterations in the blood or urine calcium levels (Gooderham et al. 2014; Scott et al. 2001). Of note, these vitamin D3 analogues are inactivated at low pH and thus cannot be used with acidic topicals like salicylic acid (Warren et al. 2008).

Calcipotriol alone is less effective than corticosteroids for the treatment of scalp psoriasis. However, vitamin D analogue and corticosteroid combination therapy is slightly more

effective than corticosteroid monotherapy. Evidence suggests that calcipotriol is better tolerated as combination therapy because corticosteroids reduce irritation caused by calcipotriol. Combination therapy causes fewer withdrawals from treatment due to adverse events than vitamin D monotherapy (Mason et al. 2013). This combined treatment may be especially useful in patients who fail to respond adequately to monotherapy because it can be safely used for as long as one year (Gooderham et al. 2014; Luger et al. 2008). However, because there is only a modest benefit to combination therapy and it has a comparable safety profile, monotherapy with potent and ultrapotent corticosteroids is preferred in the short term (Schlager et al. 2016).

Coal tar derivatives are also used in the topical treatment of psoriasis. They have multiple modes of action including antimitotic, anti-inflammatory, antibacterial, antifungal, antipruritic, and photosensitizing. Evidence is insufficient to recommend coal tar as a first-line treatment for scalp psoriasis (Mason et al. 2013). Furthermore, it is unappealing to patients because of its odor, staining properties, and mutagenic potential (Warren et al. 2008). Nevertheless, the shampoo form may be beneficial as an adjunctive treatment to stronger, first-line agents like corticosteroids and calcipotriene.

Some therapies used for psoriasis in other parts of the body are not advisable for the treatment of scalp psoriasis. Phototherapy is not effective in treating scalp psoriasis because densely packed hair follicles prevent UV radiation from reaching the skin.

Psoriasis isolated to the head at maximum involves 9% of total body surface area. Because the scalp represents a relatively small proportion of TBSA, toxicity associated with systemic therapies used for extensive or severe psoriasis in other parts of the body may outweigh the potential benefits in such limited disease. While methotrexate, for example, is an effective treatment for chronic scalp psoriasis, it associated with hepatotoxicity when used long term. Cyclosporine is associated with nephrotoxicity, immunosuppression, hypertension, and hirsutism. These systemic treatments should generally only be considered when there is concurrent involvement

of other parts of the body. Notably, medications like methotrexate and acitretin may also exacerbate hair loss associated with scalp psoriasis (Kircik and Kumar 2010). Evidence suggests that TNF inhibitors may improve scalp psoriasis, but there are also reports of new onset scalp psoriasis in patients taking these biologics for other indications (Crowley 2010).

Based on the patient's medical history and clinical picture, a diagnosis of scalp psoriasis was made. The topical therapies she was prescribed for her scalp included coal tar shampoo and betamethasone 0.05% ointment.

On follow-up, skin lesions on other parts of her body were significantly improved with topical agents. However, her scalp lesions had a poor response to the betamethasone ointment. The patient also admitted to poor compliance with coal tar shampoo. At that time, she was switched from betamethasone ointment to clobetasol foam.

## Key Points

- Scalp involvement is very common in patients with psoriasis and is difficult to treat because of both hair follicle density and cosmetic considerations associated with this anatomic location.
- Scalp psoriasis presents a diagnostic challenge and can resemble other diseases that involve the scalp. The most common among these is seborrheic dermatitis.
- Potent and very potent steroids are first-line treatment for scalp psoriasis. These are best given as foams or solutions.

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# Chapter 4
# 41-Year-Old with Nail Deformities

**Kavita Darji, Daniel No, Mina Amin, and Jashin J. Wu**

A 41-year-old female presented to the clinic with nail malformations, which she stated as occurring acutely during early pregnancy about 15 months ago. There were no complaints of joint stiffness, inflammation, or tenderness. No history of trauma or radiation to the nails was reported. The patient was otherwise healthy.

On physical examination, there was diffuse distal onycholysis with separation and breakage. On bilateral thumbnails, nail plate thickening with subungual debris was noted.

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Bilateral great toenails also had thickening and subungual debris. There were no additional skin findings on the examination.

A nail plate clipping was taken from the fingernail and toenail to rule out onychomycosis. Both fingernail and toenail clippings were periodic acid-Schiff stain negative for fungal hyphae.

The patient denies psoriatic skin lesions or a family history of psoriasis.

Based on the case description, what is your diagnosis?

1. Onychomycosis
2. Nail polish contact dermatitis
3. Yellow nail syndrome
4. Nail psoriasis
5. Iron deficiency anemia

## Diagnosis

Nail psoriasis

## Discussion

Approximately 50% of patients with psoriasis have nail involvement (Crowley et al. 2015; Jiaravuthisan et al. 2007). The lifetime incidence of nail abnormalities in psoriatic patients is 80–90% (Crowley et al. 2015; Samman and Fenton 1994). Nail disorders in psoriasis can present commonly as nail pitting and distal separation of the nail plate and less frequently as discoloration and splinter hemorrhages in the nail bed (Jiaravuthisan et al. 2007). Fingernail psoriasis tends to create more problems for patients compared to toenail psoriasis (Crowley et al. 2015). A positive association has been reported between nail abnormalities and the duration of psoriatic skin disease as well as severity of psoriasis (de Jong et al. 1996; de Vries et al. 2013; Armesto et al. 2011).

Moreover, nail psoriasis has been noted to be painful for patients, often limiting daily housekeeping and professional tasks (de Jong et al. 1996).

Pitting and deformation are the most common nail dystrophies in psoriasis (de Jong et al. 1996). Pitting manifests as depressions in the topmost layers of the nail plate, with the length of the pit indicating the amount of time that the nail matrix was affected by psoriasis (Jiaravuthisan et al. 2007). Nail matrix psoriasis involves pitting, transverse grooves or Beau's lines, leukonychia, red spots in lunula, and nail plate crumbling (Zaias 1969; Crowley et al. 2015; Rich and Scher 2003; Pasch 2016; Baran 2014). Nail bed or hyponychium involvement manifests as discoloration, onycholysis, splinter hemorrhages, "oil drop" or "salmon-colored" patches, and subungual keratosis (Zaias 1969; Crowley et al. 2015; Rich and Scher 2003). There is an increased risk of infection with onycholysis, as the separation of the nail plate allows for access and occupation by various microorganisms (Jiaravuthisan et al. 2007). Additionally, subungual keratosis can present as yellow, lubricous nails or a white-silvery counterpart, arising from an inflammatory process as well as accumulation of a glycoprotein (Zaias 1969; Jiaravuthisan et al. 2007). A white-silvery counterpart is the less common form of subungual keratosis seen in psoriatic nails (Jiaravuthisan et al. 2007). Oftentimes, with psoriatic nail changes, there is also evidence of onychomycosis. In toenails especially, a secondary fungal infection can be seen (Crowley et al. 2015). Prior literature indicates a higher incidence of onychomycosis in psoriatic patients than non-psoriatic patients (Klaassen et al. 2014).

Nail psoriasis is strongly correlated to psoriatic arthritis, with indications that nail abnormalities in psoriasis patients may shed light on the subsequent finding of joint disease (Crowley et al. 2015; Armesto et al. 2011). In fact, patients with psoriatic arthritis have psoriatic nail changes at a rate up to 70% (Crowley et al. 2015).

Topical therapies are the first-line treatment for mild cases of nail deformities in psoriasis patients. To begin with,

calcipotriol, prescribed both as monotherapy and in combination with topical steroids, is the most frequently used vitamin D derivative for treatment of nail psoriasis (Pasch 2016). Calcipotriol alone reduces subungual hyperkeratosis, onycholysis, and discoloration (Pasch 2016). Combination therapy with high-potency topical steroids has also proven to be effective for nail psoriasis. Calcipotriol use for 5 days a week with clobetasol propionate during weekends for 6 months resulted in decreased hyperkeratosis (Pasch 2016; Rigopoulos et al. 2002). Use of topical calcipotriol once daily and betamethasone dipropionate combination therapy may be as effective as monotherapy with calcipotriol used twice daily over 12 weeks for nail psoriasis, mainly causing a decrease in oil drop discoloration (Tzung et al. 2008; Pasch 2016). However, long-term topical corticosteroid use should be avoided due to adverse effects of both skin and phalanx atrophy (Edwards and de Berker 2009). Intralesional corticosteroids have been shown to be beneficial for limited nail psoriasis, but may be poorly tolerated and painful for some patients (Crowley et al. 2015; Edwards and de Berker 2009).

Furthermore, the use of topical tazarotene 0.1% gel, a topical retinoid, allows for significant improvement in limited nail psoriasis. The use of tazarotene 0.1% gel in 31 patients with fingernail psoriasis for 24 weeks resulted in a reduction of onycholysis and pitting in two target fingernails compared to the control group of patients who used vehicle gel (Scher et al. 2001). Additionally, application of tazarotene 0.1% gel to unoccluded fingernails and toenails for 12 weeks led to decreased onycholysis, hyperkeratosis, pitting, and "oil spots" in a study of 25 patients (Bianchi et al. 2003). A randomized controlled trial comparing tazarotene 0.1% cream with clobetasol propionate 0.05% cream used once daily for 12 weeks showed a reduction in pitting, hyperkeratosis, onycholysis, and salmon patches with both treatment options (Rigopoulos et al. 2007; Pasch 2016).

Systemic therapies are most commonly used if nail psoriasis presents in a patient with moderate-to-severe plaque psoriasis or psoriatic arthritis. However, systemic therapies can sometimes be considered in patients with isolated nail psoriasis

if significant symptoms, social distress, or functional impairment exists. Nonetheless, caution must be taken with the use of oral methotrexate and biologics due to adverse effects and increased risk to reward ratio. The use of methotrexate is often limited due to side effects of hepatotoxicity, leukopenia, lymphopenia, ulcerative stomatitis, and nausea (Pasch 2016). Immunosuppressive medications, such as methotrexate, or biologics, can also exacerbate or create onychomycosis (Crowley et al. 2015; Klaassen et al. 2014; Pasch 2016). For this reason, particular attention should be given to rule out onychomycosis in psoriatic patients in order to provide appropriate treatment options (Crowley et al. 2015; Klaassen et al. 2014; Pasch 2016). Treatment with systemic therapy is often limited to those with diffuse skin and joint involvement due to cost burden, adverse effects, and coverage denial by insurance companies (Edwards and de Berker 2009; Abdelnabi et al. 2016). Thus, although biologics may be useful for nail psoriasis, they may not always be covered by insurance.

For our patient, treatment was initialized with topical tazarotene 0.1% gel. Due to poor clinical response, the patient was treated with intralesional corticosteroids using a needleless injector. The left fourth and fifth digit nails were treated with intralesional kenalog 10 mg/ml (9:1 ratio of kenalog to lidocaine 1%). All other fingernails were treated with MadaJet XL pneumatic injector (kenalog 10 mg/ml at 7:3 ratio of kenalog to lidocaine 1%).

## Key Points

- Nail psoriasis occurs in approximately half of patients suffering from psoriasis and can manifest as abnormalities in the nail matrix and/or nail bed.
- Common topical treatments for limited nail psoriasis include topical calcipotriol with or without topical corticosteroids, as well as topical tazarotene 0.1% gel or cream.
- Systemic treatments, such as methotrexate and biologics, can be useful in patients with plaque psoriasis or psoriatic

arthritis. However, the risk to reward ratio may be elevated, and insurance coverage may be regulated for these options.

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# Chapter 5
# 69-Year-Old with Rash on the Axilla and Groin

**Mina Amin, Daniel J. No, and Jashin J. Wu**

A 69-year-old man presented with a three-month history of an erythematous rash in the axilla and groin. The lesions were stable with mild pruritus. The patient was referred to dermatology after failed empiric treatment with topical antifungal creams prescribed by his primary care physician. He reports being otherwise healthy and denied a family history of psoriasis.

On physical examination, there were well-defined bright red erythematous patches in the axilla and groin folds without an overlying scale. The lesions involved 1% of body surface area. A wood lamp skin examination was negative, and no skin or nail changes were found.

Based on the case description, what is your diagnosis?

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1. Erythrasma
2. Tinea cruris
3. Candidal intertrigo
4. Inverse psoriasis

## Diagnosis

Inverse psoriasis

## Discussion

Inverse psoriasis, also known as flexural or intertriginous psoriasis, is a rare form of psoriasis. It can affect any location where two skin areas can rub against each other, most commonly involving the axillary, inframammary, groin, and intergluteal regions. Inverse psoriasis is considered "inverse" because it targets the flexure surfaces, whereas psoriasis classically affects the extensor surfaces (Van de Kerkhof et al. 2007). Psoriasis typically produces erythematous scaly plaques. Inverse psoriasis, on the other hand, creates bright erythematous, well-defined patches (Wolff et al. 2013). The presence of these lesions in the intertriginous areas is often a source of psychosocial stress. Inverse psoriasis appears to be undertreated and underreported, as many patients feel uncomfortable and do not seek help from their physicians (Omland and Gniadecki 2015). Therefore, it is important to be able to diagnose and treat inverse psoriasis as it can negatively impact the quality of life for these patients.

A psoriasis etiology may be overlooked in these patients because the lesions lack the characteristic scaling that is seen in psoriasis. The lesions may or may not be pruritic and appear smooth (Syed and Khachemoune 2011). The skin in intertriginous areas is often less keratinized and contains more sweat glands compared to sites of the body that are typically affected by psoriasis (Omland and Gniadecki 2015). The shiny appearance and decreased presence of scales is mainly due to the perspiration and friction in the body folds (Syed and

Khachemoune 2011). The presentation of psoriasis in patients with HIV is often inverse psoriasis. Additionally, there has been an association between obesity and the diagnosis of inverse psoriasis (Omland and Gniadecki 2015). No histologic difference has been discovered between inverse psoriasis and psoriasis. It has not been reported that inverse psoriasis has a separate prognosis than psoriasis (Van de Kerkhof et al. 2007). Also, there has been no distinction noted in the T-cell-mediated inflammatory process in inverse psoriasis and psoriasis (Syed and Khachemoune 2011; Ghoreschi et al. 2007). Overall, there have been no clear findings that indicate a difference in the pathogenesis between inverse psoriasis and psoriasis. Of note, patients with inverse psoriasis often simultaneously have psoriatic lesions on other body areas (Van de Kerkhof et al. 2007). Thus, the detection of psoriatic lesions on other sites of the body helps in the diagnosis of intertriginous psoriasis.

The warm and moist environment of the body folds can lead to the growth of microbial and fungal organisms. Therefore, it is important to differentiate inverse psoriasis from an infectious cause. Candidal intertrigo and tinea corporis produce erythematous, pruritic, and scaling plaques (Elewski and Hazen 1989). In contrast to inverse psoriasis, tinea corporis tends to produce more annular lesions. A failed response to antifungal medication and a negative potassium hydroxide examination helped rule out candida intertrigo and tinea corporis in this patient. A negative wood lamp skin examination eliminated the possibility of erythrasma in this patient, which also produces well-demarcated plaques in the skin folds. Erythrasma creates red-brown lesions and a coral-red fluorescence on wood lamp examination, compared to the bright erythematous plaques and negative wood lamp skin examination seen in inverse psoriasis. The rubbing and perspiration that occur in the intertriginous area increase the risk of irritation and inflammation. The increased irritation in the body folds can lead to the growth of microbial and fungal organisms (Kalb et al. 2009). The simultaneous presence of these microbial and fungal organisms can complicate the treatment regimen for these patients (Menter et al. 2009).

## Treatment

The first-line treatment for short-term therapy (2–4 weeks) for inverse psoriasis is low- to mid-potency topical steroids. The intertriginous area is a sensitive site that is more prone to irritation by topical medication. Lower potency is preferred to higher potency topical steroids due to the increased chance of side effects in the intertriginous areas. Topical corticosteroids can cause atrophy, telangiectasia, and striae, especially in the sensitive areas such as the body folds (Kalb et al. 2009). Though the warm environment of the skin folds increases the penetration of the medication, this also explains the increased possibility of atrophy and irritation. For this reason, the duration of treatment should be limited to no longer than 2–4 weeks. Begin treatment with a topical low-potency corticosteroid for 2 weeks, stop for 2 weeks, and repeat as necessary. Topical tacrolimus or pimecrolimus cream can be used during the off weeks.

Topical calcipotriene or topical calcineurin inhibitor (tacrolimus or pimecrolimus) creams or lotions are first line for long-term therapy. Topical use of a lotion or cream is better tolerated than the application of an ointment or solution. Avoid ointment use in the intertriginous area due to the thick consistency of ointments. Solutions are too runny to use in the body folds. Although low-potency topical steroids are more effective, topical calcipotriene or calcineurin inhibitors are associated with a decreased risk of long-term side effects and are thus better tolerated for long-term use (Kalb et al. 2009; Menter et al. 2009). Systemic medications are frequently avoided in the treatment of inverse psoriasis upon evaluation of the risk-benefit ratio. Thus, the best approach in the management of these patients is topical treatment. Consider systemic therapy if topical medications are ineffective in treating inverse psoriasis (Kalb et al. 2009; Menter et al. 2009).

The patient was advised to apply the low-potency topical corticosteroid triamcinolone acetonide 0.1% cream twice daily for 2 weeks, to stop for 2 weeks, and to repeat as needed.

## Key Points

- Inverse psoriasis is a rare form of psoriasis that appears in the intertriginous areas.
- Differentiate from an infectious cause due to the warm moist environment of the body folds and potential lack of visible scaling.
- Begin treatment with a low-potency topical steroid for 2 weeks, stop for 2 weeks, and repeat as needed. Tacrolimus or pimecrolimus can be added in the off 2 weeks.

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# Chapter 6
# 45-Year-Old with Red Rash on Face

**Mina Amin, Daniel J. No, and Jashin J. Wu**

A 45-year-old male presented with red, scaly, indurated papules and plaques diffusely on the body and face since childhood. The patient has previously used topical agents with modest benefit. He is otherwise healthy. Of note, the patient has a remote history of tuberculosis exposure as a child that was medically treated. He is asymptomatic, and routine chest imaging studies have not shown evidence of latent tuberculosis. The patient denies a family history of psoriasis and is employed as an elementary school teacher.

On physical examination, there were diffusely distributed erythematous, scaly, indurated papules and plaques on bilateral legs, arms, elbows, groin folds, ala of the nose, bilateral cheeks, retroauricular area, and both ears (Figs. 6.1 and 6.2).

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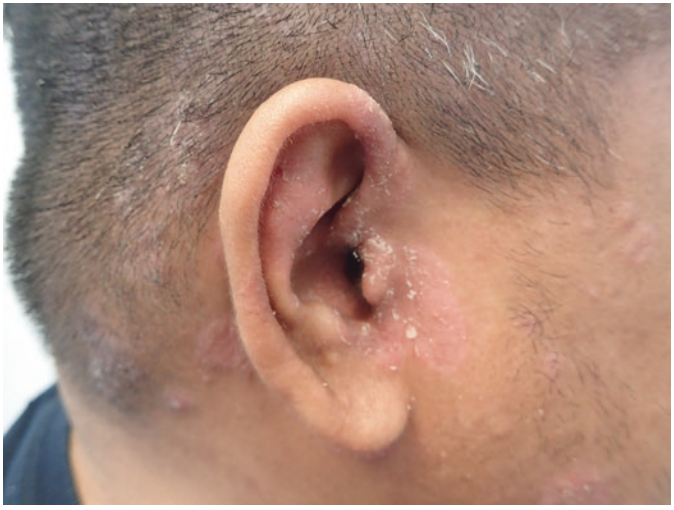

Figure 6.1 Erythematous, well-defined, indurated, scaly papules and plaques were present on the right tragus, antihelix, and retroauricular area

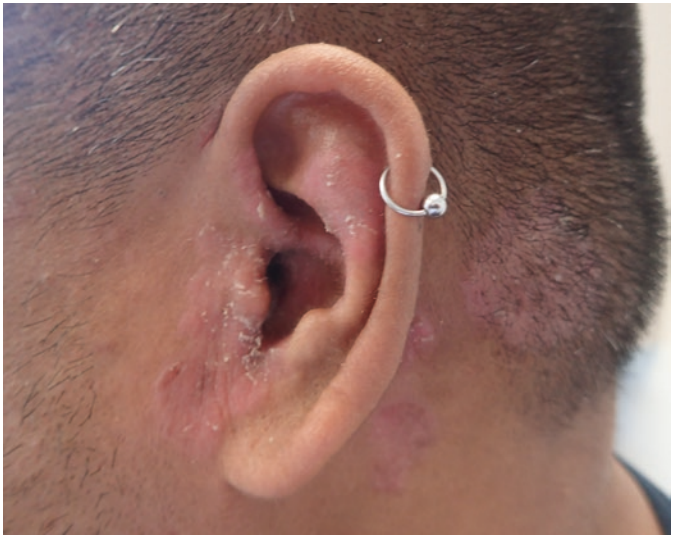

Figure 6.2 Erythematous, well-circumscribed, scaly papules and plaques were located on the left tragus, antihelix, and retroauricular area. Lesions on the face appeared more indurated and less prominent compared to lesions located on other parts of the body

The total affected body surface area was 60%. No nail deformities were found on examination.

Based on the case description, what is your diagnosis?

1. Seborrheic dermatitis
2. Atopic dermatitis
3. Psoriasis including facial psoriasis
4. Lupus tumidus erythematosus

## Diagnosis

Psoriasis including facial psoriasis

## Discussion

Facial psoriasis is a subtype of psoriasis that can cause significant discomfort for patients. Most patients with facial psoriasis also have psoriatic plaques elsewhere on the body (Van de Kerhof et al. 2007). Facial psoriasis produces plaques that arise on the neck, forehead, ears, and face that appear indurated and less prominent in comparison to the characteristic psoriatic plaques. The clinical presentation involves erythematous, scaly, well-defined plaques that are often pruritic. The presentation of psoriatic lesions on other parts of the body aids in the diagnosis (Park et al. 2004).

The visibility of the plaques can interfere with a patient's well-being (Jacobi et al. 2008). The noticeable location of the lesions can lead to a decrease in self-confidence and problems in acquiring employment (Ortonne et al. 2003). Additionally, the plaques are often treatment resistant and tend to reoccur. Facial psoriasis may indicate a more severe form of psoriasis that is diagnosed at an early age with a long duration of disease (Woo et al. 2008). Patients with facial psoriasis also often have a strong family history of psoriasis and experience the Koebner response (Kim et al. 2016). The Koebner response is the development of psoriatic lesions at a site of cutaneous trauma. Patients may also have nail and

joint involvement. The disease severity in facial psoriasis may vary based on seasons in which exacerbations may occur during certain seasons (Park et al. 2004). Facial psoriasis can also present after a patient discontinues systemic treatment as a relapse. In this situation, patients often present with a more severe disease than that prior to treatment (Park et al. 2004).

Facial plaques could be due to multiple different etiologies. Seborrheic dermatitis also presents as scaly, well-defined, erythematous lesions. In contrast to facial psoriasis, seborrheic dermatitis produces plaques that are more yellow with greasy scales (Naldi and Rebora 2009). Atopic dermatitis tends to appear on the face in infancy, but can present in older children and adults. Atopic dermatitis can also present with erythematous plaques yet are often severely pruritic. Lupus tumidus erythematosus also produces plaques that are erythematous and may appear on the face. In contrast to facial psoriasis, the plaques in lupus tumidus erythematosus often do not scale (Choonhakarn et al. 2004).

If there is isolated facial psoriasis or facial psoriasis does not clear with systemic therapy for associated severe psoriasis, topical vitamin D analogs (calcipotriene, calcitriol), tacrolimus ointment, and pimecrolimus cream are considered first-line treatments. Avoid high-potency topical corticosteroids on the face. In contrast to psoriatic lesions on other parts of the body, facial psoriasis creates thinner plaques. The decreased thickness of plaques allows for increased absorption of topical medication, which can lead to a higher risk of side effects. Skin atrophy, telangiectasia, glaucoma, acne, cataracts, and perioral dermatitis have been reported with the use of high-potency topical corticosteroids on the face (Park et al. 2004; Jacobi et al. 2008). Lower-potency corticosteroids may still be used, as these are less likely to cause severe side effects. Consider the use of class 5–6 corticosteroids for maintenance therapy (2 weeks on, 2 weeks off, repeat).

Topical vitamin D analogs, such as calcipotriene and calcitriol, are very efficacious in the treatment of facial psoriasis. Calcipotriene and calcitriol are not known to cause the atrophic skin events that are typically seen after high-potency

topical corticosteroid use. However, a facial irritation and erythema may occur, which can cause poor medication adherence (Ortonne et al. 2003).

Topical application of tacrolimus ointment is efficacious in the treatment of facial psoriasis. Calcineurin inhibitors are not as successful for psoriasis on other body areas because of the decreased ability to penetrate thick plaques (Brune et al. 2007). However, thin plaques of facial psoriasis allow for enhanced absorption of tacrolimus ointment. Topical application of tacrolimus ointment twice daily has been shown to be effective in a randomized controlled study. Patients experienced reduction in erythema, induration, and severity of facial lesions at 8-week follow-up (Lebwohl et al. 2004).

Pimecrolimus cream is also successful in the treatment of facial psoriasis. Similarly to tacrolimus, pimecrolimus is more useful in the treatment of psoriasis on the face than on other body areas because the thinner plaques allow for enhanced absorption. Topical application of pimecrolimus twice daily in a randomized controlled study showed substantial improvement at 8-week follow-up. Topical pimecrolimus cream is favorable to topical corticosteroids because it is well tolerated; however a short-lived warm or burning sensation has been reported (Jacobi et al. 2008).

Ideally, treat with a low-potency topical corticosteroid twice daily for 2 weeks, followed by a topical vitamin D analog, tacrolimus ointment, or pimecrolimus cream twice daily for 2 weeks, and then resume with the low-potency topical corticosteroid. Another option is to treat simply with a topical vitamin D analog, tacrolimus ointment, or pimecrolimus cream twice daily. The patient was started on adalimumab due to the widespread distribution of affected skin. Concomitant use of hydrocortisone butyrate was used intermittently for the face and intertriginous areas. Topical fluocinonide was used for resistant lesions on the body. The patient experienced significant improvement at 6-week follow-up. Psoriasis was well controlled for 4.5 years with this treatment regimen.

## Key Points

- Facial psoriasis presents with pruritic, erythematous, indurated, and well-demarcated plaques on the face.
- The disease can begin in childhood and has a prolonged duration of disease that can be treatment resistant.
- Topical vitamin D analogs, tacrolimus ointment, and pimecrolimus cream are first-line treatments for isolated facial psoriasis.

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# Chapter 7
# 16-Year-Old with Rash on Genitals

**Mina Amin, Stacey Pun, Daniel No, and Jashin J. Wu**

A 16-year-old male presented to the clinic with a two-year history of an erythematous, pruritic rash on his penis and scrotum. Over-the-counter topical antifungal medication for self-presumed tinea cruris did not provide any benefit. Of note, the patient admits to developing secondary infections in the past due to perpetual scratching and poor care of affected sites. More recently, the patient has also developed red, scaly lesions on his neck, ears, and trunk. He denied joint pain, joint stiffness, and nail deformities. He is otherwise healthy, does not use medications, and has no known allergies. The patient has a family history of psoriasis.

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On physical examination, there were bright, erythematous, well-defined plaques over the groin folds that extend to the dorsal penis, scrotum, and crease of buttocks. There was also some slight, fine scaling at the lateral edges in the pubic area. Examination of the remainder of the body revealed erythematous, well-defined, scaly plaques on the hairline at the nape of the neck, chest, abdomen, and postauricular skinfold.

Based on the clinical case description, what is the most likely diagnosis?

1. Tinea cruris
2. Fixed drug eruption
3. Candidal intertrigo
4. Genital psoriasis
5. Erythrasma

## Diagnosis

Genital psoriasis

## Discussion

Genital psoriasis is a subtype of psoriasis that creates thin, bright, erythematous, well-defined plaques in the genital area. Genital psoriasis affects approximately one-third of patients with psoriasis (Ryan et al. 2015). The lesions produce minimal scaling; however, scales can appear in the keratinized areas of the genital region such as the penile shaft, scrotum, and near the labia majora. If scales are present, the Auspitz phenomenon also occurs upon removal of scales (Meeuwis et al. 2011). Genital psoriasis is associated with an early onset of disease and worse prognosis. It is more prevalent in males. The shaft of the penis is affected most, followed by the scrotum and glans penis. In females, genital psoriasis most commonly involves the labia majora, followed by the perineum and labia

minora. Patients also frequently present with concomitant scalp, flexure, and nail involvement (Ryan et al. 2015).

Genital psoriasis serves as a source of discomfort, embarrassment, and psychosocial stress (Buechner 2002). Patients with genital psoriasis report a significantly lower quality of life compared to patients with psoriasis that does not affect the genital area. The location of the lesions contributes most to the profound impact of genital psoriasis on the quality of life. However, patients with genital psoriasis suffer from pruritus, pain, dyspareunia, and burning at the site of the lesions. Patients report a decrease in sexual activity after the onset of psoriasis. The Koebner phenomenon arises in patients with genital psoriasis as evidenced by an increase in disease severity after intercourse (Meeuwis et al. 2011; Ryan et al. 2015). Females experience dyspareunia more often than males. Patients with vulvar involvement experience a decrease in sexual functioning and subsequent depression (Zamirska et al. 2008; Ryan et al. 2015).

The diagnosis of genital psoriasis may be delayed as a result of patient embarrassment. Also, the genital area may be overlooked during routine examination in the outpatient clinic. A significant number of patients with genital psoriasis reported in a questionnaire-based study that it would be beneficial for healthcare professionals to evaluate for problems with sexual functioning. Physicians should encourage the discussion about genital lesions so that appropriate treatment can be initiated and counseling can be offered to help improve the quality of life for these patients (Meeuwis et al. 2011).

Although psoriasis is the most common inflammatory condition that involves the genitals in males, a variety of lesions manifest in the genital region. Fixed drug eruptions create well-demarcated erythematous lesions but are often duskier, painful, pruritic, and bullous (Buechner 2002). Fixed drug eruptions can also become hyperpigmentated. Erythrasma produces well-defined plaques but is more pruritic, and Wood's lamp examination is positive in these patients. Candidal intertrigo often presents with papules and pustules.

Tinea cruris also produces erythematous well-defined plaques, but these often exhibit central clearing. A negative KOH examination would eliminate the possibility of candida intertrigo and tinea cruris. Patients with genital psoriasis may have simultaneous candida or tinea infections that need to be assessed. Treatment-resistant penile plaques should be evaluated for squamous cell carcinoma in situ (Buechner 2002).

The first-line treatments for genital psoriasis include topical vitamin D analogs (calcipotriene, calcitriol), tacrolimus ointment, pimecrolimus cream, and low- to mid-potency topical corticosteroids. The increased sensitivity of the genital skin makes treatment difficult. The genital skin is thin and absorption of topical medication is often increased (Meeuwis et al. 2011). Vitamin D analogs, tacrolimus ointment, or pimecrolimus cream are preferred for long-term management. Lower-potency topical corticosteroids are more efficacious and can be tapered down as the psoriasis improves after 2–4 weeks of application to avoid the risk of side effects (Kalb et al. 2009).

Topical vitamin D analogs (calcipotriene and calcitriol) are effective in the treatment of genital psoriasis. In a double-blind randomized study, tacrolimus was found to be significantly more effective than calcitriol in the treatment of psoriasis in the genitofemoral region. While both medications were generally well tolerated, they were not without side effects. Calcitriol caused erythema around the lesion site. Of note, calcitriol has a lower risk of skin irritation than calcipotriol in the sensitive skin areas (Liao et al. 2007). Irritant contact dermatitis may develop as a side effect of topical calcipotriene treatment. Treatment that involves both topical vitamin D analogs and corticosteroids can decrease side effects and increase effectiveness of both therapies (Buechner 2002).

Topical tacrolimus ointment is effective in the treatment of genital psoriasis. Calcineurin inhibitors are not as successful for psoriasis on other body areas because the thick plaques lead to decreased absorption of topical medication. In contrast, the thin plaques in the genital area allow for increased effectiveness of tacrolimus ointment (Lebwohl et al. 2004; Brune et al. 2007).

Topical tacrolimus has been reported to cause burning and folliculitis in the genital region (Liao et al. 2007).

Pimecrolimus cream is also efficacious in the treatment of genital psoriasis due to the thin plaques present in the genital area. A double-blind randomized controlled study demonstrated a reduction in lesions in the genital area at 4-week follow up. However, a small minority of patients did experience pruritus and burning after application (Kreuter et al. 2006).

Consider the use of systemic treatment only if there is significant body surface area involvement. Ointment is generally avoided in the genital area due to thick consistency. Higher-potency topical steroids are also avoided due to the increased risk of side effects such as striae, skin atrophy, and telangiectasia (Kalb et al. 2009).

The patient was treated with calcitriol ointment twice per day and tacrolimus ointment at night. He experienced complete resolution of genital psoriasis at 1-month follow-up.

## Key Points

- Genital psoriasis creates thin, bright, erythematous, well-defined plaques in the genital area with minimal scaling.
- Patients experience severe discomfort, embarrassment, and psychosocial stress, which can inhibit discussion with healthcare professionals and delay treatment.
- Treat with topical vitamin D analogs, calcineurin inhibitors, or class 5–6 topical corticosteroids. Avoid high-potency topical corticosteroids due to the increased risk of side effects in the genital region.

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# Chapter 8
# 70-Year-Old Male with Red Rash on Palms

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A 70-year-old man presented with a 5-year history of persistent, pruritic, non-tender, erythematous thick plaques on both hands and feet. He denied any prior bleeding or ulceration at the site of the rash. He had previously used topical antifungal creams that were discontinued after they proved to be ineffective. The patient is retired and denied excessive exposure to water or contact with irritants such as detergents, solvents, and adhesives. The patient also complained of distal fingernail separation and thickening but denied joint stiffness and tenderness. He was otherwise healthy and denied accompanying fevers, chills, or weight loss.

On physical examination, the palmar surfaces of the palms and fingers had well-defined, erythematous, indurated,

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confluent scaly plaques with minimal extension to the dorsal and lateral aspects of both hands. The dorsal aspect of the hands had a few scattered erythematous plaques with scale. Both plantar surfaces of the feet were erythematous, minimally indurated, with scaly confluent plaques. No lichenification, pustules, desquamation, wrinkling, or fissures were discerned. Distal onycholysis was noted on several fingernails.

Based on the clinical case description, what is the most likely diagnosis?

1. Tinea manuum
2. Palmar-plantar psoriasis
3. Exfoliative keratolysis
4. Contact dermatitis
5. Hallopeau acrodermatitis

## Diagnosis: Palmar-Plantar Psoriasis

Palmar-plantar psoriasis produces well-demarcated erythematous, scaly plaques on the palms and soles. Patients tend to have psoriasis on other anatomical sites, yet less frequently may present with palmar-plantar psoriasis in isolation. Palmar-plantar psoriasis has the potential to be severely debilitating as patients often experience severe pain and discomfort at the site of the lesions. Patients may have a profound occupational impact and express difficulty in completing daily tasks when the hands are affected (Fig. 8.1). Plantar involvement can make it unbearable to walk, which can cause a severe impairment in the quality of life for these patients (Farley et al. 2009; Janagond et al. 2013).

The primary concerns for patients with palmar-plantar psoriasis are pain and discomfort. A randomized cross-sectional study surveyed 317 patients and found that patients with palmar-plantar psoriasis report more physical distress and disability than patients with plaque psoriasis (Pettey et al. 2003). Patients do not report significant psychosocial stress perhaps because the lesions are relatively easy to disguise. Yet, patients may avoid handshaking to prevent

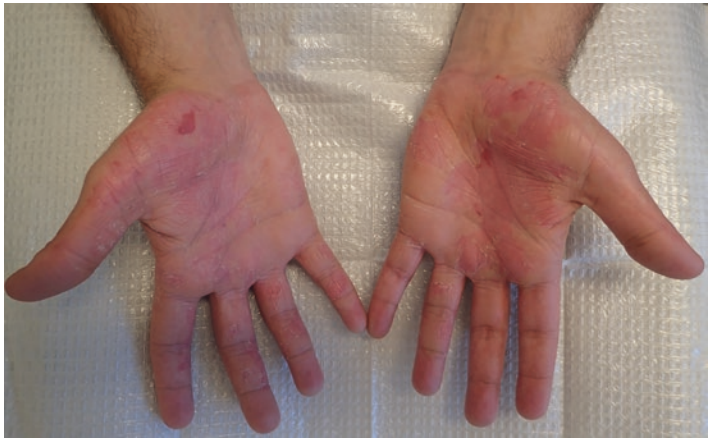

Figure 8.1 Erythematous, well-demarcated, indurated, confluent scaly plaques were present on the palmar surfaces of both hands. No pustules were observed

embarrassment (Pettey et al. 2003; Farley et al. 2009). For patients with palmar-plantar psoriasis, disease severity is considered a separate entity than the amount of body surface area affected (Farley et al. 2009). The palms and soles account for less than 5% of the total body surface area. However, patients report more functional disability than patients with psoriasis involving a greater body surface area (Ortiz et al. 2013; Pettey et al. 2003). Treatment should be aimed toward reducing pain and enhancing function even if palmoplantar lesions are not completely resolved (Pettey et al. 2003).

Mild cases of palmar-plantar psoriasis can be treated with topical corticosteroids alternating with topical vitamin D analogs (calcipotriene, calcitriol). Palmar-plantar psoriasis is characteristically difficult to treat, likely because the thickened stratum corneum acts as a barrier in preventing adequate percutaneous absorption. High-potency topical corticosteroids are more efficacious to try to penetrate the plaques. Occlusive methods may be utilized to help with absorption such as plastic wraps, gloves, and hydrocolloid occlusion.

For severe cases or cases with significant body surface area involvement, consider treatment with retinoids, methotrexate, or cyclosporine. Systemic medication is often limited to patients with over 10% body surface area. However, systemic medication should be considered for patients with palmar-plantar psoriasis because many cases are resistant to topical therapy and recurrence rates are high. Acitretin can decrease the severity of the painful lesions, which leads to patient satisfaction even though the lesions may not be completely resolved. The most common side effects seen with acitretin are the alterations in lipid levels and mucosal dryness (Ortiz et al. 2013). Since the side effects are dose-dependent, it is not necessary to increase the amount of systemic medication to completely resolve lesions if patients report an improvement in functional ability. A prospective randomized study compared methotrexate and acitretin and found both to significantly improve psoriatic lesions in both populations. Methotrexate may cause nausea and vomiting and changes in liver function tests, which are both reduced with daily folic acid supplementation (Janagond et al. 2013).

Apremilast and ustekinumab may also be used to treat palmar-plantar psoriasis (Pettey et al. 2003). Apremilast has been shown to improve palmar-plantar psoriasis at follow-up and was tolerated well with the most significant side effect of nasopharyngitis (Deeks 2015). Cyclosporine can provide the ability of patients to retain functional ability (Janegond et al. 2013). Cyclosporine is beneficial for highly resistant plaques or flares because it is fast acting. However, cyclosporine produces prominent side effects and is not suitable for chronic management of palmar-plantar psoriasis.

Avoid tumor necrosis factor (TNF)-α inhibitors in the treatment of palmar-plantar psoriasis as they may paradoxically induce palmar-plantar pustular psoriasis. Multiple cases have reported the association between TNF-α inhibitors such as etanercept, infliximab, and adalimumab and new-onset or exacerbated cases of psoriasis. Patients have reported the transformation of palmar-plantar psoriasis to palmar-plantar pustular psoriasis after TNF-α inhibitor therapy (Collamer

and Battafarano 2010; Raposo and Torres 2016; Schmidt et al. 2012; Wollina et al. 2008). A possible explanation is a discrepancy in the amount of TNF-α and IFN-α molecules in genetically susceptible patients (Raposo and Torres 2016).

The patient was managed with 25 mg of acitretin daily and advised to apply topical clobetasol twice daily for 2 weeks, alternate with calcitriol topical ointment twice daily for 2 weeks, and to repeat as needed.

## Key Points

- Palmar-plantar psoriasis involves the palms and soles.
- Treat mild cases with a high-potency topical corticosteroid for 2 weeks, and then alternate with a topical vitamin D analog. Consider retinoids, methotrexate, cyclosporine, apremilast, or ustekinumab for severe cases or significant body surface area involvement.
- Avoid TNF-alpha inhibitors as they can create palmar-plantar pustular psoriasis.

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# Chapter 9
# Noncompliant 57-Year-Old Patient with Psoriasis

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A 57-year-old female with a long history of poorly managed psoriasis presented for an evaluation of her psoriasis. She complained of pruritus and was unsatisfied with her current medication. She had been using etanercept for 2 years with intermittent clearance of lesions. At presentation, her psoriasis was widespread. Of note, the patient had an extensive history of self-discontinuing medications and requesting alternate treatments. In the past, she had used acitretin, PUVA therapy, adalimumab, and infliximab. All of these medications provided inconsistent results.

Upon further questioning, the patient admitted to using her medication sporadically and not following the recommended

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schedule. Despite the reassurance given at numerous office visits, e-mails, and telephone conversations, the patient feared the potential side effects. She also explained that her busy schedule and many responsibilities hindered her from keeping up with the medication regimen. The patient requested for a new medication that required fewer injections.

The patient was employed as a semitruck driver. She was unmarried and lived in a homeless shelter. She no longer used intravenous drugs; however, she still struggled with alcohol abuse. She had a family history of psoriasis.

On physical examination, there were sharply demarcated indurated erythematous papules and plaques on the scalp, chest, abdomen, and bilateral upper and lower extremities (Figs. 9.1, 9.2, and 9.3). Approximately 12% of

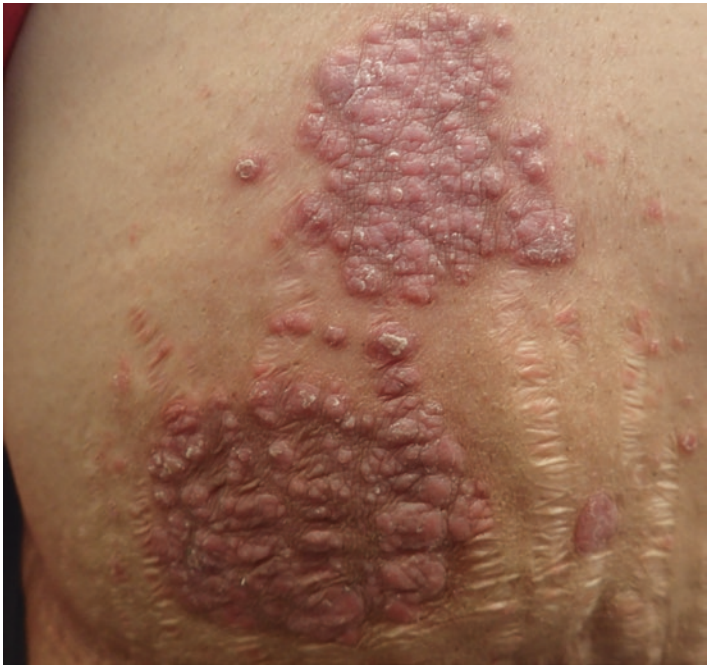

FIGURE 9.1 Erythematous, well-defined, thick papules and plaques with overlying silver scale were present on the upper back and shoulder

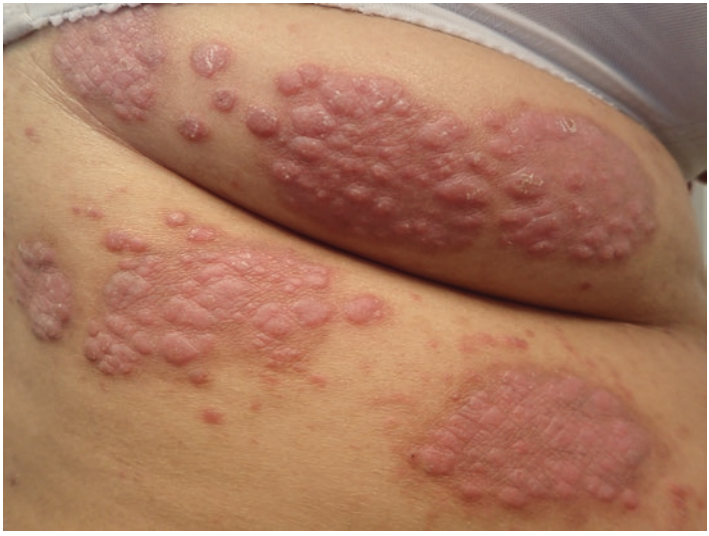

FIGURE 9.2 Erythematous, well-defined papules and plaques with fine scale were present on the lateral trunk. These lesions had less prominent scale than those on the extensor surfaces of the extremities

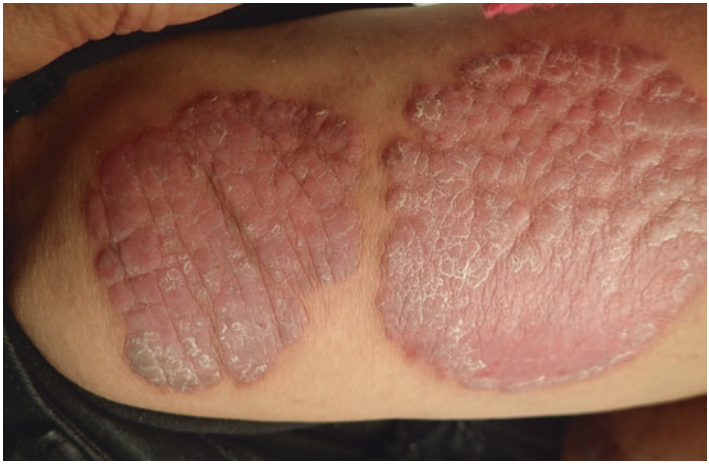

FIGURE 9.3 Erythematous, well-defined, thick papules and plaques with overlying silver scale were present on the anterior thigh

the patient's body surface area was affected. No nail changes were noted.

Based on the case description, what is the best treatment recommendation for this patient?

1. Apremilast
2. Ustekinumab
3. Methotrexate
4. UVB phototherapy
5. Cyclosporine

## Treatment

Ustekinumab

## Discussion

Treatment noncompliance represents a significant challenge for both healthcare professionals and their patients with chronic diseases. In discussing noncompliance, it is important to understand the subtleties of relevant terminology. Compliance is patient behavior that results in following the instructions given by their healthcare provider. In contrast, adherence refers to meeting therapeutic goals set mutually by patient and provider. The need for this similar yet distinct term arose from the understanding that individual patient needs and characteristics impact their ability to meet treatment goals. Treatment noncompliance can be unintentional when instructions are misunderstood or forgotten, or deliberate. While it may at first be difficult to understand why patients seek medical advice for these chronic conditions to which they ultimately fail to comply, numerous factors contribute to deliberate treatment noncompliance. Broadly speaking, variables that affect this type of noncompliance include the doctor-patient relationship, patient beliefs about their condition and medications, and medication side effects (Richards et al. 1999).

Maximizing compliance and adherence in psoriasis patients is of particular importance because it is a chronic, highly prevalent systemic inflammatory condition with numerous medical and psychiatric comorbidities including arthritis, depression, and cardiovascular and metabolic diseases (Augustin et al. 2011). Poor compliance is associated with decreased patient satisfaction, reduced quality of life, and unfavorable treatment outcomes. In fact, for every 10% decrease in adherence, there is an associated 1-point deterioration of psoriasis on a 9-point scale (Carroll et al. 2004). Poor adherence also has economic implications such as increased medication costs, increased utilization of resources, inadequate usage of healthcare professionals' time, and increased sickness-related work absences (Vangeli et al. 2015).

In psoriasis studies, noncompliance rates range between 8 and 73%. The rate reported varies based on both objective and subjective measures used to determine compliance. For example, studies that measure prescription redemption may underestimate noncompliance because they do not account for actual usage of medication. The same applies to studies that use direct patient interviews or patient-to-provider reports because patients may misrepresent their compliance in order to avoid disappointing their provider or negatively impacting future treatment prospects. Conversely, the highest rates of noncompliance are seen in studies that use very stringent criteria for compliance. One study that used the weight of unused medication as a proxy for noncompliance found a rate of 60%. Several studies using anonymous surveys in both Europe and the USA found noncompliance rates of ~40% (Richards et al. 1999; Brown et al. 2006).

In the anonymous survey-based study by Richards et al., non-compliers were significantly younger, had a younger age of psoriasis onset, and had higher self-rated disease severity than compliers. Noncompliant patients also rated both psoriasis and its associated treatments as having a greater impact on their daily lives than did compliant ones, although their overall well-being was not significantly different (Richards et al. 1999). There is conflicting data regarding the association between

gender, marital status, smoking, and employment on compliance. Interestingly, there is a positive association between higher levels of education and treatment compliance (Gokdemir et al. 2008; Zaghloul and Goodfield 2004). The distribution and extent of psoriatic lesions also affect compliance. Noncompliance is more likely in patients with facial lesions, higher numbers of lesions, and greater body surface area involved by lesions (Zaghloul and Goodfield 2004). Depression is a significant comorbidity of psoriasis, occurring in 10–62% of patients, and it is also correlated with noncompliance. Similarly, resignation or feelings of having "had enough" correlate negatively, while optimism and a lack of "why me?" thinking correlate positively with compliance (Zalewska et al. 2007).

Many treatment-related factors affect compliance in psoriasis patients. In selecting therapy for patients, it is important to consider that compliance can be negatively impacted by the belief that dependency on or late side effects of medication often outweigh the patients' subjective assessment of their need for the medication. Of note, it is primarily fear of side effects that affects compliance, not their actual occurrence (Brown et al. 2006). Interestingly, compliance is more likely when patients are treated with a drug for the first time, when the drug is used long term (as opposed to less than 2 months), when the drug is used only once per day, and when the drug has a rapid onset of action (Zaghloul and Goodfield 2004; Atkinson et al. 2004; Uhlenhake et al. 2010). A survey of 1281 patients in Europe showed that the main reasons for noncompliance are low efficacy, poor cosmetic properties, time-consuming use, and occurrence of side effects (Fouéré et al. 2005). There are a number of concerns specific to topical therapies including not only cosmetics but also galenic properties and smell of the preparation. Furthermore, the lower efficacy and longer amount of time needed for application of topical medications compared to systemic agents negatively impact compliance with this treatment modality, which can be as low as 27% (Fouéré et al. 2005). In their survey of 120 patients, Richards et al. found that treatment preference was as

follows: 44% systemic, 26% creams, 17% ointments, 3% phototherapy, and 10% no preference.

With regard to systemic treatments, patients prefer injectable to oral agents, presumably due to the lower dosing frequency of injectable agents (Augustin et al. 2011). There is conflicting compliance data for specific biologic therapies in the studies that have examined this association as of 2015. Two studies found that ustekinumab had higher compliance than adalimumab or etanercept (Clemmensen et al. 2011; Umezawa et al. 2013). One study found patients are more likely to remain on infliximab than adalimumab or etanercept (Gniadecki et al. 2011), while another found that they are more likely to remain on etanercept than infliximab or adalimumab (Esposito et al. 2013). Regardless of the biologic agent used, noncompliance was associated with increased frequency of dosing (Vangeli et al. 2015). First-line treatments for patients with a history of noncompliance consist of agents with high efficacy and infrequent dosing. These include ustekinumab (maintenance dosing every 12 weeks), secukinumab (maintenance dosing every 4 weeks), and ixekizumab (maintenance dosing once every 4 weeks). Conversely, treatments that require frequent dosing or are otherwise time-consuming are best avoided in noncompliant patients. Examples of this type of treatment include phototherapy (often requires multiple, time-consuming treatment sessions per week), infliximab (requires 3 h infusions every 8 weeks), and etanercept (dosed twice per week for the first 3 months).

The patient was started on ustekinumab. At 2-month follow-up, examination showed complete clearance of her psoriatic lesions. She did not report any adverse effects.

## Key Points

- Compliance refers to following treatment instructions set by the provider, while adherence refers to meeting therapeutic goals mutually set by provider and patient.

- Compliance is greatest when using systemic treatments that require infrequent dosing, have a rapid onset of action, and have minimal perceived side effects. An example of this type of treatment is ustekinumab.
- Compliance with topical therapies is low, not only because of cosmetic and tactile properties of these medications but also because of their lower efficacy.

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# Chapter 10
# Severely Obese 42-Year-Old with Psoriasis

**Kavita Darji, Mina Amin, Daniel J. No, and Jashin J. Wu**

A 42-year-old male with a history of psoriasis, class 3 severe obesity (199 kg; BMI 65.5), and hypertension presented for progressive worsening of psoriasis. The patient has used adalimumab 40 mg every week and methotrexate 15 mg every week for the past 18 months. He reported a gradual worsening of psoriasis symptoms in the last 6 months despite adherence to his medication. He expressed his dissatisfaction with the results of his medications and requested a reevaluation of his treatment regimen. The patient denied any injection site reactions, fever, joint stiffness, joint swelling, or pruritus. The remainder of the review of systems was unremarkable. He denied a family history of psoriasis.

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On physical examination, erythematous, scaly indurated papules and plaques were found on the buttocks, intergluteal cleft, bilateral elbows, legs, and knees (Figs. 10.1, 10.2, and 10.3). Approximately 8% of the patient's body surface area was affected.

Based on the case description, what is the best treatment recommendation for this patient?

1. Infliximab 5 mg/kg
2. Acitretin
3. Methotrexate
4. Cyclosporine
5. Etanercept

## Treatment

Infliximab 5 mg/kg

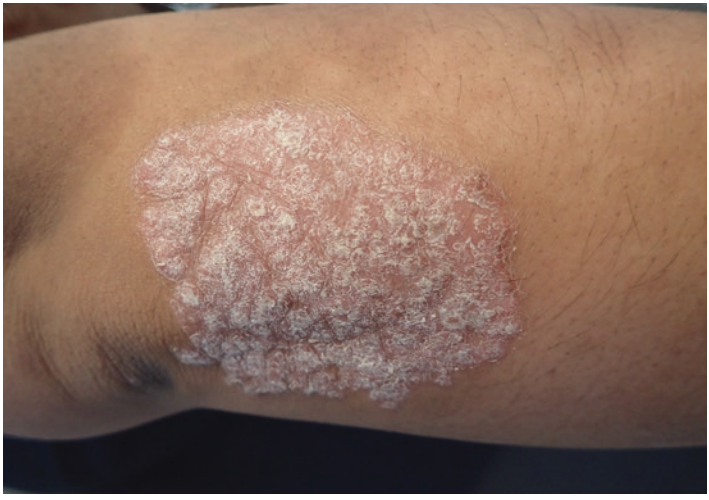

Figure 10.1 A pink-colored plaque with overlying silver scale was found on the patient's knee

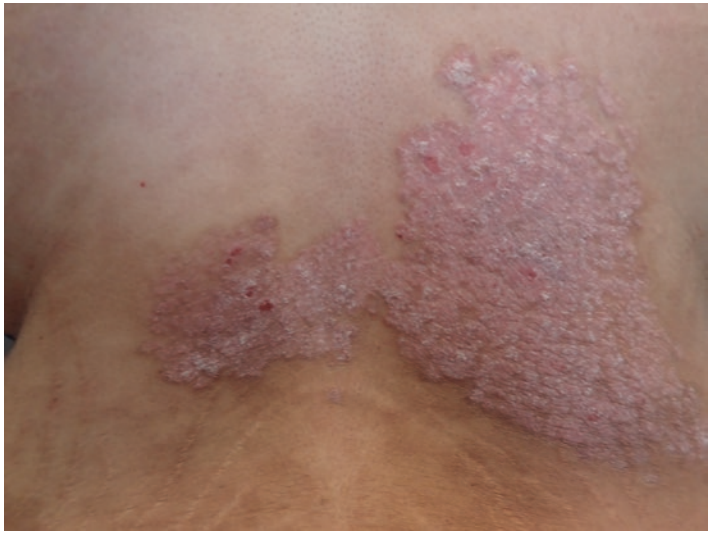

FIGURE 10.2 An erythematous plaque with overlying silver scale was found on the patient's back

## Discussion

Obesity can be defined as a body mass index (BMI) of 30 or more, while morbid obesity is represented by a BMI of 35 or more (Bremmer et al. 2010). In a study conducted early on by Lindegard evaluating 159,200 Swedish patients over a 10-year period, it was shown that psoriasis was associated with various diseases, including obesity (Lindegard 1986). Multiple subsequent studies also supported this association. For instance, a case-control study evaluating 560 patients psoriatic patients showed that the odds of having psoriasis with a BMI between 26 and 29 or above 30 were 1.6 and 1.9, respectively, compared to non-obese control subjects (Naldi et al. 2005). Furthermore, another prior study showed increased odds of obesity in patients with severe psoriasis (odds ratio [OR] = 1.8) and mild psoriasis (OR = 1.3)

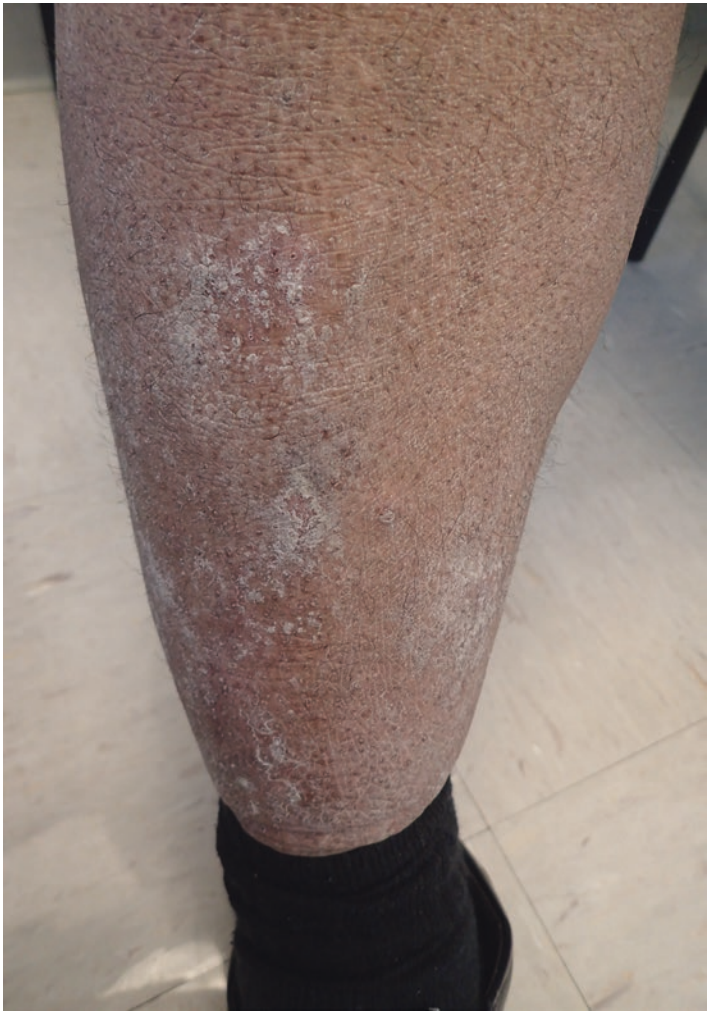

Figure 10.3 An erythematous plaque with overlying silver scale was found on the patient's lower anterior leg

compared to control patients without psoriasis (Neimann et al. 2006). As a result, cardiovascular risk factors associated with metabolic syndrome are more prevalent in patients with psoriasis than control subjects, with severe psoriasis patients having a higher odds ratio than mild psoriasis patients (Neimann et al. 2006). A prior case series showed that patients from the Utah Psoriasis Initiative had a higher prevalence of obesity than the general Utah population (34% vs. 18%) as well as non-psoriatic clinic patients (Herron et al. 2005). Moreover, 13% of morbidly obese patients, 11% of obese patients, and 5% of non-obese patients self-reported having inverse psoriasis (Herron et al. 2005). This study also demonstrated that obesity might occur as a consequence of psoriasis, instead of being a risk factor for disease onset (Herron et al. 2005). Research also shows that psoriasis is positively associated with increased incidence of metabolic syndrome, cardiovascular disease, diabetes mellitus, and dyslipidemia (Frieder and Ryan 2016). For instance, a systematic review of 17 articles with 28,939 total patients, of which 3791 suffered from psoriasis, showed that the odds ratio (OR) for metabolic syndrome and psoriasis ranged from 1.39 to 4.49 and the adjusted OR ranged from 1.29 to 5.14. This review also found that psoriatic patients had increased prevalence of the individual components of metabolic syndrome (Singh et al. 2016).

There is debate about which comes first—psoriasis or obesity (Bremmer et al. 2010). "The aforementioned case series of over 500 psoriatic patients found that the majority of obese patients became obese after the diagnosis of psoriasis and were not obese at age 18, thus showing that psoriasis preceded obesity." (Herron et al. 2005). Psoriasis could pave the way for obesity for a variety of reasons, including isolation from society, unhealthy diet, negative mood, alcohol intake, and reduced physical exercise, often due to psoriatic arthritis (Bremmer et al. 2010). Greater lifetime Dermatology Life

Quality Index (DLQI) correlated with a greater discrimination as work and in social settings and a greater likelihood of believing that psoriasis caused weight gain, as impaired self-confidence is linked to obesity (Kim et al. 2015).

There is also literature that shows that obesity serves as a predilection to psoriasis and can double the rate of incidence of psoriasis (Gisondi et al. 2016). Although the exact mechanism causing the association between psoriasis and obesity is unclear, obesity is thought to involve the proliferation of pro-inflammatory cytokines and adipokines (Bremmer et al. 2010; Setty et al. 2007).

A variety of treatment options are available for obese psoriasis patients. A review study of three clinical trials showed that infliximab, which is weight-based, demonstrated consistent efficacy across patients with varying BMIs, both obese and not obese (Reich et al. 2006). Overall efficacy of ustekinumab in obese patients has been shown to be high in psoriatic patients, but weight did seem to influence efficacy at fixed doses (Papp et al. 2008). More partial responders at week 28 who received ustekinumab 90 mg every 8 weeks achieved PASI 75 at week 52 (68.8%) than did those who continued to receive the same dose every 12 weeks (33.3%) (Papp et al. 2008). Thus, in heavier patients, first-line biological drug choices include infliximab and ustekinumab because they are weight based (Carrascosa et al. 2014). PUVA is an effective treatment option that is unaffected by obesity since the dose of psoralen is weight based (Herron et al. 2005). Another study showed that patients with increased weights were less responsive to etanercept and needed higher doses in order to have increased efficacy in obese patients with psoriasis (Gordon et al. 2006). Therefore, increased cost and drug exposure should be evaluated when treating obese psoriasis patients who responded to doubled doses, but not to conventional doses of etanercept and adalimumab (Carrascosa et al. 2014).

Careful attention must be applied when selecting treatment for obese patients with psoriasis. Since adipose tissue plays a key role in glucose and lipid metabolism, it is important to note

that systemic treatments can cause adverse effects and derangements in liver enzymes, renal function, and serum lipids in obese patients with psoriasis (Bremmer et al. 2010; Gisondi et al. 2016). As a result, these obese patients can have worsened liver and renal function if given treatments such as cyclosporine and methotrexate (Gisondi et al. 2016). Moreover, obesity may hinder the effect of systemic treatment in psoriatic patients. The biologic with weight-based dosing is infliximab, 5 mg/kg (Bremmer et al. 2010). Of note, etanercept has been shown to cause weight gain and increased BMI in patients with psoriasis (Esposito et al. 2009). Additionally, acitretin treatment for psoriasis in obese patients is often complicated by hypercholesterolemia with decreased high-density lipoproteins (Garcia-Patos 2005).

The patient elected to change to infliximab treatment. Follow-up at the 9 months, which occurred 2 months after bariatric surgery, showed that his BSA decreased from 8% to 2%. If the patient continues to lose weight, reducing the dosage of infliximab will be considered.

## Key Points

- Psoriasis is associated with obesity, as well as several related conditions, including metabolic syndrome, cardiovascular disease, dyslipidemia, and diabetes mellitus.
- Treatment of obese psoriatic patients includes weight-based biologic therapy, especially the first-line options of infliximab and ustekinumab, as well as phototherapy.
- Systemic treatments such as methotrexate and cyclosporine should be avoided due to adverse effects.

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# Chapter 11
# 62-Year-Old Male with Rash Induced by Tumor Necrosis Factor Inhibitor

**Mina Amin, Daniel J. No, and Jashin J. Wu**

A 62-year-old male with a history of Crohn's disease and ankylosing spondylitis presented to the clinic with a 3-week history of new-onset pruritic erythematous scaly papules on bilateral upper extremities. The patient stated that the rash had started on the dorsal aspect of his hands and progressively extended to his forearms, elbows, and axillae. The patient had tried applying emollients to the lesions with no benefit. He denies fever, chills, unintentional weight loss, and recent travel. The patient has no known allergies and denies the recent use of new medications. He has been using infliximab for 2 years for the management of Crohn's disease and

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ankylosing spondylitis. He denies a family history of skin disorders.

On physical examination, there were multiple scattered 1 cm erythematous papules with fine white scales on the plantar and dorsal aspects of both hands. A few lesions were extending up to bilateral forearms. There were also 2–3 cm erythematous well-demarcated plaques with thicker white scales on bilateral elbows and axillae.

Based on the clinical case description, what is the most likely diagnosis?

1. Seborrheic dermatitis
2. Atopic dermatitis
3. Nummular eczema
4. Psoriasis secondary to TNF inhibitor therapy
5. Acute generalized exanthematous pustulosis

## Diagnosis

Psoriasis secondary to TNF inhibitor therapy

## Discussion

Tumor necrosis factor alpha (TNF-alpha) is a proinflammatory cytokine that plays an important role in the development of a variety of inflammatory disorders. TNF inhibitors are widely used to treat rheumatoid arthritis, inflammatory bowel disease, spondyloarthropathies, and even psoriasis. Multiple reports have described a paradoxical exacerbation of preexistent psoriasis or de novo psoriasis in patients on TNF inhibitor therapy (López-Robles et al. 2012; Wollina et al. 2008).

Infliximab, adalimumab, and etanercept are all associated with development or aggravation of psoriasis (Famenini and Wu 2013). A comprehensive literature review of 142 cases reveals the onset of psoriasis to occur 13.6, 7.6, and 8.2 months after initiation

of infliximab, adalimumab, and etanercept, respectively (Famenini and Wu 2013). Palmoplantar pustular psoriasis and pustular psoriasis are rare forms of psoriasis. However, these are the most common types of psoriasis that develop in patients on TNF inhibitor therapy. Patients with inflammatory bowel disease are more likely to develop psoriasis with infliximab therapy. Alternatively, patients with rheumatologic diseases are more likely to develop psoriasis on adalimumab. Additionally, women are at a slightly higher risk than men to develop psoriasis on TNF inhibitor therapy (Famenini and Wu 2013).

A literature review of 241 cases demonstrated that patients with exacerbation of psoriasis from TNF inhibitor therapy most commonly developed novel forms of psoriasis at different body sites than their initial site of psoriasis. Also, patients with de novo psoriasis that were switched to a different TNF inhibitor experienced the same type of psoriasis as seen with the first TNF inhibitor. Therefore, psoriasis secondary to TNF inhibitor therapy is perhaps de novo and not an exacerbation of underlying psoriasis (Joyau et al. 2012).

The leading hypothesis for the development of psoriasis after TNF inhibitor therapy is a discrepancy in the amount of TNF-alpha and IFN-alpha molecules in genetically susceptible individuals (Raposo and Torres 2016). Plasmacytoid dendritic cells accrue in the skin of psoriasis patients, and the production of IFN-alpha by these cells appears to play a critical role in the development of psoriasis (Nestle et al. 2005). Interestingly, psoriasis can develop or worsen in patients after initiation of IFN-alpha therapy (Famenini and Wu 2013; Ladoyanni and Nambi 2005). An important regulator of IFN-alpha production is TNF-alpha. TNF-alpha inhibits the production of IFN-alpha by plasmacytoid dendritic cells and inhibits maturation of plasmacytoid dendritic cells (Richette et al. 2007; Famenini and Wu 2013; Palucka et al. 2005). TNF inhibitor therapy can, therefore, lead to the accumulation of IFN-alpha, ultimately promoting the development of psoriasis (Famenini and Wu 2013).

Acute generalized exanthematous pustulosis refers to the rapid development of multiple pustules covering an

erythematous area of the skin within hours to days after beginning a new drug (Speeckaert et al. 2010). Seborrheic dermatitis creates well-defined erythematous plaques, yet frequently presents with a yellow scale and appears greasy. Atopic dermatitis produces papules and vesicles, which are more associated with pruritus and xeroderma. Nummular eczema presents with multiple pruritic lesions that appear coin-shaped (Jiamton et al. 2013).

The first-line treatment for psoriasis secondary to TNF inhibitor therapy is class 1 topical corticosteroids, methotrexate, and discontinuation of the TNF inhibitor. High-potency topical steroids have been most efficacious in improving or completely clearing psoriasis in these patients (Famenini and Wu 2013; Joyau et al. 2012; Rallis et al. 2010; Wollina et al. 2008). Ideally, discontinue treatment of the TNF inhibitor. Patients frequently experience substantial improvement upon discontinuation of TNF inhibitor therapy and addition of topical corticosteroids (Famenini and Wu 2013). A decision to discontinue TNF inhibitor therapy should take into consideration the severity of the psoriasis. Efforts of switching patients to a different TNF inhibitor have created a wide range of conflicting results that remain inconclusive (Famenini and Wu 2013; Hawryluk et al. 2012). Systemic therapy with methotrexate should be initiated if topical corticosteroids are ineffective (Famenini and Wu 2013).

Infliximab therapy was continued in this patient because of adequate control of Crohn's disease and ankylosing spondylitis. Topical therapy was initiated with desonide for the axillae and clobetasol for the upper extremities.

## Key Points

- TNF inhibitors can exacerbate preexistent psoriasis or create de novo psoriasis.
- An explanation for the development of psoriasis in these patients is a disproportion in the amount of TNF-alpha and IFN-alpha molecules.
- First-line treatments for psoriasis secondary to TNF inhibitor therapy are class 1 topical corticosteroids, methotrexate, and discontinuation of the TNF inhibitor.

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# Chapter 12
# 33-Year-Old Female with Psoriasis Planning for Pregnancy

**Daniel J. No, Stacey Pun, Mina Amin, and Jashin J. Wu**

A 33-year-old female with a 20-year history of moderately controlled psoriasis presented to the clinic seeking advice on how to best manage her psoriasis if she were to become pregnant. She and her spouse were planning on conceiving a child in 6 months. Her current treatment regimen included adalimumab and methotrexate. She denied experiencing side effects with her medications. She was otherwise healthy and does not have any other medical illnesses.

On physical examination, there was a single isolated erythematous scaly indurated plaques on the right leg. There were also well-demarcated hyperpigmented macules and patches on the bilateral upper and lower extremities. No nail

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deformities were appreciated. There was no evidence of joint swelling or inflammation.

Based on the case description, what is the best treatment recommendation(s) for this patient?

1. Continue current regimen (adalimumab and methotrexate).
2. Discontinue methotrexate and continue adalimumab.
3. Discontinue current regimen and prescribe topical agent.
4. Discontinue current regimen and recommend ultraviolet phototherapy.
5. Discontinue methotrexate and switch to ustekinumab.

## Treatment: Discontinue Current Regimen and Prescribe Topical Agent or Discontinue Current Regimen and Recommend Ultraviolet Phototherapy

A large proportion of women affected by psoriasis experience the onset of disease during their reproductive years. In the USA alone, it has been estimated that over 100,000 births occur in women with psoriasis (Horn et al. 2009). The progression of psoriasis during pregnancy is unpredictable. Data compiled from multiple studies found that approximately 37% of patients with psoriasis reported an improvement during pregnancy. Conversely, 18% of patients reported worsening of severity (Murase et al. 2005). The improvement in psoriasis is likely due to the hormone-mediated immunosuppression that occurs during pregnancy. Of note, the majority of women who experienced improvement during pregnancy returned to their baseline severity postpartum.

Some studies have demonstrated an association with psoriasis and poor pregnancy outcomes. The outcomes among the studies have not been consistent. However, women with psoriasis during pregnancy were more likely to have a spontaneous abortion, cesarean delivery, and/or deliver

newborns of low birth weights (Ben-David et al. 2008; Yang et al. 2011). Additionally, pregnant women are at a higher risk of developing pustular psoriasis (impetigo herpetiformis), a severe generalized form of psoriasis. This can occur in women with or without preexisting psoriasis. Pustular psoriasis has the potential of causing life-threatening complications and therefore requires immediate intervention.

## Treatment

Topical medications are frequently used among pregnant psoriasis patients. They are generally considered to be safe due to their negligible systemic absorption and fetal exposure. In particular, topical corticosteroids remain the mainstay of treatment and are considered the first-line therapy. Low to moderate potency topical steroids are preferred over high potency steroids. High potency corticosteroids have been associated with low birth weight and fetal growth restriction (Chi et al. 2016). However, when high potency steroid use is warranted, application should be limited to the second and third trimester and not exceed 300 g for the duration of the entire pregnancy (Chi et al. 2013; Bae et al. 2012).

Second-line therapy for pregnant women is ultraviolet phototherapy. Narrowband ultraviolet B (UVB) is preferred due to its greater efficacy and reduced side effects compared to broadband UVB and ultraviolet A phototherapy (Barbagallo et al. 2001). The lack of systemic and fetal toxicity gives phototherapy an advantage over systemic therapies. However, decreased folic acid levels have been observed in patients exposed to ultraviolet phototherapy (El-Saie et al. 2011). The theoretical increased risk of fetal neural tube defects warrants daily folic acid supplementation for women of child-bearing potential undergoing phototherapy. Phototherapy is also associated with melasma.

Cyclosporine is a third-line agent and can be considered for the management of severe or disabling forms of psoriasis (e.g., pustular psoriasis of pregnancy) in pregnant patients.

The majority of current recommendations are extrapolated from studies that observed pregnant transplant recipients immunosuppressed with cyclosporine. Cyclosporine has not been associated with birth defects; however, a compelling amount of data has associated cyclosporine with low birth weight and prematurity (Bae et al. 2012). Additionally, some literature have noted an increase in the incidence of maternal hypertension and preeclampsia. A follow-up study of children exposed to cyclosporine in utero did not reveal any long-term disabilities (Nulman et al. 2010; Cochat et al. 2004). Despite the safety profile demonstrated in the literature, pregnant psoriasis patients requiring cyclosporine must be counseled appropriately and closely monitored.

Of the biologic medications, tumor necrosis factor (TNF) inhibitors are the most frequently used biologics during pregnancy. Multiple case reports and studies have demonstrated that TNF inhibitor treatment was not associated with unfavorable pregnancy outcomes or congenital malformations (Hyrich and Verstappen 2014). Within the studies, a large proportion of women discontinued treatment during the first trimester; however, the evidence still suggests that they are safe to use throughout the entire pregnancy. However, although controversial, there has been speculation of VACTERL abnormalities associated with etanercept use (Carter et al. 2006). Despite the generally safe profile of TNF inhibitors exhibited in the overwhelming majority of studies, the consensus remains that TNF inhibitors should be used with caution and reserved for severe debilitating forms of psoriasis. Other classes of biologic agents have not been adequately studied for their use in pregnancy and therefore are not recommended at this time.

Methotrexate is a well-documented teratogen and abortifacient and is absolutely contraindicated during pregnancy (Table 12.1). If it is used by a woman of child-bearing potential, simultaneous use of a highly effective form of contraception is required. However, if a patient is using methotrexate and is planning to conceive, many experts recommend discontinuing methotrexate use for a minimum of 3 months

Table 12.1 Pregnancy risk categories defined by the US Food and Drug Administration (FDA) and evidence-based recommendations of commonly used medications for the management of psoriasis (Murase et al. 2014)

| Medication | FDA category | Recommendations |
|---|---|---|
| Topical corticosteroids | C | First-line agent: Prefer low to moderate potency |
| Topical pimecrolimus | C | Minimal data: Avoid |
| Topical tacrolimus | C | Minimal data: Avoid |
| Topical calcipotriene | C | < 100 g/week of 0.05% solution has no effect on calcium homeostasis. Use on small surface permissible |
| Cyclosporine | C | Third-line agent: Risk of low birth weight and prematurity. Consider only for severe cases. No long-term effects observed in children |
| Methotrexate | X | Contraindicated |
| Apremilast | C | Minimal data: Not recommended |
| Etanercept | B | Third-line agent: Consider only for severe cases |
| Adalimumab | B | Third-line agent: Consider only for severe cases |
| Infliximab | B | Third-line agent: Consider only for severe cases |
| Ustekinumab | B | Not recommended |
| Secukinumab | B | Not recommended |
| Ixekizumab | – | Not recommended |
| Acitretin | X | Teratogenic |
| Tazarotene | X | Teratogenic |

FDA categories: A, B, C, D, X

before conception to permit adequate systemic clearance (Menter et al. 2009).

Acitretin is absolutely contraindicated in pregnancy due to its association with major birth defects. To prevent inadvertent exposure, its use should be avoided in women of childbearing age. Additionally, pregnancy is contraindicated for no less than 3 years after discontinuing acitretin. Their topical counterparts (e.g., tazarotene) are also contraindicated in pregnancy.

Our patient was advised to discontinue methotrexate at a minimum of 3 months before attempting to conceive a child. The patient was also informed of the potential risks of continuing adalimumab during pregnancy. She ultimately discontinued adalimumab before becoming pregnant and opted to use mid-potency topical steroids concurrently with narrowband UVB phototherapy for maintenance therapy.

## Key Points

- First-line agents for pregnant psoriasis patients are low- to moderate-potency topical corticosteroids. Avoid excessive use of high potency topical steroids (no more than 300 g total).
- UVB phototherapy use is safe during pregnancy and is considered to be a second-line agent.
- Cyclosporine and tumor necrosis factor inhibitor use in pregnancy is reserved for severe or recalcitrant forms of psoriasis.

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# Chapter 13
# Infected Joint Prosthesis in a 56-Year-Old with Psoriasis

**Mina Amin, Kavita Darji, Daniel J. No, and Jashin J. Wu**

A 56-year-old female with an extensive history of psoriasis, psoriatic arthritis, and systemic lupus erythematosus presented for evaluation of worsening psoriasis after discontinuing adalimumab. Her adalimumab was stopped 6 weeks earlier when an infected right elbow prosthesis was discovered. The patient's surgeon planned to reassess her after completing an extended intravenous antibiotic regimen to determine if further intervention would be necessary. Since stopping adalimumab, she noticed worsening of her psoriasis on her face, scalp, and both upper and lower extremities. The patient had used adalimumab for the past 5 years with good

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results, marginal side effects, and no prior serious infections. She was otherwise healthy and denied fever, chills, and night sweats.

On physical examination, there were erythematous indurated papules and plaques with overlying silver-colored scales on the face, occipital scalp, chest, abdomen, upper back, and bilateral elbows and knees. Approximately 10% of the body surface area was affected. The right elbow was not erythematous, not swollen, and non-tender to palpation.

Based on the case description, what is the best treatment recommendation for this patient?

1. Apremilast and topical corticosteroids
2. Adalimumab
3. Methotrexate
4. Etanercept
5. Delay treatment until infection resolves

## Treatment

Apremilast and topical corticosteroids.

## Discussion

Immunomodulatory therapy significantly enhances the functional ability and quality of life for patients with psoriasis and psoriatic arthritis. Methotrexate, cyclosporine, and the following eight biologic agents are Food and Drug Administration (FDA)-approved for the treatment of psoriasis, psoriatic arthritis, or both: etanercept, adalimumab, infliximab, golimumab, secukinumab, ustekinumab, certolizumab pegol, and ixekizumab (Choi et al. 2016).

Tumor necrosis factor (TNF)-alpha is a cytokine that stimulates the inflammatory response and plays a major role in tissue healing and host defense against infection. TNF-alpha also stimulates angiogenesis, collagen production, and exists in higher amounts in areas of tissue destruction

(Choi et al. 2016; Bibbo and Goldberg 2004; Barrientos et al. 2008). Infectious complications reported with TNF inhibitor therapy include septic arthritis, respiratory tract infections, opportunistic infections, urinary tract infections, and abscess formation (Bibbo and Goldberg 2004). Consequently, perioperative TNF inhibitor therapy may interfere with proper wound healing and increase the risk of infections postoperatively (Fabiano et al. 2014).

The combination of immunosuppressive therapy and the stress of surgery can increase the risk of postsurgical infections (Fabiano et al. 2014). Surgery itself increases the risk of infection, as it is associated with immunosuppression. Surgery impedes the normal immune response by reducing leukocyte function, lymphocyte response, complement activation, and IgG serum levels. Different elements of surgery, such as anesthesia, blood transfusion, and blood loss, can also impair normal immunity (Esposito 2001).

Immunosuppressive therapy puts patients at a greater risk of developing infections postoperatively (Fabiano et al. 2014). A retrospective review evaluated the perioperative use of TNF inhibitor therapy on 17 psoriasis patients. Complications were noticed in two patients that continued therapy: one patient with colon resection experienced erythema and infection at the area of incision, and another experienced a wound site infection during root canal surgery. Complications did not occur in the patients that discontinued TNF inhibitor therapy 1–2 weeks before surgery and resumed 1 week after surgery. However, five out of six patients that discontinued therapy experienced psoriasis exacerbations (Reinstadler et al. 2010).

Another retrospective review examined 131 psoriasis patients on TNF inhibitor therapy or ustekinumab. Out of 44 patients that discontinued TNF inhibitor therapy four half-lives before surgery, two experienced surgical wound infections. Out of the 87 patients that did not discontinue therapy, only one patient developed a postoperative wound infection. This data suggests that there is no significant difference in postsurgery complications when TNF inhibitor or IL-12/23 inhibitors are discontinued (Fabiano et al. 2014; Choi et al. 2016).

A retrospective analysis of 77 surgeries performed on 42 patients with psoriasis, psoriatic arthritis, or both on biologic therapy compared the risk of postoperative infection among patients who continued therapy perioperatively and those who discontinued therapy. No difference in risk of postoperative complications, such as infections or delayed wound healing, was observed among patients that continued therapy and patients that stopped treatment. On the other hand, patients that discontinued treatment experienced more psoriasis exacerbations compared to patients that continued therapy (Bakkour et al. 2016).

Perioperative methotrexate use in patients with psoriasis and psoriatic arthritis is important and needs to be further studied. The data on methotrexate use perioperatively in patients with rheumatoid arthritis has been conflicting. However, the majority of guidelines conclude that methotrexate use is safe throughout surgery in patients with rheumatoid arthritis, and the dosing for methotrexate in rheumatoid arthritis and psoriasis are comparable. Studies on cyclosporine use in patients with inflammatory bowel disease did not demonstrate an increased risk of complications postoperatively (Choi et al. 2016).

The modest and safest approach to management of patients on biologic therapy is discontinuation of treatment four half-lives before surgery (Choi et al. 2016). However, interruption of immunomodulatory therapy can result in a relapse of psoriasis symptoms. This is especially important in patients who need to undergo periodic surgical procedures, such as dental operations or skin cancer patients (Fabiano et al. 2014). Therefore, it has been suggested that infliximab, methotrexate, cyclosporine, etanercept, and adalimumab can be maintained during low-risk surgery, whereas modified assessment is required on a case-by-case basis for intermediate and high-risk surgeries. It has been recommended to discontinue biologic agents at least four half-lives before major surgery. Methotrexate or cyclosporine can be considered during the intermittent period to decrease the risk of psoriasis exacerbation. Further studies need to examine the safety

of golimumab, ustekinumab, certolizumab pegol, apremilast, secukinumab, and ixekizumab for psoriasis and psoriatic arthritis patients undergoing surgery (Choi et al. 2016).

Apremilast, phototherapy, topical agents, and acitretin are optimal treatment options for patients with psoriasis or psoriatic arthritis previously on immunosuppressive therapy that are now actively infected. Apremilast, a phosphodiesterase-4 inhibitor, is efficacious in psoriasis and psoriatic arthritis yet may lead to nausea, weight loss, diarrhea, and upper respiratory tract infections (Yiu and Warren 2016). Phototherapy and topical agents are treatment options that do not pose the risk of causing systemic toxicity in comparison to the immunomodulatory agents (Menter et al. 2008). It is recommended to avoid immunomodulatory therapy, while the patient is actively infected.

Our patient was prescribed apremilast during the interim period, along with fluocinonide solution for the scalp and topical clobetasol cream for the body. The infection resolved, and thus follow-up appointment with surgery deemed further intervention unnecessary. The patient was switched back to adalimumab with complete resolution of symptoms (Tables 13.1 and 13.2).

## Key Points

- Immunomodulatory therapy and the stress of surgery can simultaneously increase the risk of postoperative complications in psoriasis and psoriatic arthritis patients, such as delayed wound healing and infections.
- Apremilast, phototherapy, topical agents, and acitretin can be used to treat patients with psoriasis or psoriatic arthritis that are actively infected. Avoid immunomodulatory agents during active infection.
- Consider maintaining immunosuppressive therapy for low-risk surgeries and perhaps discontinuing treatment 4 half-lives before intermediate to high-risk surgery.

Table 13.1 Classification of operations based on risk (reproduced from Choi et al. 2016)

| |
|---|
| *Low risk* |
| Breast biopsy or excision |
| Bronchoscopy |
| Cystoscopy |
| Dermatologic procedure |
| Endoscopy |
| Hysteroscopy |
| Ophthalmologic operation |
| Outpatient procedure |
| *Intermediate risk* |
| Abdominal or thoracic operation (uncomplicated) |
| Carotid endarterectomy |
| Head and neck procedure (uncomplicated) |
| Orthopedic procedure |
| Prostate operation |
| Urologic procedure |
| *High risk* |
| Aortic or main vascular operation |
| Cardiac surgery |
| Emergency procedure |
| Extended surgery time (>4 h) |
| Major thoracic surgery |
| Peripheral arterial vascular operation |

Table 13.2 Suggested preoperative discontinuation time and half-lives of immunomodulatory therapy for psoriasis or psoriatic arthritis (reproduced from Choi et al. 2016)

| Immunomodulatory medication | Half-life | Suggested preoperative discontinuation period |
|---|---|---|
| Adalimumab | 14–19 days | 8–11 weeks |
| Certolizumab pegol | 14 days | 8 weeks |
| Cyclosporine | 8 h | 1.5 days |
| Etanercept | 3–5 days | 2–3 weeks |
| Golimumab | 13 days | 7 weeks |
| Infliximab | 8–9 days | 4–5 weeks |
| Ixekizumab | 14–18 days | 8–10 weeks |
| Methotrexate | 6–8 h | 1–1.5 days |
| Secukinumab | 21–28 days | 12–16 weeks |
| Ustekinumab | 21 days | 12 weeks |

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# Chapter 14
# 43-Year-Old with Recurrence of Red, Scaly Rash

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A 43-year-old male with a 9-year history of well-controlled plaque psoriasis presented with concerns of progressive worsening of his psoriasis symptoms. His psoriasis had been well managed with adalimumab for the past 5 years with less than 1% body surface area affected. However, the patient states that new lesions formed on both upper and lower extremities in the past 4 months. The patient is compliant with his medication regimen and denies any interruptions in treatment. He does not complain of side effects from his medication. The review of systems did not reveal any pertinent positive or negative findings. He denies recent illness,

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trauma to the skin, or use of new medications. He has no other medical conditions and does not use any other medications. The patient has a maternal family history of psoriasis. The patient is a former smoker and denies the use of alcohol.

On physical examination, bilateral knees, dorsal hands, and elbows had erythematous, indurated papules and plaques with overlying silvery scales. Less prominent papules with fine scales were also found on the back and face. A total of 5% body surface area was affected.

Based on the case description, what is the best treatment recommendation for this patient?

1. Continue current regimen (adalimumab).
2. Add topical agent to current regimen.
3. Discontinue current regimen and prescribe alternate biologic agent.
4. Discontinue current regimen and recommend ultraviolet phototherapy.
5. Add methotrexate to current regimen.

## Treatment

Add methotrexate to current regimen.

## Discussion

The effectiveness in managing psoriasis has vastly improved since the emergence of biologic medications. However, biologic drugs tend to lose efficacy with extended use (Levin et al. 2014). Although the specific mechanism that causes the clinical decline is not completely understood, evidence suggests that an immune-mediated mechanism is partially responsible. Biologic drugs are recognized by the immune system as foreign and elicit a helper T-cell-dependent humoral response that leads to the development of antidrug antibodies (ADAs) (van Schouwenburg et al. 2013). ADAs are

considered to be either neutralizing or non-neutralizing. Neutralizing ADAs bind to the drug's active site and prevent it from interacting with its end target. Non-neutralizing ADAs may form immune complexes with the drug, thereby increasing drug clearance (Jullien et al. 2015). Nonetheless, both neutralizing and non-neutralizing ADAs likely alter the bioavailability, excretion, binding sensitivity, and ultimately the efficacy of biologic medications. In order to maximize the utility of biologic agents, additional studies must be conducted to find effective methods of reducing biologic drug immunogenicity and identifying risk factors for loss of response.

## Treatment

Patients experiencing a loss of effect from biologic agents are managed differently depending on the severity of recurrence. A topical corticosteroid may be adequate if less than 3% of the body surface area (BSA) is affected. Apply the topical steroid BID for 2 weeks and alternate with a steroid-sparing agent BID for 2 weeks and repeat as needed. If recurrence involves more than 3% BSA, add methotrexate (7.5–25 mg weekly) to the patient's current medication regimen for 3–6 months. If symptoms do not improve, consider switching to a different biologic agent with a long-term drug survival (e.g., ustekinumab).

The theory that concurrent methotrexate use can be used to overcome loss of efficacy is supported by retrospective studies of infliximab and adalimumab. Vermeire et al. demonstrated that simultaneous methotrexate use reduces the risk of ADA formation (Vermeire et al. 2007). The group of patients using infliximab with concurrent methotrexate had a lower incidence of ADA formation (46%) compared to the infliximab monotherapy group (73%). Lower serum infliximab levels were also seen in patients not simultaneously using methotrexate. The evidence for concomitant methotrexate use in minimizing loss of biologic effect appears reassuring, although further studies are needed to clarify the exact mechanism and proper dosage.

In a 52-week randomized control trial, 71% of participants treated with adalimumab obtained a 75% reduction in their Psoriasis Area and Severity Index score (PASI 75) after 16 weeks (Menter et al. 2008). During the study, 9% of patients developed anti-adalimumab antibodies (AAAs). Forty-three percent of AAA-positive participants lost clinical response by week 52. In the 3-year open-label extension study, 83% and 76% of participants who received uninterrupted adalimumab therapy maintained PASI 75 at week 100 and week 160, respectively (Gordon et al. 2012). Asahina et al. further demonstrated the correlation of AAAs and poor clinical response. Patients with AAAs fared worse with significantly lower PASI 75 response (23% vs. 73% in AAA-positive patients vs. AAA-negative patient, respectively), PASI 50 response (39% vs. 87%), and PASI 90 response (0% vs. 52%) at week 16 and week 24 (Asahina et al. 2010).

The long-term efficacy of ustekinumab has been well established in two long-term studies (PHOENIX 1 and PHOENIX 2) (Kimball et al. 2013; Langley et al. 2015). In the PHOENIX 2 study, 63.1% and 72% of participants achieved a PASI 75 response by week 12 when administrated 45 mg or 90 mg of ustekinumab, respectively (Papp et al. 2008). About 5% of the participants developed anti-ustekinumab antibodies. Of note, from the group who attained PASI 75, only 2% of participants were found to have anti-ustekinumab antibodies. In contrast, 13% of patients with partial response were found to have anti-ustekinumab antibodies. The authors also noted that partial responders had trough serum drug levels two to three times lower than PASI 75 responders. To further assess the long-term efficacy of ustekinumab, participants who achieved PASI 75 at week 40 were given an every-12-week maintenance treatment to complete 244 weeks of treatment. Approximately 80% of the patients maintained a PASI75 response through 244 weeks of therapy (Papp et al. 2013).

Secukinumab has exhibited low immunogenicity in two 52-week studies. In the ERASURE study, 82% of participants who received 300 mg of secukinumab attained PASI 75

at week 12 (Langley et al. 2014). Similarly, the FIXTURE study showed a 77% response (Langley et al. 2014). Of note, 81% of patients in the ERASURE study maintained PASI 75 from week 12 to week 52. The FIXTURE study showed comparable results with 84% of patient maintaining PASI 75. The FIXTURE study detected anti-secukinumab antibodies in four patients (0.4% of 980 secukinumab-treated patients). None of the antibodies were neutralizing and were not associated with loss of efficacy. In the ERASURE study, anti-secukinumab antibodies were found in two patients (0.3%), one of which was a neutralizing ADA. However, neither patient experienced a loss of efficacy.

The long-term efficacy of ixekizumab is demonstrated in three 60-week phase 3 trials. In the UNCOVER-3 trial, 87% of patients achieved PASI 75 by week 12 (Gordon et al. 2016). The long-term efficacy of ixekizumab is demonstrated by the 83% of patients who maintained PASI 75 at week 60 with an every-4-week maintenance therapy. Anti-ixekizumab antibodies were found in 103 of 1150 patients (9%) in all three UNCOVER trials. The 19 patients with high titers (>1:1280) of antidrug antibodies had decreased clinical efficacy and collectively did not attain PASI 50 at week 12. However, patients with low to moderate titers had clinical efficacy that was comparable to their counterparts without detectable levels of ADAs.

In a large multicenter 24-week study, 49% of patients achieved PASI 75 by week 12 when administered 50 mg of etanercept twice weekly. Of the patients who achieved PASI 75 at week 12, 77% maintained a PASI 75 response at week 24 (Papp et al. 2005). About 2% of the participants developed anti-etanercept antibodies. The ADAs were non-neutralizing and did not have an effect on drug efficacy. In a longer randomized control study with an open-label extension, 47.3% of participants using etanercept 50 mg twice weekly achieved PASI 75 in the first 12 weeks of the study (Tyring et al. 2007). At week 96, the PASI 75 response was 51.1%. Anti-etanercept antibodies were found in 18% of the participants. Similar to the previous study, the ADAs were non-neutralizing with no appreciable effect on clinical response.

Intravenous infusions of infliximab may be challenging to patients. Additionally, infliximab is known to have a predilection for causing severe infusion reactions in patients with anti-infliximab antibodies (Baert et al. 2003). Patients with anti-infliximab antibodies also have a higher tendency to lose clinical efficacy. In the EXPRESS I study, only 39% of participants who developed anti-infliximab antibodies and achieved PASI 75 by week 10 were able to maintain PASI 75 to week 50 (Reich et al. 2005). In contrast, patients who tested negative for anti-infliximab antibodies, 81% were able to maintain PASI 75 until week 50. Patients with anti-infliximab antibody were also found to have lower serum infliximab concentrations and lower steady-state trough concentrations (Takahashi et al. 2013).

A prospective observational cohort study assessed the drug survival of biologic agents (Warren et al. 2015). Ustekinumab was shown to have a significantly higher survival rate in comparison to TNF inhibitors. Among the tumor necrosis factor (TNF) inhibitors, adalimumab has the longest drug survival time. When ineffectiveness was the reason for discontinuing therapy, the 3-year survival rate for ustekinumab was 89%, adalimumab 79%, infliximab 76%, and etanercept 55%.

Methotrexate was added to our patient's current regimen of adalimumab and was advised to follow-up in 2 months. He was also prescribed a high-potency topical corticosteroid to apply to more resistant lesions.

## Key Points

- Biologic therapies lose efficacy over time. Although the exact mechanism is unknown, antidrug antibodies likely play a role in drug survival.
- Depending on the extent of clinical worsening, consider adding a topical corticosteroid, methotrexate, or substituting the current biologic with a more effective biologic agent.

- Further studies are needed to find successful methods of reducing biologic drug immunogenicity, identifying clinically relevant risk factors, and increasing the sensitivity and specificity of antidrug antibody detection assays.

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# Chapter 15
# Joint Stiffness in a 45-Year-Old with Psoriasis

**Daniel J. No, Mina Amin, Kavita Darji, and Jashin J. Wu**

A 45-year-old male with a 27-year history of psoriasis and psoriatic arthritis was referred for evaluation of worsening psoriasis and joint stiffness. Etanercept and methotrexate provided moderate relief of his symptoms; however, lately the patient experienced "flares" in both wrist and finger joints. These episodes occurred about once a month and caused significant swelling and stiffness in his joints that last for approximately 3 days. He stated that stiffness and pain are worse in the mornings and moderately improved with activity or nonsteroidal anti-inflammatory drugs. The patient denied fever, recent illness, physical trauma, muscle weakness, and tingling or numbness in the extremities. He denied a family history of psoriasis or psoriatic arthritis.

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Physical examination revealed thick, indurated erythematous papules and plaques with micaceous scales on the bilateral upper and lower extremities, occipital scalp, face, abdomen, and upper back (Figs. 15.1 and 15.2). The scrotum had thick excoriated plaques. The total body surface area affected was approximately 50%. There was some pitting of the second, third, and fourth digit nails bilaterally. On musculoskeletal examination, there was decreased range of motion with tenderness in both wrist joints. No swelling was noted. The metacarpophalangeal joints did not show any signs of acute synovitis or tenderness bilaterally. There was minimal soft tissue swelling. There were no abnormalities noted on the elbows or shoulders. Lower extremity joint examination did not reveal any abnormalities.

Based on the case description, what is the best treatment recommendation for this patient?

1. Intra-articular steroid injection
2. Start physical therapy
3. Prescribe adalimumab
4. Prescribe opioid analgesic
5. Start psoralen-UVA phototherapy

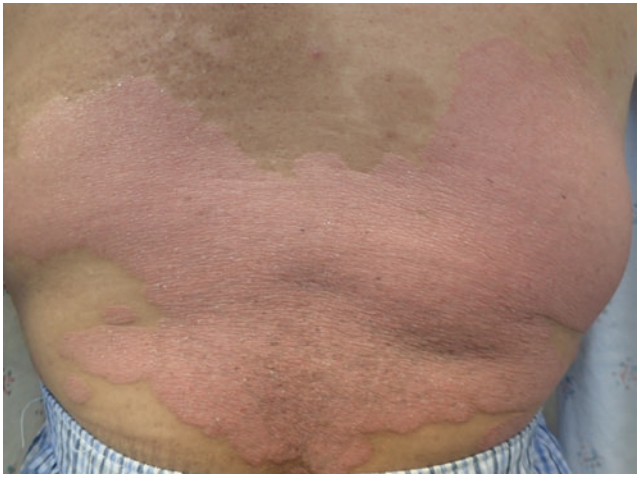

Figure 15.1 Large, confluent, sharply demarcated, erythematous plaque on the trunk

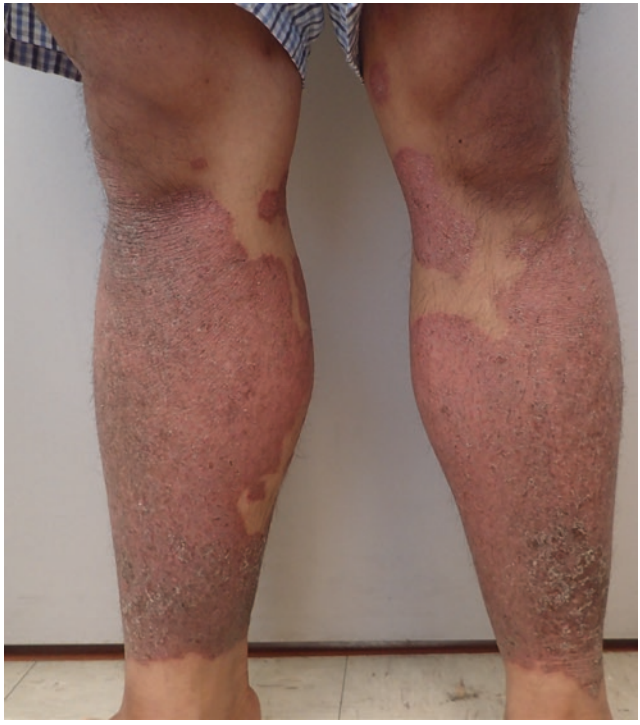

Figure 15.2 Erythematous, scaly plaques on the anterior surface of bilateral lower extremities

## Treatment

Prescribe adalimumab.

## Discussion

Psoriatic arthritis (PsA) is an inflammatory, seronegative, human leukocyte allele-B27 (HLA-B27) associated spondyloarthropathy. The exact prevalence of PsA is controversial, but estimates vary from 0.3% to 1.0% (Gladman et al. 2005). Among patients with psoriasis, the prevalence of coexisting

PsA varies significantly from 6% to 42% (Gottlieb et al. 2008). Patients with PsA often have a family history of psoriasis or PsA. Some studies indicate up to 39% of patients with PsA are HLA-B27 carriers (Queiro et al. 2016). Patients with PsA can present with tenderness, stiffness, reduced range of motion, and swelling of the affected joints. Any joint can be affected; however, PsA has a predilection to affect the distal joints of the upper and lower extremities. Involvement of the sacroiliac, wrist, knee, or ankle joints is also possible. Classically, the patient will experience prolonged morning stiffness with symptoms that are worse at rest and alleviated with activity. In a large clinical trial, 84% of patients with PsA had cutaneous psoriasis for a mean of 12 years before clinically recognized PsA (Gottlieb et al. 2006).

The distribution and extent of joint inflammation in PsA can differ considerably. Patients can develop peripheral arthritis, skin and nail disease, axial disease, dactylitis, or enthesitis. The course and severity of PsA can range from mild and nondestructive to severe with debilitating destruction of joints. The severity of skin disease and arthritis do not necessarily correlate with each other (Cohen et al. 1999). Nail changes or dystrophy is commonly found in patients with PsA. Studies have shown that 40–60% of patients with PsA develop erosive and deforming arthritis. If left untreated, patients will develop severe physical limitations and reduced quality of life. Characteristic radiographic findings of PsA include joint erosions, joint space narrowing, periosteal reaction, joint lysis, ankylosis, spur formation, and spondylitis. Dactylitis is common in PsA and can indicate a greater degree of radiologic damage (Brockbank et al. 2005). The time from arthritis symptom onset to radiographic evidence of disease varies considerably. Kane et al. demonstrated that joint erosions were present in 27% of patients at initial assessment and in 47% of patients at 2-year follow-up (Kane et al. 2003).

Tumor necrosis factor (TNF) inhibitors have proven to be a viable treatment option in the management of PsA. The efficacy of adalimumab was demonstrated in the ADEPT trial, a double-blind randomized controlled trial. At the

conclusion of the 24-week study, adalimumab was found be effective in reducing the symptoms of arthritis and inhibiting the progression of structural changes seen on radiographs. By week 24 57% of patient receiving adalimumab achieved a 20% improvement in tender joint counts as well as a 20% improvement in three of five other criteria mandated by the American College of Rheumatology (ACR20). Likewise, the ACR50 and ACR70 response rates were 39% and 23%, respectively (Mease et al. 2005). Similar response rates were observed in the 48-week open-label extension (Gladman et al. 2007). Their study also demonstrated sustained inhibition of radiographic disease progression.

Patients with PsA were randomized to receive etanercept or placebo for 24 weeks. Fifty-nine percent of patients in the etanercept group achieved ACR20 at week 12 (Mease et al. 2004). In the open-label 48-week extension, the majority of patients who received etanercept sustained or improved their clinical response. Additionally, patients who were initially in the placebo arm and switched to receive etanercept exhibited a similar response to therapy. Imaging analysis of the hands and wrists demonstrated inhibition of radiographic disease progression. The PRESTA (Psoriasis Randomized Etanercept STudy in Subjects with Psoriatic Arthritis) trial documented significant reduction in the number of participants with dactylitis and enthesitis (Sterry et al. 2010).

A double-blind trial evaluating the efficacy of infliximab in 200 patients with active PsA showed a considerable improvement in ACR20 response at week 14. ACR50 and ACR70 responses continued to improve throughout the 24-week study (Antoni et al. 2005). A significant proportion of patients with dactylitis and enthesitis at baseline experienced improvement. At the conclusion of a 2-year study, 62% of patients maintained an ACR20 response (Antoni et al. 2008). Additional studies have shown radiographic evidence of infliximab preventing disease progression (Kavanaugh et al. 2006).

Two double-blind, multicenter, controlled trials demonstrated that patients who received ustekinumab for PsA

experienced clinically meaningful improvements in physical function and health-related quality of life (Rahman et al. 2016). The first study included 615 biologic naïve patients with active PsA from 104 sites (PSUMMIT 1). Patients were randomized to receive 45 mg ustekinumab, 90 mg ustekinumab, or placebo. Of the three groups, 42%, 50%, and 23% of patients achieved ACR20 at week 24, respectively (McInnes et al. 2013). The majority of participants reported improvements in dactylitis and enthesitis and maintained an ACR20 response through week 100 (Kavanaugh et al. 2015a, b). Of note, despite the limitations of cross-study comparisons, ustekinumab appears to have a longer time to maximum effect when compared to TNF inhibitor studies. The second study (PSUMMIT 2) had efficacy findings that were consistent with the PSUMMIT 1 study. However, more than half of the participants had previously discontinued a TNF inhibitor due to lack of efficacy or intolerance (Ritchlin et al. 2014). In both studies, patients treated with ustekinumab had significantly less evidence of joint damage and disease progression on radiography when compared to placebo (Kavanaugh et al. 2014a, b).

Two double-blind, phase 3 studies were conducted to evaluate the efficacy of secukinumab in patients with psoriatic arthritis. The first study (FUTURE 1) observed 606 participants for 104 weeks. At week 24, among the patients who were biologic-naïve, 54.5% of patients who received 150 mg of secukinumab achieved ACR20 response (Mease et al. 2015). A lower (39%) ACR20 response was seen among patients with prior exposure to TNF inhibitors. At week 104, 67% of patients achieved ACR20 response (Kavanaugh et al. 2016). Eighty-four percent of patients did not show radiographic disease progression. Of note, there was no significant difference in ACR20 response rates in patients who were using methotrexate simultaneously. At the conclusion of the second study (FUTURE 2), the ACR20 response rate was 51% in patients who received 150 mg of secukinumab for 24 weeks (McInnes et al. 2015). Similar to the FUTURE 1 study, response rates were higher in the TNF inhibitor naïve group compared to the group with prior TNF inhibitor exposure.

Methotrexate is considered to be a second-line agent in the treatment of PsA. There is an insufficient amount of evidence demonstrating the efficacy of methotrexate in PsA (Ravindran et al. 2008). A randomized placebo-controlled trial with 221 patients found no statistically significant evidence that methotrexate improves any rheumatology-related response indices in PsA (Kingsley et al. 2012). Additionally, there was no observed benefit on objective measures of synovitis (joint counts, ESR, and CRP levels). However, methotrexate did seem to improve subjective symptom assessments. A study comparing the effectiveness of TNF inhibitors and methotrexate showed that disease activity and clinical improvement were significantly larger in the TNF inhibitor group (Heiberg et al. 2007). Of note, many randomized controlled trials studying biologic agents allow the concomitant use of methotrexate during study participation. The majority of the studies have not documented a significant difference in ACR20 response rates in patients taking a biologic in combination with methotrexate and patients taking a biologic alone (Combe et al. 2016).

Apremilast is also considered to be a second-line agent in the management of PsA. At week 16 in the PALACE 1 study, 40% of patients who received apremilast 30 mg BID achieved ACR20 (Kavanaugh et al. 2014a, b). The 24-week analysis showed similar results. A dose-related effect was observed with higher clinical response in patients receiving 30 mg BID compared to 20 mg BID. Similar to biologic studies, biologic-naïve patients had higher ACR20 response rates compared to patients with prior exposure to biologics. In the 52-week follow-up of the PALACE 1 study, 55% of patients receiving apremilast 30 mg BID achieved an ACR20 response (Kavanaugh et al. 2015a, b). However, only 25% and 14% of patients achieved ACR50 and ACR70, respectively. Improvements from baseline enthesitis and dactylitis were also noted. Efficacy results from the PALACE 2 study showed 53% of patients achieving ACR20 response at week 52 (Cutolo et al. 2016). Similar to PALACE 1, there was a significant decline in ACR50 and ACR70 response rates. The progression of radiographic joint damage has not been documented.

Cyclosporine is not frequently used in the management of PsA. Cyclosporine is poorly tolerated, and evidence for its efficacy is lacking when compared to alternate therapies (Salvarani et al. 2001). In addition, cyclosporine is generally utilized for short-term use in patients experiencing severe flares of psoriasis. Because of the side effects associated with cyclosporine, published guidelines in the United States limit its use to 1 year, making it a poor long-term maintenance treatment for PsA.

Systemic retinoids no longer play a role in the treatment of PsA. There is insufficient amount of data on the efficacy and long-term benefits of systemic retinoids. In addition, retinoids can cause many undesirable side effects.

The patient was switched from etanercept to adalimumab. At follow-up, the patient denied experiencing exacerbations of his PsA in the past 3 months. There was also significant improvement in cutaneous psoriasis. The patient noted diminished swelling and stiffness in his hand joints.

## Key Points

- The presentation and severity of PsA varies significantly. Early diagnosis and intervention is essential to prevent chronic joint damage and disability.
- The efficacy of biologic agents in the treatment of PsA is well documented. Numerous studies exhibit clinically significant improvements in arthritis symptoms, patient quality of life, and inhibition of radiographic disease progression.
- Methotrexate and apremilast are both second-line agents in the management of PsA. Both treatments have not shown radiologic evidence of inhibiting disease progression.

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# Chapter 16
# 69-Year-Old with Psoriasis and a History of Skin Cancer

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A 69-year-old female with a long history of psoriasis presented to the clinic for follow-up after undergoing electrodesiccation and curettage of nonmetastatic squamous cell carcinoma on the left knee. Her psoriasis and psoriatic arthritis have been managed with methotrexate for the past 5 months. She has no prior history of cancer, but multiple actinic keratoses and squamous cell carcinoma have been noted in previous visits. Two previous squamous cell carcinomas were found on the left forearm and left lateral shin and treated similarly with electrodesiccation and curettage. Follow-up visits have not shown signs of recurrence. The

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patient denies a history of smoking, exposure to radiation, and use of other immunosuppressant medications. She does admit to excessive ultraviolet light exposure and minimal use of sunscreen. The patient has a family history of psoriasis. However, she denies a family history of cancer, including skin cancer.

On physical examination, there were erythematous scaly papules and plaques on the face and legs. Erythematous well-demarcated plaques were found on both inframammary skin folds. The total affected body surface area was approximately 10%. The left lateral knee showed a well-healed scar with no visible signs of recurrence. Multiple rough, scaly actinic keratoses were found on the face, hands, and ears.

Based on the case description, what is the best treatment recommendation for this patient?

1. Ustekinumab
2. Acitretin
3. Methotrexate
4. Adalimumab
5. Cyclosporine

## Treatment

Acitretin

## Discussion

The chronic inflammatory nature of psoriasis and the frequent use of immunosuppressive medications both raise concern for malignancy. Although some systemic medications used in the treatment of psoriasis increase the risk of malignancy, studies have shown that they are not the sole cause. Pouplard et al. demonstrated that patients with a history of psoriasis had a statistically significant increased risk of developing non-melanoma skin cancer (NMSC) (Pouplard et al. 2013). Melanoma, however, does not appear to be associated

with psoriasis (Chiesa Fuxench et al. 2016). Of note, many studies exhibit a trend of increased risk of malignancy with increasing psoriasis severity.

The majority of systemic medications used in the treatment of psoriasis are considered immunomodulators. Although the level of immunosuppression is relatively low, theoretically they have the potential to increase the risk of NMSC and cancer. It is widely recognized that solid organ transplant recipients receiving long-term immunosuppression are at a significantly increased risk of developing NMSC (Tessari and Girolomoni 2012). Skin cancer likely results from the downregulation of mechanisms involved in cancer immunosurveillance (Ulrich et al. 2008). Consequently, all patients using medications associated with malignancy should consider routine skin cancer surveillance and follow general measures such as photoprotection. Patients with a known history of NMSC should avoid the use of medications correlated with an increased risk of malignancy.

Unlike many systemic medications used in the treatment of psoriasis, acitretin does not suppress the immune system or increase the potential for malignancy. Acitretin is a well-documented chemopreventive agent commonly used in immunosuppressed patients such as organ transplant recipients. Numerous studies have shown acitretin to be effective in reducing the incidence of NMSC in high-risk patients (Bettoli et al. 2013). Given these facts, acitretin is a valuable form of treatment for patients with psoriasis and a personal history of NMSC.

Apremilast, a phosphodiesterase-4 inhibitor, modulates key inflammatory mediators that are vital to the pathogenesis of psoriasis. The effect of apremilast is primarily anti-inflammatory and thus far has not shown clinical signs of immunosuppression (Chimenti et al. 2015). A 52-week study evaluating the safety of apremilast reported the development of cutaneous squamous cell carcinoma (SCC) in only 2 out of 804 patients (Papp et al. 2015). Additionally, the incidence rates of malignancies in ESTEEM 1 and ESTEEM 2 trials were comparable between apremilast and placebo (Paul et al. 2015).

Biologic agents are considered immunosuppressive medications and can theoretically increase the risk of cancer. In spite of this, IL-17-targeting biologics have not been shown to increase the risk of cutaneous malignancies. The findings of a 52-week study demonstrated that the incidence of NMSC and tumors are not increased in patients using secukinumab (Blauvelt 2016). Of the participants who developed NMSC, the majority had a history of prior phototherapy.

Narrowband ultraviolet B (NB-UVB) phototherapy is generally considered to be safe, and the majority of published data suggests no associated cancer risk. A study found no significant increase in the incidence of NMSC or melanoma in 3876 patients receiving NB-UVB treatment (Hearn et al. 2008). A literature review of 11 studies with approximately 3400 patients came to a consensus that none of the published studies showed an increase in skin risk with UVB phototherapy (Lee et al. 2004). However, one study did show an increased incidence of genital SCC in men exposed to both PUVA and UVB radiation. The data on melanoma incidence is not as complete; however, the risk of melanoma does not appear to be increased in comparison to the general public. Caution should be exercised in those with a history of melanoma or multiple NMSC.

Oral psoralen and ultraviolet A light (PUVA) treatments of psoriasis increase the risk of cutaneous malignancies. A systemic literature review determined the most frequent malignancy reported with PUVA therapy is SCC (Archier et al. 2012). Additionally, their analysis revealed a significant correlation between the amount of exposure and level of risk. A higher incidence of BCC was also observed in patients who received over 100 PUVA sessions. The incidence of melanoma was doubled in patients who received at least 200 PUVA treatments. Other studies have demonstrated an additive interaction between PUVA and other systemic therapies. Patients using cyclosporine were at a higher risk of developing SCC if they were exposed to PUVA (Marcil and Stern 2001).

Cyclosporine use is associated with an increased risk of lymphoma, internal malignancy, and NMSC. The majority of findings are described in solid organ transplant recipients who require cyclosporine at high doses for long periods of time. Patients with psoriasis receive considerably lower doses for limited durations. Nonetheless, a long-term cohort study and multiple case studies have demonstrated that cyclosporine, given as a standard dose for treatment of psoriasis, increases the risk of NMSC (Lain and Markus 2004; Paul et al. 2003). For this reason, the use of cyclosporine in a patient with a history of cutaneous malignancy is discouraged.

The majority of studies examining the safety of methotrexate and its potential for malignancy have come from the rheumatoid arthritis (RA) literature. The current studies have not been able to fully ascertain the risk of NMSC with methotrexate use. Stern and Laird demonstrated that high-dose exposure to methotrexate doubled the risk of SCC in psoriasis patients exposed to PUVA (Stern and Laird 1994). The effect of methotrexate as an independent risk factor was not as clear. In the RA literature, Buchbinder et al. found a threefold increased risk of melanoma in RA patients exposed to methotrexate. However, the authors attributed some of the increased risk of melanoma to environmental factors and the fact that the incidence of melanoma is higher in Australia (Buchbinder et al. 2008). Nonetheless, the current data is insufficient to fully assess the risk of cutaneous malignancies.

Tumor necrosis factor (TNF) inhibitors can theoretically increase the risk of cancer. A multicenter study demonstrated a higher incidence of NMSC and melanoma in 3010 psoriasis patients exposed to adalimumab when compared to the general population (Burmester et al. 2013). However, the majority of the patients with melanoma had previous exposure to other treatments associated with skin malignancies. Moreover, at week 16 of a phase 3 randomized control trial (REVEAL), a higher incidence of NMSC was observed in adalimumab-treated patients (1.6 per 100 patient years

[PYs]) compared with placebo-treated patients (Menter et al. 2008, 2010). These findings contrast with data from long-term studies and surveillance registries. The 3-year open-label extension of the REVEAL study showed a decrease in NMSC rate (0.8 per 100 PYs) relative to the REVEAL study (Gordon et al. 2012). A 5-year review of an ongoing adalimumab observational registry (ESPRIT) did not reveal an increased incidence of cutaneous malignancies (Menter et al. 2015). At year 5, the overall rate of NMSC and melanoma was 0.6 and <0.1 per 100 PYs of adalimumab exposure, respectively, a decline from the 1-year rate of 0.8 and 0.8 per 100 PYs. For etanercept, the assessment of a 5-year surveillance registry (OBSERVE-5) found the rates of NMSC lower than the standardized expected incidence rate (Kimball et al. 2015). In two infliximab studies, REALITY and RESTORE2, NMSC occurred in infliximab-treated patients at rates of 0.3 and 0.2 per 100 PYs, respectively (Reich et al. 2013; Shear et al. 2014). Caution should be used when considering tumor necrosis factor (TNF) inhibitor use in patients with a history of NMSC.

Pooled safety data from four studies of ustekinumab, including PHOENIX 1 and PHOENIX 2, demonstrated that the overall incidence of NMSC in patients using ustekinumab for up to 5 years was consistent with the general population (Papp et al. 2013; Langley et al. 2015). In fact, the number of SCC cases was lower than what would be expected to be seen in the general public. However, a higher incidence of NMSC has been observed in patients with prior PUVA exposure. Additionally, the FDA has cited post-marketing reports of the rapid appearance of multiple cutaneous SCCs in patients receiving ustekinumab who had risk factors for developing NMSC. Despite the evidence of its safety, the FDA has labeled ustekinumab as a possible carcinogenic risk because of its theoretical potential of increasing the risk of NMSC. Data from long-term studies and surveillance registries are needed to help clarify this discrepancy. Patients who are receiving ustekinumab and have a personal history of NMSC should be monitored for the appearance of NMSC.

The patient was advised to discontinue methotrexate. As a substitute, she was prescribed acitretin and was asked to follow-up in 2 months.

## Key Points

- Patients with psoriasis are at increased risk of developing SCC and BCC in comparison to the general population.
- Psoriasis patients who have a personal history of cutaneous malignancy and require a systemic medication should consider using acitretin, apremilast, or an IL-17-targeting biologic.
- Patients with a history of skin cancer should avoid using PUVA, cyclosporine, TNF inhibitors, and ustekinumab.

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# Chapter 17
# Herpes Zoster Reactivation in a 40-Year-Old with Psoriasis

**Stacey Pun, Mina Amin, Daniel J. No, and Jashin J. Wu**

A 40-year-old male with an 8-year history of psoriasis and psoriatic arthritis presented to the clinic after discontinuing his medication following a herpes zoster outbreak 2 months ago. The shingles rash is completely resolved, and he denied residual pain, sensitivity to light touch, itching, or numbness. Before the infection, the patient's psoriasis was moderately controlled with etanercept. The patient denied experiencing adverse side effects with etanercept. Since stopping the medication, he believed his psoriasis had worsened with new lesions appearing on his face, scalp, and extremities. He was interested in restarting a biologic agent as previous attempts

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with phototherapy and methotrexate were not beneficial. He was otherwise healthy and did not use other medications. He has a family history of psoriasis.

On physical examination, there were erythematous papules and plaques with micaceous scales diffusely on the face, scalp, and bilateral lower extremities. There was less involvement of the chest, abdomen, back, and bilateral upper extremities. Approximately 20% of the body surface area was affected.

Based on the case description, what is the best treatment recommendation for this patient?

1. Avoid systemic agents in this patient; use topical therapy only.
2. Topical therapy and restart etanercept 1 month after zoster vaccination.
3. Immediately restart etanercept without vaccinating patient.
4. Treat with etanercept and methotrexate.

## Treatment

Topical therapy and restart etanercept 1 month after zoster vaccination.

## Discussion

Herpes zoster (HZ) occurs when varicella-zoster virus, latent in the neurons of dorsal root ganglia, reactivates and spreads to involve the corresponding peripheral nerve. HZ classically presents with a prodrome of intense pain and dysesthesia in a dermatomal distribution. This prodromal syndrome is usually followed by the development of painful, grouped vesicles on erythematous bases in the same dermatome. However, pain occasionally occurs without the subsequent development of lesions and in this case is referred to as *zoster sine herpete*. The most common body area involved is the trunk,

followed by the face, neck, scalp, and extremities. In other words, involvement of the thoracic, cervical, and ophthalmic dermatomes is most common. HZ may be mimicked by zosteriform herpes simplex virus, localized contact dermatitis, and bacterial infections like bullous impetigo (Bolognia et al. 2014).

While HZ is typically self-limited in children and young adults, it is more likely to be severe or persistent in the elderly and immunocompromised. In these patients, the virus can disseminate outside of the primary dermatome. True cutaneous dissemination occurs in up to 37% of these patients without antiviral treatment (Harpaz et al. 2008). Dissemination signifies viremia and puts patients at increased risk for involvement of viscera such as the liver, lungs, and central nervous system. In contrast, systemic complications are rare in immunocompetent hosts. Instead, they are more likely to suffer from postherpetic neuralgia and itch (~10–15%), Ramsay Hunt syndrome, or ophthalmic zoster (10%) when the V1 branch of the trigeminal nerve is involved. Local complications, such as scarring, motor paralysis, and secondary bacterial infection, may also occur in immunocompetent hosts (Bolognia et al. 2014).

While 98% of adults worldwide are seropositive for VZV, HZ is more likely to arise in those who are immunocompromised or of advancing age due to a decrease in specific cell-mediated immunity. The majority (68%) of cases occur in individuals aged 50 years and older (Yawn et al. 2007). As a result, the CDC recommends vaccination for individuals aged 60 and over, even if previously exposed to HZ. In those who have recently had shingles, vaccination should at minimum be deferred until the acute illness is over. Some recommend that vaccination be deferred for 6–12 months after resolution of shingles so that a more robust boost in immunity can be produced. However, vaccination should absolutely be avoided in people who are allergic to components of the vaccine, are pregnant, or have weakened immune systems.

The Advisory Committee on Immunization Practices (ACIP) recommends that vaccination be deferred for at least

1 month after the discontinuation of immunosuppressive therapy. Included in this category are high-dose corticosteroids (≥20 mg/day of prednisone or equivalent) for a duration of 2 or more weeks. Immunosuppressive regimens not considered sufficient to warrant delay in vaccination include low–moderate-dose steroids (<20 mg/day of prednisone or equivalent) for <2 weeks, low-dose methotrexate (≤0.4 mg/kg/week), azathioprine (≤3.0 mg/kg/day), or 6-mercaptopurine (≤1.5 mg/kg/day). Thus, patients receiving the aforementioned therapies for psoriasis are not contraindicated for the administration of the zoster vaccine (Harpaz et al. 2008).

There are no specific guidelines for the treatment of psoriasis in patients with a history of herpes zoster. However, patients anticipating immunosuppressive medications should avoid administration of zoster vaccine for at least 14 days before initiation of therapy. Some advise waiting as long as 1 month after vaccination to initiate immunosuppressive therapy, only if this delay is feasible for the patient (Harpaz et al. 2008). There are no specific guidelines for the treatment of moderate-to-severe psoriasis in patients with a history of herpes zoster. As a result, it is reasonable to follow the same treatment guidelines in this patient population as in the general population of patients with moderate-to-severe psoriasis.

There is contradictory evidence regarding systemic therapy for psoriasis and the risk of HZ. A large population-based, 500,000 person-year study demonstrated that there is no statistically significant increase in HZ risk associated with single-agent systemic therapy (acitretin, methotrexate, cyclosporine) or biologic therapy (infliximab, adalimumab, etanercept, ustekinumab, alefacept, and efalizumab) for psoriasis. However, there is a statistically significant increased risk of HZ in those receiving combination therapy with methotrexate and biologic agents. Thus, combination immunomodulators should be avoided in psoriasis patients. Of note, this study also showed that acitretin is associated with a decreased risk of HZ (Shalom et al. 2015).

Another study examined the association between initiation of therapy with TNF inhibitors and the risk of HZ in

rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis-psoriatic arthritis-ankylosing spondylitis (PsO-PsA-AS) patients. The results of this study demonstrated that crude incidence rates are highest in RA patients and lowest in PsO-PsA-AS patients. The study also found that there is no significant difference in HZ rates between PsO-PsA-AS patients initiating TNF inhibitors and those initiating treatment with non-biologic DMARDs. Within the study's RA subgroup, increasing age, female gender, overall health status, and higher-dose corticosteroid usage were associated with increased HZ risk. Of note, a similarly small proportion of these patients were hospitalized because of their HZ within the TNF inhibitor group and the non-biologic DMARD group. Although this is not a direct assessment of this parameter, it suggests that TNF inhibitors do not increase the risk of complications due to HZ dissemination (Winthrop et al. 2013).

Other studies suggest that biologic therapy for psoriasis may increase the risk of developing HZ. In a retrospective study of 215,656 person-years and 1321 HZ cases, no patient treated with alefacept, efalizumab, or adalimumab developed HZ. While there was no significant increase in the incidence of HZ among patients treated with any biologic, the increase in incidence seen with infliximab approached statistical significance (Dreiher et al. 2012). Similarly, a systematic review conducted in 2014 found multiple studies suggesting that infliximab increases the risk of HZ. In contrast, adalimumab, etanercept, and ustekinumab remain controversial (Adelzadeh et al. 2014).

Our patient was restarted on etanercept 1 month after receiving the zoster vaccination. He was also prescribed tacrolimus for his face and clobetasol for his body.

## Key Points

- Zoster vaccination is recommended for those 60 and older. However, vaccination should be delayed for a month after discontinuing immunosuppressive therapy.

- Ideally, zoster vaccination should be administered 2–4 weeks before initiating immunosuppressive therapy.
- Combined immunomodulators significantly increase the risk of developing HZ and should thus be avoided in psoriasis patients.

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# Chapter 18
# Tuberculosis Infection in a 58-Year-Old with Psoriasis

**Daniel J. No, Kavita Darji, Mina Amin, and Jashin J. Wu**

A 58-year-old male with a 10-year history of psoriasis presented to the clinic for worsening of psoriasis after a month-long hospital admission for a military tuberculosis infection. The patient received antituberculous medications during his admission and was advised to continue the regimen for an additional 8 months. At that time, his psoriasis medication, adalimumab, was immediately discontinued. Subsequently, his psoriasis worsened, affecting a significant proportion of his body. The patient was previously using adalimumab for 3 years with considerable benefit. Of note, before starting adalimumab, the patient tested positive for

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latent tuberculosis and was prescribed isoniazid. However, it was unclear if the patient was compliant with his medication. The patient denied fever, chills, and night sweats. However, he continued to experience fatigue and poor weight gain. He did not have any other medical conditions.

On physical examination, erythematous scaly indurated papules and plaques were found diffusely affecting the vertex of the scalp, occipital scalp, chest, abdomen, bilateral elbows, forearms and dorsal hands, and bilateral knees, thighs, and legs. Approximately 75% of the body surface area was affected.

Based on the case description, what is the best treatment recommendation for this patient?

1. Start adalimumab.
2. Start ustekinumab.
3. Start methotrexate.
4. Start acitretin.
5. No treatment is indicated with concurrent tuberculosis infection.

## Treatment

Start acitretin.

## Discussion

The transmission of tuberculosis (TB) is by inhalation of aerosolized *Mycobacterium tuberculosis*. If the inhaled bacilli are not cleared by pulmonary host defenses, latent or active infection can be established. In the United States, a total of 9421 tuberculosis cases (rate of 2.96 cases per 100,000 persons) were reported in 2014 (CDC 2015). Carriers with untreated tuberculosis of the respiratory tract are the most common source of infection (Getahun et al. 2015). The majority of patients with latent TB infection (LTBI) are asymptomatic. LTBI occurs when *M. tuberculosis* bacilli are

contained within macrophages and granulomas, thereby limiting replication and spread of infection (Getahun et al. 2015). Reactivation of *M. tuberculosis* can result in hematologic dissemination and involve any tissue. Common sites of extrapulmonary disease include the meninges, cervical lymph nodes, kidneys, and lumbar vertebrae. The reactivation and progression of latent infection to active disease is dependent on multiple factors such as age, initial bacterial load, and suppression of immunity (e.g., HIV infection, systemic corticosteroid, tumor necrosis factor inhibitors, organ or hematologic transplantation) (Getahun et al. 2015). Tumor necrosis factor (TNF)-alpha is a critical component in the prevention of *M. tuberculosis* dissemination. TNF-alpha increases the phagocytic capacity of macrophages and the formation of granulomas to restrict infections (Ehlers 2005). This provides a possible explanation as to why TNF inhibitor use is associated with increased TB infections (Keane 2005).

Before initiating a TNF inhibitor or other immunosuppressive medication indicated for psoriasis, the prescribing physician should obtain a thorough history to screen for TB exposure and risk factors. Additionally, a baseline and annual purified protein derivative (PPD) skin test or interferon-gamma release assay (IGRA) must be obtained (Mazurek et al. 2010). For patients with a positive PPD or IGRA, a chest x-ray should be performed to rule out active tuberculosis. Those with normal findings on chest radiograph should receive treatment for LTBI. The preferred treatment for most patients with LTBI is isoniazid (INH) with vitamin B6 (pyridoxine) for 9 months (Cohn et al. 2000). For patients with LTBI who are initiating biologic therapy, the CDC recommends completing the full 9-month course of treatment prior to starting a biologic agent. However, some psoriasis experts believe 1–2 months of INH prophylaxis before starting biologic therapy is sufficient (Doherty et al. 2008). Those with active TB must defer psoriasis treatment and be referred to a specialist for standard multidrug antituberculosis drug therapy (RIPE).

## Treatment

Narrowband ultraviolet B (NB-UVB) phototherapy is not immunosuppressive and is not associated with the reactivation of TB (Doherty et al. 2008) Therefore, NB-UVB phototherapy is an ideal treatment option for patients with LTBI and psoriasis affecting more than 10% of body surface area (BSA). Screening for LTBI is not necessary before initiating UVB phototherapy.

Unlike many systemic medications used in the treatment of psoriasis, acitretin does not suppress the immune system or increase the risk for TB reactivation. Similarly, apremilast's mechanism of action is primarily anti-inflammatory and has yet to have shown clinical signs of immunosuppression or increased incidence of TB (Chimenti et al. 2015). Therefore, both acitretin and apremilast are safe for use in patients with coexisting psoriasis and LTBI.

Topical corticosteroids have not been associated with the reactivation of TB. Other topical treatments such as vitamin D analogs (calcipotriene and calcitriol) and topical calcineurin inhibitors (pimecrolimus and tacrolimus) do not cause systemic immunosuppression and are also considered to be safe (Doherty et al. 2008). However, an alternative option should be considered for patients with more than 10% of BSA affected, as in the case of our patient.

Serious and potentially life-threatening TB infections have been reported in patients using TNF inhibitors (infliximab, etanercept, adalimumab). In effect, all three TNF inhibitors contain black box warnings for potential disseminated and extrapulmonary TB. A voluntary reporting system established by the US FDA found 335 cases of infliximab-associated TB and 39 cases of etanercept-associated TB worldwide from 1998 to 2002 (Wallis et al. 2004). The authors also reported 54 and 28 cases of TB per 100,000 patients in the United States from infliximab and etanercept use, respectively. Additionally, Keane et al. reported 70 cases of active tuberculosis after initiating treatment with infliximab (Keane et al. 2001). A 5-year review of an ongoing adalimumab

observational registry revealed 18 cases (<0.2 events per 100 patient-years (PYs) of total adalimumab exposure) of TB, three of which were active TB (Menter et al. 2015). Of note, prior to the implementation of LTBI screening for TNF inhibitor use, a clinical trial of adalimumab revealed a TB infection rate of 1.5/100 PYs (Schiff et al. 2006). Upon the use of screening procedures and prophylactic medications, the overall rate of TB infection has decreased to 0.2/100 PYs (Burmester et al. 2013). Thus, all patients should be thoroughly evaluated for TB risk factors and screened for LTBI. Patients who screen positive for LTBI must receive TB infection prophylaxis for at least 1–2 months before initiating a TNF inhibitor. However, LTBI prophylaxis is known to only prevent 60–90% of patients from progressing to active TB (Lobue and Menzies 2010). Therefore, it is imperative to recognize that there is still potential for TB reactivation in spite of antituberculosis prophylaxis.

Ustekinumab is a monoclonal antibody against IL-12 and IL-23 cytokines. Both cytokines are involved in pathways critical for protection against infections and intracellular pathogens. Across five studies of ustekinumab-treated patients, 167/3177 participants were identified to have latent TB infections (Tsai et al. 2012). No cases of active TB were reported in patients who simultaneously received ustekinumab and isoniazid prophylaxis. Additionally, concomitant INH prophylaxis and ustekinumab therapy did not increase the incidence INH-related adverse effects. Of note, one patient who did not receive simultaneous antituberculosis prophylaxis experienced TB reactivation. This incidental finding further underscores the importance of properly screening and treating patients for latent TB infections prior to initiating biologic agents.

Multiple 52-week studies testing the efficacy and safety of ixekizumab have not reported any cases of tuberculosis (Gordon et al. 2014; Griffiths et al. 2015; Saeki et al. 2016). Similarly, a pooled safety analysis of ten phase II and phase III clinical studies demonstrated that secukinumab has not been associated with the reactivation of latent TB (van de

Kerkhof et al. 2016). However, because ixekizumab and secukinumab have a theoretical potential of reactivating LTBI, the FDA has required both drug manufacturers to include TB infection as a warning and precaution.

Cyclosporine is a well-documented immunosuppressant that has been associated with the reactivation of LTBI (Vachharajani et al. 2002). The majority of findings are described in organ transplant recipient who require cyclosporine at high doses and extended periods of time. No cases of disseminated TB have been described in the psoriasis literature. This is likely due to the fact that patients with psoriasis receive considerably lower doses for limited durations. Nevertheless, caution should be taken when used in a patient with known latent TB infection. Additionally, screening for latent TB infection is recommended for patients starting cyclosporine.

There are several case reports in psoriasis and rheumatoid arthritis literature reporting TB dissemination with methotrexate use. Additionally, methotrexate and isoniazid are both inherently hepatotoxic and should be used with caution when simultaneously administered. Before initiating methotrexate, the National Psoriasis Foundation recommends screening for latent TB infection (Doherty et al. 2008).

Given the patient's recent miliary TB infection, he was informed of the risks of using immunosuppressive medications. The patient was prescribed acitretin and topical corticosteroids. Follow-up at 2 months demonstrated moderate improvement. The patient agreed to restart adalimumab at the conclusion of his TB therapy.

## Key Points

- Prior to initiating treatment with a biologic agent, all patients should be screened for LTBI with a PPD skin test or IGRA.
- If a patient is diagnosed with LTBI, TB prophylaxis must be initiated for a minimum of 1–2 months prior to starting a biologic drug.

- Patients who are diagnosed with LTBI and are at high risk for TB reactivation (immunosuppressed, non-compliant, or intolerant to TB prophylaxis), consider safer forms of therapy such as NB-UVB, acitretin, apremilast, and topical medications.

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# Chapter 19
# 50-Year-Old with Psoriasis and Hepatitis B Virus Infection

**Mina Amin, Stacey Pun, Daniel J. No, and Jashin J. Wu**

A 50-year-old female with a 14-year history of psoriasis presented for follow-up after consultation for systemic psoriasis therapies. Previous treatments with ultraviolet phototherapy and topical medications were marginally effective. Before initiating adalimumab, routine screening revealed mildly elevated AST and positive serological markers indicative of chronic hepatitis B infection. The patient denied prior knowledge of infection. She was otherwise healthy and did not complain of fatigue, poor appetite, nausea, abdominal pain, dark urine, light stool color, or fever. The patient has a family history of psoriasis.

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On physical examination, the patient appeared comfortable with no signs of distress. There was no appreciable right upper quadrant tenderness, hepatomegaly, ascites, or splenomegaly. On skin examination, there were erythematous plaques and papules with thick overlying silver-colored scales on bilateral knees and elbows, upper and lower back, abdomen, and occipital scalp. The affected body surface area was approximately 15%. The remainder of the skin examination did not reveal any jaundice, spider angiomata, or palmar erythema.

Based on the case description, what is the best treatment recommendation for this patient?

1. Begin treatment with adalimumab.
2. Begin antiviral therapy before initiating adalimumab.
3. Begin treatment with acitretin.
4. Begin treatment with methotrexate.

## Treatment

Begin antiviral therapy before initiating adalimumab.

## Discussion

Tumor necrosis factor alpha (TNF-alpha) plays an important role in the pathogenesis of psoriasis and immunologic host defense. Patients with acute and chronic hepatitis B have higher amounts of soluble TNF-alpha and TNF-alpha receptors in their serum and hepatocytes. The production of TNF-alpha is crucial in inhibiting viral replication and viral clearance (Fotiadou et al. 2011). The inhibition of TNF-alpha can result in evasion of protective host defenses and can ultimately lead to reactivation of hepatitis B and fulminant hepatitis, cirrhosis, or liver failure. Thus, it is critical to determine hepatitis B disease status before administering TNF inhibitor therapy (Fotiadou et al. 2011; Motaparthi et al. 2014).

Reactivation of hepatitis B presents as a sudden rise in serum HBV DNA along with elevations in the amounts of alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The clinical presentation can vary from asymptomatic to lethal hepatic failure. Evaluation of serum levels of hepatitis B markers can determine the likelihood of reactivation (Abramson et al. 2012). Hepatitis B surface antigen (HBsAg) denotes active disease state; however, the presence of HBsAg alone is insufficient to determine if a patient is acute or chronically infected. Also, a patient that is positive for HBsAg may be asymptomatic and has normal liver function tests. The risk of reactivation is highest in HBsAg carriers, predominantly patients with high viral loads, which may indicate inadequate immunologic control (Fotiadou et al. 2011; Motaparthi et al. 2014).

The presence of the hepatitis B surface antibody (HBsAb) signifies that the patient is not actively infected and has either recovered from hepatitis B virus infection or received an immunization. Another sign of initial infection is hepatitis B core IgM antibody (HBcIgM). In contrast to HBsAg, HBcAb is present for life, which is helpful in determining disease status. Patients that are HBsAg negative, anti-HBs positive, and anti-HBc positive are at a very low risk of reactivation of hepatitis B due to sufficient immune protection against viral replication (Motaparthi et al. 2014).

Hepatitis B envelope antigen (HBeAg) is a serum marker that is associated with significant amounts of viral DNA. It indicates active replication and is often associated with high ALT levels. The presence of the antibody to hepatitis B envelope antigen (HBeAb) indicates lower amounts of viral DNA in the serum, reduced symptoms, and normalization of ALT amounts (Cho et al. 2012; Motaparthi et al. 2014).

The CDC currently recommends screening patients for HBsAg, HBsAb, and HBcAb prior to TNF inhibitor therapy (Centers for Disease Control and Prevention: Hepatitis B Information for Health Professionals 2016a). Liver function tests should also be examined prior to treatment. Triple negative serology indicates that the patient is non-immunized and

has never been infected with hepatitis B. TNF inhibitor therapy can be given to these patients safely. Consider HBV vaccination prior to treatment (Rahier et al. 2010). Patients that have been vaccinated against hepatitis B will only be positive for HBsAb, and these patients can be started on TNF inhibitor therapy. Consider administering a booster vaccination if HBsAb titer is below 10 mIU/mL (Motaparthi et al. 2014).

If positive for HBsAg and HBcAb, but negative for HBsAb, acute or chronic infection is indicated and HBcIgM should be measured. HBcIgM positivity implies acute infection and TNF inhibitor therapy should not be administered. HBcIgM negativity suggests chronic infection, and these patients should undergo further testing for HBeAg, HBeAb, and HBV DNA quantification to establish if these patients are active carriers (Motaparathi et al. 2014).

If positive for HBsAb and HBcAb, and negative for HBsAg, these patients were once infected with hepatitis B virus and are now recovered. The risk of reactivation is very low in these patients, and these patients do not need to be given antiviral therapy before starting TNF inhibitor therapy. Observe these patients for reactivation and discuss the treatment regimen with a hepatologist if possible. Consider testing for a baseline amount of HBV DNA. Patients that are only positive for HBcAb can be started on TNF inhibitor therapy after discussion with a hepatologist and would benefit from baseline detection of HBV DNA levels (Motaparthi et al. 2014).

Active hepatitis B carriers are positive for HBeAg and have DNA viral loads $>10^5$ copies/mL. These patients should be started on antiviral medication prophylactically. TNF inhibitor therapy may be administered, ideally under the supervision of a hepatologist, and reactivation of disease should be closely monitored (Cho et al. 2012; Motaparthi et al. 2014).

First-line therapy for patients with psoriasis and known hepatitis B are topical medications, phototherapy, ustekinumab, secukinumab, and ixekizumab. Topical preparations and phototherapy are optimal treatment options for

these patients, as these medications produce an insignificant risk of hepatitis B reactivation or liver injury. A retrospective study of 25 patients with psoriasis and coexisting hepatitis B or C virus infection that were treated with ustekinumab showed the safety of ustekinumab in four patients (Navarro et al. 2013). Another study evaluated the efficacy of ustekinumab in 18 patients with hepatitis B or C infection and found that antiviral prophylactic therapy decreased the likelihood of reactivation of hepatitis B at follow-up with measurement of viral amounts (Chiu et al. 2013). Secukinumab is efficacious for psoriasis in these patients and has not been associated with an increased risk of hepatitis B reactivation (Blauvelt 2016). Ixekizumab is a relatively safe treatment option that produces rapid clinical improvement for patients with psoriasis yet has been associated with the adverse effects of cellulitis, Candida infections, nasopharyngitis, and injection-site reactions. However, the development of severe infections or reactivation of hepatitis B during ixekizumab treatment has not been reported (Griffiths et al. 2015; Gordon et al. 2016).

TNF inhibitor therapy is considered second-line therapy for treating psoriasis in patients with hepatitis B. Antiviral therapy has been shown to reduce the risk of reactivation during TNF inhibitor therapy. Antiviral prophylaxis should begin 2–4 weeks before the onset of TNF inhibitor therapy and remain 3–6 months after discontinuing therapy because flares occur after therapy is discontinued (Fotiadou et al. 2011). Observation for reactivation should be done regularly by measuring LFTs, HBsAg, HBeAg, and HBV DNA amounts at follow-up. The presence of $10^8$ or $10^9$ copies/mL or 10 times the baseline number of copies implies HBV reactivation. Follow-up is recommended after termination of TNF inhibitor therapy for a minimum of 6 months since reactivation may occur after termination of TNF inhibitor therapy (Motaparthi et al. 2014; Nosotti et al. 2010; Prignano et al. 2011).

Methotrexate is contraindicated in patients with a history of hepatitis B, as it has been associated with the reactivation

of hepatitis B in many cases. Reactivation of hepatitis B for patients on methotrexate has occurred after discontinuation of methotrexate and in patients that were negative for HBsAg (Motaparthi et al. 2014). Acitretin is not associated with hepatitis B reactivation because it is not an immunosuppressive therapy. However, liver injury can occur evidenced by the correlation of acitretin with elevated liver function tests and hepatitis (Lee and Li 2009; Roenigk et al. 1999).

The patient received lamivudine for 3 months before adalimumab was initiated and was maintained on lamivudine. Hepatitis B DNA PCR levels and liver function tests for hepatitis B reactivation were monitored every 3 months with no signs of reactivation (Table 19.1).

Table 19.1 Analysis of hepatitis B serologic test results (reproduced from Centers for Disease Control and Prevention: interpretation of hepatitis B serologic test results 2016b)

| Serologic marker | Result | Hepatitis B infection status |
|---|---|---|
| HBsAg<br>Anti-HBc<br>Anti-HBs | Negative<br>Negative<br>Negative | Susceptible to infection |
| HBsAg<br>Anti-HBc<br>Anti-HBs | Negative<br>Positive<br>Positive | Immunity due to prior infection |
| HBsAg<br>Anti-HBc<br>Anti-HBs | Negative<br>Negative<br>Positive | Immunity due to hepatitis B vaccination |
| HBsAg<br>Anti-HBc<br>IgM anti-HBc<br>anti-HBs | Positive<br>positive<br>positive<br>Negative | Acute infection |
| HBsAg<br>Anti-HBc<br>IgM anti-HBc<br>anti-HBs | Positive<br>positive<br>Negative<br>negative | Chronic infection |

Table 19.1 (continued)

| Serologic marker | Result | Hepatitis B infection status |
|---|---|---|
| HBsAg<br>Anti-HBc<br>Anti-HBs | Negative<br>positive<br>Negative | Hepatitis B status uncertain. Four potential interpretations:<br>1. Recovery from infection<br>2. False-positive anti-HBc, vulnerable to disease<br>3. Chronic infection with low disease severity<br>4. Resolution of acute infection |

## Key Points

- TNF inhibitors have been associated with reactivation of hepatitis B.
- First-line treatment for patients with psoriasis and hepatitis B is topical agents, phototherapy, ustekinumab, secukinumab, and ixekizumab. TNF inhibitors are considered second-line therapy. Avoid methotrexate and acitretin.
- Screen patients with psoriasis for hepatitis B prior to TNF inhibitor therapy by analysis of the triple serology: HBsAg, HBsAb, and HBcAb.

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# Chapter 20
# 54-Year-Old with Psoriasis and Hepatitis C Virus Infection

**Kavita Darji, Daniel J. No, Mina Amin, and Jashin J. Wu**

A 54-year-old female with a 9-year history of hepatitis C presented to the clinic to discuss alternate treatments for her psoriasis. Topical corticosteroids and ultraviolet phototherapy have not provided adequate results for the patient. She complains of moderate pruritus but denies joint stiffness and pain. The patient contracted hepatitis C through intravenous drug abuse but never received treatment. She also has an extensive history of alcohol abuse. She denied fatigue, nausea, abdominal pain, photosensitivity, dark urine, light stool color or fever.

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On skin examination, there were erythematous scaly indurated papules and plaques diffusely on the scalp, abdomen, chest, lower back, and bilateral elbows and bilateral knees and posterior thighs. Approximately 15% of the body surface area was affected. Physical examination did not reveal right upper quadrant abdominal tenderness, hepatomegaly, ascites, or splenomegaly.

Based on the case description, what is the best treatment recommendation for this patient?

1. Calcipotriene
2. Coal tar
3. Etanercept
4. Acitretin
5. Methotrexate

## Treatment

Etanercept.

## Discussion

Infection by the hepatitis C virus (HCV) is prevalent in approximately 4 million people in the United States, where it is the most common blood-borne infectious disease, and 20 million people worldwide (Frankel et al. 2009). Chronic HCV infection must be monitored carefully, as it may pave the way for eventual cirrhosis of the liver, end-stage liver disease, or hepatocellular carcinoma (Frankel et al. 2009). One unfavorable drawback to a treatment option for this infection, pegylated interferon and interferon alfa, is the initiation or worsening of psoriasis and psoriatic arthritis in patients who have concomitant hepatitis C infection and psoriasis (Frankel et al. 2009; Citro et al. 2007; Taylor et al. 2007). Tumor necrosis factor (TNF) alpha is a common cytokine in both diseases, leading to psoriatic skin and joint inflammation and HCV-associated liver cirrhosis and diabetes

mellitus. Thus, a prior study found that HCV infection might play a role in triggering psoriasis due to overproduction of TNF-alpha (Imafuku et al. 2013). In another study, biopsies of both lesional and non-lesional HCV-positive patients showed increased mRNA levels of cathelicidin, TLR9, and IFN-γ. Therefore, it has been demonstrated that HCV infection enhances various inflammatory cytokines, increasing the chances of being diagnosed with psoriasis (Chun et al. 2016). The severity of psoriasis can also be measured by the presence of HCV antibodies and overexpression of apoptosis-regulating proteins, such as p53 and tTG (Gabr et al. 2014).

The National Psoriasis Foundation suggested that first-line treatment for patients with moderate to severe psoriasis and HCV includes ultraviolet (UV) phototherapy in combination with topical therapy, such as topical corticosteroids, vitamin D3 derivatives, keratolytics, coal tars, and calcineurin inhibitors (Frankel et al. 2009). Phototherapy works locally on the skin and is not highly related to reactivation of hepatitis C infection; therefore, it is recommended for treating psoriasis with concurrent hepatitis C infection (Frankel et al. 2009; Bonifati et al. 2016). Second-line treatment agents include TNF inhibitors (etanercept, infliximab, adalimumab). A prior review study evaluated 38 cases of patients with psoriatic arthritis and HCV infection treated with the short-term use of TNF inhibitors, finding that use of etanercept and adalimumab is efficacious and reasonably safe (Caso et al. 2015). In a retrospective, multicenter study, Navarro et al. evaluated the effect of ustekinumab and TNF inhibitors in 20 patients with concurrent hepatitis C and five patients with hepatitis B. They found that the three HCV-inflicted patients treated with ustekinumab showed no aggravation of their hepatitis C after a mean follow-up period of 15 months (Navarro et al. 2013). Various studies have also reported benefits from using TNF inhibitors in combination with standard HCV therapy, including interferon and ribavirin (Frankel et al. 2009). A double-blind, randomized, placebo-controlled trial conducted by Zein et al. evaluated the effect of etanercept given for 24 weeks as adjuvant therapy with interferon alfa-2b and

ribavirin to 50 patients with chronic HCV. The results of etanercept adjuvant therapy showed significantly decreased virologic response, or absence of HCV RNA at 24 weeks in 12/19 (63%) etanercept patients, and reduced side effects of interferon and ribavirin (Zein and Etanercept Study Group 2005).

A blind study conducted by Nyfors et al. evaluated liver biopsies pre- and post- PUVA treatment for 1 year in 12 patients, finding no significant changes. As a result, PUVA has been shown to have minimal liver toxicity when used for 1 year and can therefore be used as therapy for psoriasis with HCV (Nyfors et al. 1986).

Due to the caution needed when treating psoriatic patients with hepatitis C infection, consultation of and ongoing communication with a hepatologist is necessary before beginning and throughout the course of immunosuppressive treatment (Bonifati et al. 2016). Before starting TNF inhibitor therapy, HCV-infected patients should be evaluated by a hepatologist to decide upon the necessity of liver disease assessment with liver biopsy and other serological techniques as well as the indication for antiviral treatment. It is advised that patients with HCV infection who are treated with TNF inhibitors should undergo liver function monitoring every 3 months (Pompili et al. 2013).

Particular therapies should not be used when psoriatic patients also have HCV infection. Acitretin, which is not an immunosuppressant and is unlikely to result in reactivation of chronic hepatitis C infection, may cause rare hepatic toxicity and therefore should be used cautiously in patients with pre-existing liver disease or HCV infection (Bonifati et al. 2016; Katz et al. 1999). Approximately one in three patients treated with acitretin showed increased serum AST, ALT, and LDH, all of which normalized after decreasing the dose or discontinuing acitretin (Katz et al. 1999). For this reason, patients on acitretin therapy should undergo routine liver enzyme monitoring (Katz et al. 1999). Moreover, methotrexate is associated with liver damage and drug-induced hepatitis. For this reason, methotrexate increases the risk of hepatotoxicity and is contraindicated in patients with existing

risk factors for liver disease, such as hepatitis C infection (Frankel et al. 2009). Additionally, although IL-17 inhibitors such as secukinumab and ixekizumab are used for treatment of psoriasis patients, there is little to no literature of their use in psoriasis patients with concurrent hepatitis C infection.

Concerning the management of our patient, routine laboratory studies did not reveal abnormal liver function tests. The patient was referred to a hepatologist for further work-up of her hepatitis C. She was prescribed adalimumab.

## Key Points

- HCV infection has been shown to trigger psoriasis, partly due to the inflammatory cytokine TNF that is present in both diseases.
- Common treatment options for HCV infection, including interferon and ribavirin, have been reported to lead to the development and exacerbation of psoriasis.
- Treatment options for concomitant HCV infection and psoriasis include topical therapies, UV phototherapy, and TNF inhibitors; however, modalities such as acitretin and methotrexate should be avoided in these patients due to adverse reactions.

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# Chapter 21
# HIV Infection in a 44-Year-Old with Psoriasis

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A 44-year-old male with a 4-year history of HIV presented for follow-up of the management of his psoriasis after a failed trial with acitretin. The patient discontinued acitretin due to transaminitis and gastrointestinal-related side effects. He previously used narrowband ultraviolet phototherapy and topical corticosteroids with minimal benefit. The review of systems was unremarkable, and there was no evidence of AIDS-defining conditions. He denies other medical conditions. The patient is compliant with his combination antiretroviral medications.

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On physical examination, there were erythematous scaly indurated papules and plaques on the back, chest, and bilateral upper and lower extremities. Approximately 10% of the body surface area was affected.

Based on the case description, what is the best treatment recommendation for this patient?

1. Methotrexate
2. Infliximab
3. Acitretin
4. Apremilast
5. Cyclosporine

## Treatment

Apremilast.

## Discussion

The prevalence of psoriasis in the HIV-infected population is similar to that of the general population, although HIV-infected individuals frequently present with a more severe form of psoriasis (Bartlett et al. 2007). Psoriasis can present at any stage of HIV infection at different degrees of severity (Mallon and Bunker 2000). Psoriasis may be the initial manifestation of HIV infection and can indicate a poor prognosis, as the degree of psoriasis is correlated with the level of immunodeficiency. Therefore, it may be beneficial to consider HIV testing in patients with new-onset psoriasis (Montazeri et al. 1996; Bartlett et al. 2007).

Plaque, guttate, inverse, and erythrodermic psoriasis are the most common types of psoriasis that present in HIV-infected individuals (Menon et al. 2010). Multiple types of psoriasis can occur in one patient simultaneously. Psoriatic arthritis more commonly affects HIV-positive than HIV-negative patients with psoriasis. The condition presents as asymmetric involvement of multiple joints and is difficult to

manage with standard therapy. The histologic examination of skin specimens from HIV-infected psoriasis patients classically displays an elevated number of plasma cells (Montazeri et al. 1996).

Patients with a prior history of psoriasis develop a paradoxical exacerbation of symptoms once becoming HIV-positive. Psoriasis has been reported to increase in severity as the disease advances to AIDS. An exacerbation of psoriasis can place patients with AIDS at a higher risk of developing a systemic infection, a finding that is rare in psoriasis patients without HIV (Mallon and Bunker 2000; Menon et al. 2010). The treatment of psoriasis in HIV-positive individuals is difficult, as psoriasis is facilitated by T lymphocytes. However, HIV patients have diminished amounts of T lymphocytes (Montazeri et al. 1996). Psoriasis has been reported to improve in patients that begin retroviral therapy as immunity is reestablished. The effect of retroviral therapy on psoriasis is paradoxical, as drugs that treat psoriasis target the T lymphocytes, though a low CD4 cell count can lead to exacerbations of psoriasis (Bartlett et al. 2007).

Psoriasis is an immune-mediated process and the negative impact of HIV on immunity may explain the development of psoriasis in these patients. HIV infection can stimulate the increased proliferation of keratinocytes. Patients with AIDS have been reported to have higher levels of interferon-gamma, which is associated with the pathogenesis of psoriasis. A reduced number of Langerhans cells in the skin of HIV-infected patients with psoriasis have also been reported (Montazeri et al. 1996). Tumor necrosis factor-alpha (TNF-alpha) is a proinflammatory cytokine that is correlated with psoriasis and HIV. Specifically, TNF-alpha can stimulate nuclear factor κβ, which is necessary for the progression to chronic HIV infection. An association between HIV viral load and plasma levels of TNF-alpha has also been described (Aboulafia et al. 2000).

Management of HIV-associated psoriasis is challenging since lesions are often treatment resistant and medications can create significant complications. The extent of psoriasis

should guide the treatment regimen for HIV-associated psoriasis. The first-line treatments for HIV-associated psoriasis are topical agents and phototherapy. Topical preparations include calcipotriene, corticosteroids, and the combination formula of calcipotriol and betamethasone dipropionate (Menon et al. 2010). Topical preparations can be used in isolation or with phototherapy and systemic medications. Ultraviolet therapy, including UVB or psoralen plus UVA, can be considered for moderate to severe HIV-associated psoriasis. Phototherapy is beneficial because it lacks systemic toxicity and does not interact with antiretroviral medications. However, it should be used carefully as the UV radiation is immunosuppressive, theoretically worsening the degree of HIV. Antiretroviral therapy has been reported to treat HIV-associated psoriasis as well as control the severity of HIV. Treatment is recommended for HIV patients with an AIDS-defining illness or CD4 count less than 350 cells/mm$^3$, but may also be used in patients with CD4 count greater than 350 cells/mm$^3$. It is imperative to treat patients with CD4 count below 350 cells/mm$^3$ with antiretroviral therapy (Menon et al. 2010). Oral retinoids are second-line treatment and may be used in more severe forms of HIV-associated psoriasis (Menon et al. 2010). If topical therapy, UV, and antiretroviral therapy are unsuccessful, consider systemic medication. Acitretin is beneficial because it is not immunosuppressive; however, the systemic effect can interfere with retroviral therapy (Menon et al. 2010). Apremilast, a phosphodiesterase-4 inhibitor, has been reported to be efficacious in moderate to severe psoriasis and psoriatic arthritis (Deeks 2015; Yiu and Warren 2016). It is generally safe and well tolerated with side effects of nausea, diarrhea, weight loss, and upper respiratory tract infections (Yiu and Warren 2016).

The use of immunosuppressants, such as methotrexate and cyclosporine, should be avoided. Methotrexate is contraindicated in advanced HIV infection, as immunosuppression can worsen disease severity (Kalb et al. 2009). A patient with

HIV-associated psoriasis refractory to standard therapy was started on cyclosporine and developed rapid improvement of symptoms, although oral candidiasis was noted (Allen 1992). Biologic agents, including TNF inhibitor therapy, ustekinumab, secukinumab, and ixekizumab, may be considered only in refractory cases and should be used carefully. A retrospective study assessed the safety of TNF inhibitor therapy in eight HIV-infected individuals with CD4 count above 200 and HIV viral amount below 60,000 copies/mm$^3$. The study found no adverse effects and no fluctuations in viral amount or CD4 count, suggesting the benefit of TNF inhibitor therapy in HIV-infected patients with psoriasis resistant to standard therapy (Cepeda et al. 2008). Another HIV-positive individual noted the efficacy of etanercept for the treatment of sudden onset immobilizing psoriatic arthritis. However, the patient developed repeated microbial infections while on etanercept despite significant improvement of psoriasis at 8-week follow-up (Aboulafia et al. 2000).

Our patient was treated with apremilast and continued on narrowband ultraviolet phototherapy. Persistent lesions were treated with topical corticosteroids and calcitriol. He experienced complete resolution of HIV-associated psoriasis at 3-month follow-up.

## Key Points

- The prevalence of HIV-associated psoriasis is similar to the general population, yet with a higher degree of severity and increased difficulty to treat.
- The first-line treatments for psoriasis are topical agents and phototherapy. Acitretin and apremilast may also be beneficial for HIV-associated psoriasis.
- Avoid immunosuppressant medications including methotrexate and cyclosporine, which can theoretically worsen the severity of HIV. Biologic agents can be considered in refractory cases and should be used cautiously.

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