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Educational Case

Educational Case: Psoriasis

Ryan C. Saal, BS [a], Abby S. Van Voorhees, MD [b], Richard M. Conran, MD, PhD, JD [c,*]

[a] School of Medicine, Eastern Virginia Medical School, Norfolk, VA, USA
[b] Department of Dermatology, Eastern Virginia Medical School, Norfolk, VA, USA
[c] Department of Pathology & Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.academicpathologyjournal.org/pcme.[1]

Keywords: Pathology competencies, Organ system pathology, Skin, Immune-related disorders of the skin, Chronic inflammatory dermatoses, Psoriasis

Primary objective

Objective SK3.2: Immune Diseases of the Skin. Describe the clinical features and pathologic basis for immunologically driven skin diseases with a genetic component such as eczema, psoriasis, and vitiligo.

Competency 2: Organ System Pathology; Topic: Skin (SK); Learning Goal 3: Immune-Related Disorders of the Skin.

Patient presentation

A 53-year-old woman presents to her dermatologist with a chief concern of several red areas of skin with crusting on her knees, elbows, and lower back. She reports she developed the first of these lesions one year ago, after she fell and scraped her leg on the pavement. Since then, multiple lesions have appeared. These lesions do not itch and do not cause her pain. She works as a receptionist indoors and denies sun exposure. She tried using some over-the-counter hydrocortisone cream, which provided some resolution for the smaller lesions in the beginning, but now, is completely ineffective. Past medical history is significant for hypertension. Her only medication is metoprolol. She is sexually active with two male partners and uses contraception inconsistently.

Diagnostic findings, Part 1

Her vital signs are blood pressure of 142/88 mmHg, heart rate of 91 beats per minute, respiratory rate of 17 breaths per minute, and temperature of 98.8 °F. Physical examination is notable for a woman with Fitzpatrick skin type VI (dark brown) and brown eyes. Erythematous plaques with a silvery-white scale (16.3–19.1 cm) are present on the extensor surfaces of her bilateral arms. These plaques are thick and symmetrical. Numerous, well-defined plaques (3.3–20.1 cm) with silver scale are scattered symmetrically across her middle and lower back and upper buttocks (Fig. 1). Upon scraping these lesions, pinpoint bleeding is observed. There is no involvement of mucosal membranes. Body surface area involved is 10 %. BMI is 32 kg/m^2.

Head and neck examination shows no signs of icterus or infection. No lymphadenopathy of the anterior or posterior cervical lymph node chains or thyromegaly is detected. Upon auscultation, cardiac examination reveals normal S1 and S2 sounds and regular rate and rhythm. Her lungs are clear on auscultation, with no wheezing, rhonchi, or rales. The abdomen is soft and nontender with no palpable abdominal mass. Bowel sounds are present.

Question/discussion points, Part 1

What is the differential diagnosis based on the clinical presentation and history?

The patient is presenting with multiple erythematous plaques with an overlying silvery scale, which is suspicious for an inflammatory or infectious disease. The differential diagnosis would include but would not be limited to atopic dermatitis, lichen planus, secondary syphilis, mycosis fungoides, and psoriasis.

* Corresponding author. Eastern Virginia Medical School, Pathology & Anatomy, 700 West Olney Road, Norfolk, VA 23507, USA.
E-mail address: conranrm@evms.edu (R.M. Conran).

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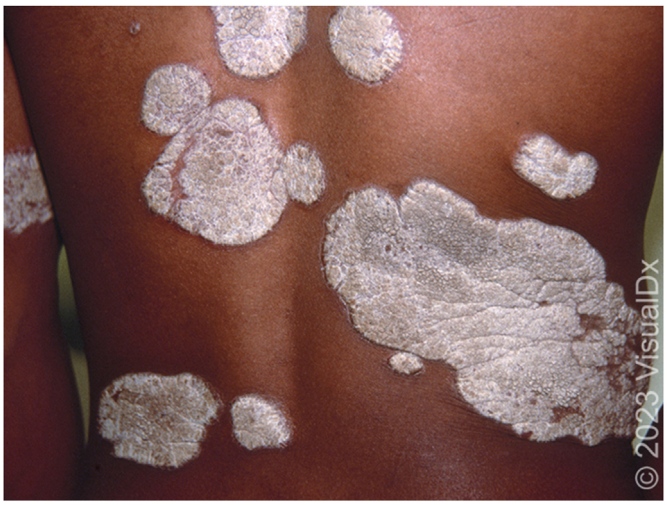

Fig. 1. Well-demarcated plaques with silvery-white scale located on the middle and lower back. Image used with permission from VisualDx (www.visualdx.com).

Atopic dermatitis, also known as eczema, is a chronic inflammatory disease that presents as erythematous, pruritic patches commonly located on the face, upper trunk, and flexural surface of the elbows and knees. Chronic atopic dermatitis can also present with lichenification due to prolonged pruritus. This disease typically develops in childhood and is associated with a personal and/or family history of atopy, allergic rhinitis, and asthma.[2]

Lichen planus is a chronic inflammatory eruption that presents as polygonal, extremely pruritic, papules or plaques located on the wrists, extremities, lower back, scalp, mucous membranes, genitalia, and nails. These lesions can be covered by lacy, white lines called Wickham striae, particularly seen with involved oral mucosa. This disease is associated with occurrence after trauma, also known as the Koebner phenomenon. Upon resolution of these lesions, post-inflammatory hyperpigmentation can result.[2,3]

Syphilis is a sexually transmitted infection caused by *Treponema pallidum*. Primary syphilis presents as a chancre at the site of inoculation in the genital region. Yet, this lesion of primary syphilis goes unnoticed in 60 % of cases as it is usually painless.[4] Secondary syphilis presents as a widespread cutaneous eruption involving the trunk, palms, soles, and extremities.[2] This disease has been nicknamed the "dermatological mimicker" since it has a variety of presentations, such as macular, maculopapular, grouped follicular, papular, corymbose papular, and psoriasiform papular patterns.[5–7] Given the patient's sexual history, serological testing (e.g. Rapid Plasma Reagin) or a biopsy is required to rule out secondary syphilis.

Although rare, mycosis fungoides is a cutaneous T-cell lymphoma. This disease causes well-marginated, erythematous patches and/or plaques to develop in numerous sun-protected anatomical regions, such as the extremities, buttocks, groin, and lower back. These lesions often increase in size both over time and in the absence of treatment. Early forms of mycosis fungoides are difficult to differentiate from atopic dermatitis clinically and pathologically, thus requiring additional histological testing.[2,8]

Plaque psoriasis often presents as well-marginated, erythematous plaques with silvery-white scale located on the extensor surfaces of the elbows, knees, scalp, and lower back.[9] These lesions are usually asymptomatic, but can be pruritic and/or painful due to fissuring. Plaques can regress over time, leaving behind a clear center with a persistent erythematous border. Pinpoint bleeding upon scraping psoriasis lesions is known as Auspitz sign.[10] Post-inflammatory hypopigmentation and hyperpigmentation can be seen during regression.[9,10] Koebner phenomenon, or development after trauma, can also be associated with the formation of psoriatic lesions.[9] Current medications, such as beta-blockers, have also been known to trigger plaque psoriasis.[9]

There are several other psoriasis subtypes: pustular psoriasis, inverse psoriasis, guttate psoriasis, psoriatic erythroderma and nail psoriasis. Of all the subtypes of psoriasis, plaque psoriasis is the most common, accounting for approximately 80 % of psoriatic cases.[9,10]

Given the patient's pinpoint bleeding upon scraping (Auspitz sign), the onset of lesions triggered by trauma (Koebner phenomenon), current medication of metoprolol, and physical presentation of thick plaques with silvery scale, a diagnosis of plaque psoriasis is at the top of the differential. However, skin biopsies and additional staining must be performed to solidify the diagnosis.

Diagnostic findings, Part 2

The skin lesion was biopsied and shown in Fig. 2. Special stains for spirochetes, CD3, CD4, and CD8 were also performed.

Describe the histologic features observed in the biopsy

The biopsy shows hyperkeratosis, confluent parakeratosis, collections of neutrophils in the stratum corneum (Munro microabscesses), collections of neutrophils in the superficial epidermis (Kogoj pustule), and regular acanthosis. There is also elongated rete pegs (ridges), hypogranulosis, and a moderate lymphocytic infiltrate with perivascular

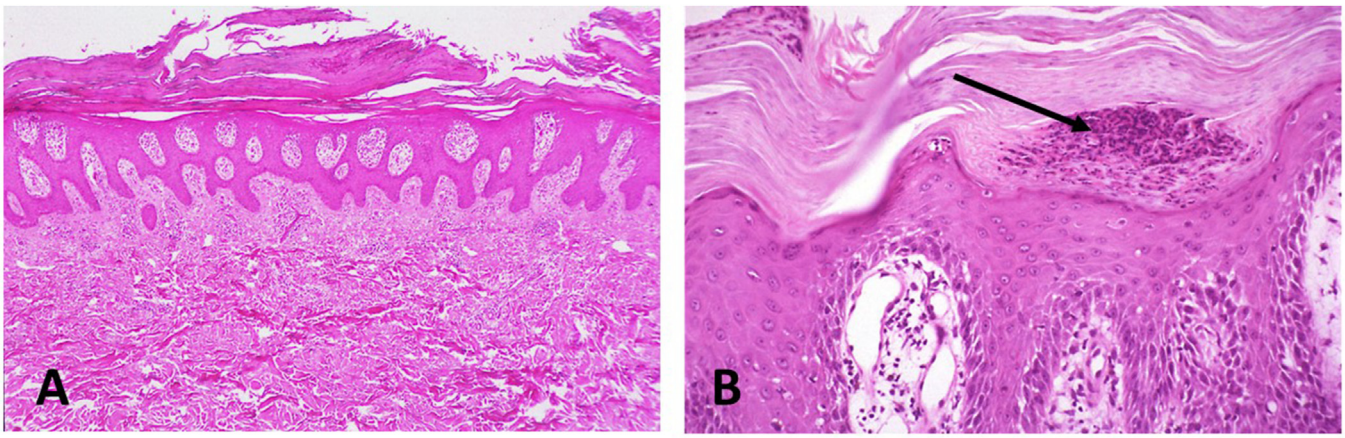

Fig. 2. A. Regular acanthosis with confluent parakeratosis and elongation of rete ridges. (H&E, intermediate magnification). **B.** Parakeratosis and acanthosis with neutrophils present in the stratum corneum (Munro microabscess) are identified by the arrow. (H&E, intermediate magnification).

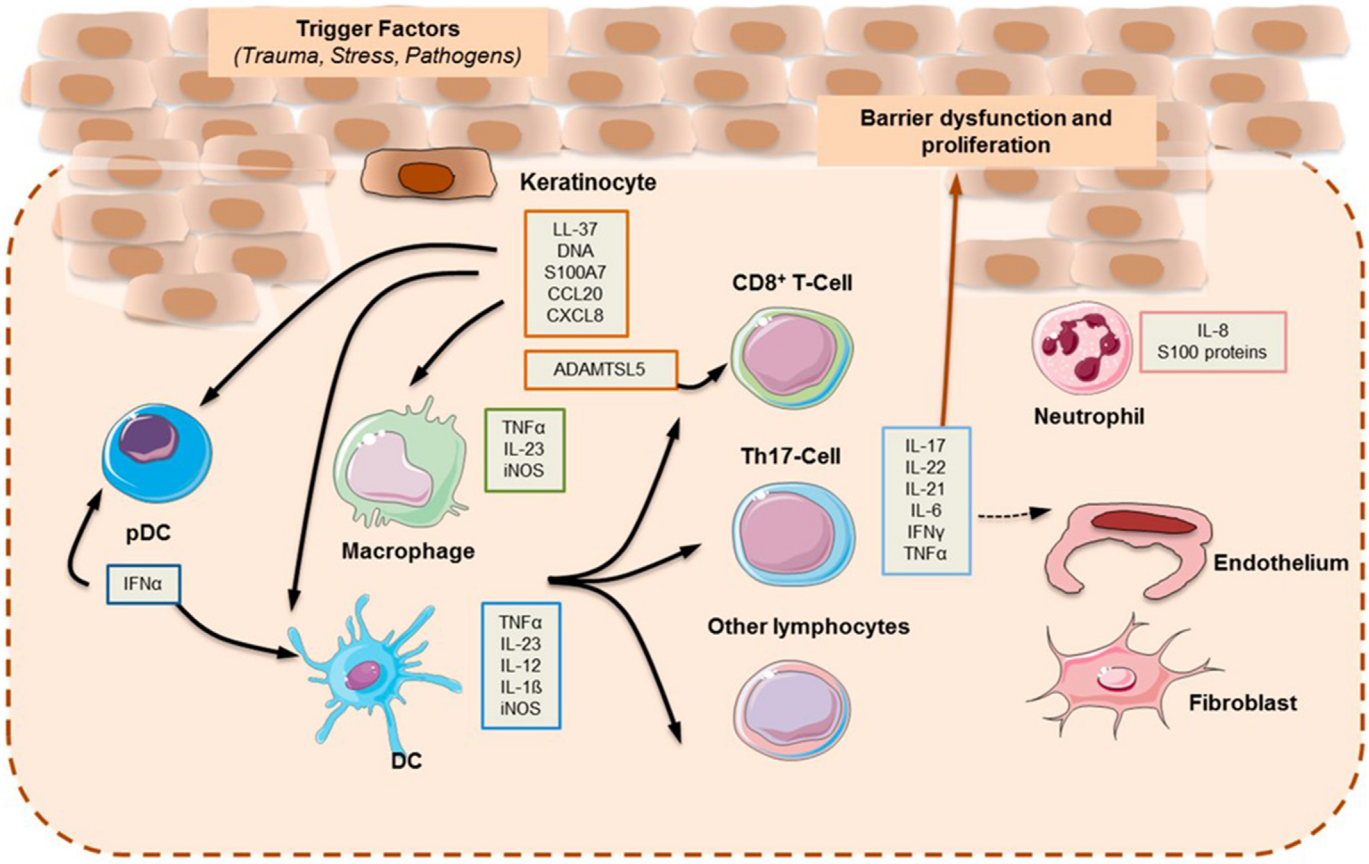

Fig. 3. An overview of the pathogenesis of psoriasis. Trauma, stress, and infection damage keratinocytes, resulting in the release of antimicrobial peptides (e.g. LL37, S100 proteins, cathelicidin). These peptides activate plasmacytoid dendritic cells, responsible for secreting TNF-α, IL-12, and IL-23. CD8 cells, Th17 cells, and other lymphocytes are then activated, and release cytokines such as TNF-α, IL-17, and IL-22. These cytokines are responsible for epidermal hyperplasia and skin barrier dysfunction. Reproduced under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/) from Figure 5 in Psoriasis Pathogenesis and Treatment by Rendon A and Schakel K in the *International Journal of Molecular Sciences* 2019 20 (6): 1475. doi:10.3390/ijms20061475.

involvement in the upper and mid dermis. Other findings of note include thinning of the suprapapillary plates and dilated papillary dermal capillaries.[11]

Serological testing and immunohistochemistry for spirochetes, used to detect the infectious agent responsible for secondary syphilis (Treponema pallidum), were negative. Immunohistochemistry for CD3, CD4, and CD8 was performed to detect the presence or loss of surface markers linked with mycosis fungoides. Mycosis fungoides is associated with an elevated CD4/CD8 ratio and CD3 positivity.[8] The CD4/CD8 ratio in this case was within normal limits. PAS staining or the lesion to exclude a superficial fungal infection was negative.

Based on the biopsy and immunohistochemistry, what is the diagnosis?

Biopsy and normal immunohistochemistry results are consistent with a diagnosis of psoriasis. The different histological features for atopic dermatitis, lichen planus, secondary syphilis, mycosis fungoides, and psoriasis are depicted in Table 1.[2–11] Psoriasis is a chronic, inflammatory skin disease that affects 2–4% of western population.[12] Demographic characteristics for this disease include a bimodal age of onset of 15–25 and 50–60 years and a higher incidence among women and whites.[12,13]

Question/discussion points, Part 2

What is the pathogenesis of psoriasis? Fig. 3

The pathogenesis of psoriasis is dependent upon the relationship between the epidermal keratinocytes and the innate and adaptive immune system. Trauma, stress, specific drugs, infection, and other stimuli are hypothesized factors that trigger the initial phase of this disease.[14] Damaged keratinocytes then release markers of injury, such as antimicrobial peptides (e.g. LL37, β-defensins, S100 proteins, LL37, cathelicidin).[14,15] These compounds lead to the activation of plasmacytoid dendritic cells.[15] These innate immune cells are then responsible for secreting TNF-α, IL-12, and IL-23. IL-12 induces the production of cytokines, such as IFN-γ, from T helper 1 cells (Th1).[14,16] However, this Th1 pathway is not enough to trigger the formation of psoriatic lesions. Another immune pathway involving T helper 17 cells (Th17) leads to the secretion of IL-17, the critical cytokine involved in psoriasis development (Fig. 3).[16]

Secreted IL-23 goes on to prompt the differentiation of Th17, an important player in the pathology of psoriasis.[14,16] Th17 cells release IL-17 and IL-22, which both act on the keratinocytes. Together, TNF-α, IL-17, and IL-22 are crucial promoters of epidermal hyperplasia, the recruitment of neutrophils, and the production of antimicrobial peptides, which encourage the continuous cycle of inflammation and keratinocyte

Table 1
Differential diagnosis for widespread, scaly plaques.[2–11]

Disease	Clinical Presentation	Histology
Atopic Dermatitis	• Erythematous, pruritic skin with associated exudative and/or vesicular lesions on flexural surfaces • Associated atopy, allergic rhinitis, and/or asthma	• Crusting • Focal parakeratosis • Variable acanthosis • Spongiosis • Perivascular lymphocytes
Lichen Planus	• Polygonal, planar, very pruritic, purplish, papules and plaques • Reticulated white plaques in mouth (Wickham's striae) • Koebner phenomenon	• Hyperkeratosis • Hypergranulosis • Acanthosis involving rete ridges in sawtooth formation • Band-like lymphocytic infiltrate at dermal-epidermal junction
Secondary Syphilis	• Initial chancre • Widespread cutaneous eruption that can present in macular, maculopapular, grouped follicular, papular, corymbose papular, and psoriasiform papular patterns	• Mild lichenoid infiltrate with non-caseating granulomas in dermis • Heavy lymphocytic and plasma cell infiltrate • Positive spirochete immunostaining
Mycosis Fungoides	• First stage: well-marginated, erythematous plaques and/or patches • Secondary stage: papulosquamous plaques • Final stage: tumor nodules	• Atypical lymphocytes with cerebriform, hyperchromatic nuclei, with Halo artifact in the epidermis (epidermotropism) • Lymphoid cells along the dermal-epidermal junction • Fibrosis and inflammatory infiltrate in dermis • Elevated CD4/CD8 ratio and positive CD3
Psoriasis	• Erythematous or salmon pink, well demarcated plaques with slivery-white scale on extensor surfaces • Koebner phenomenon • Auspitz sign	• Munro microabscesses • Hypogranulosis • Hyperkeratosis • Regular acanthosis • Confluent parakeratosis • Perivascular lymphocytes • Thinning of the suprapapillary plates • Dilated papillary dermal capillaries

proliferation seen in psoriasis.[14,16] IL-22 also contributes to plaque formation by increasing epidermal hyperplasia.[16]

Certain genetic factors can predispose a patient's risk of developing this disease. For example, histocompatibility complex HLA-C*06:02, also known as HLA-Cw6, has been linked to the early onset of psoriasis in 85.3 % of patients with this antigen.[13] Fifty-five to 80 % of white psoriasis patients carry this antigen, greatly contributing to their disease development.[13,14] Still, the genetic component involved in this multifactorial pathogenesis is not fully understood.

In addition, abnormal dermal vascularization is an aspect of this disease. Elevated vascular endothelial growth factor (VEGF) has been associated with increased psoriasis severity, and it has been proposed that TNF-α is involved in VEGF's signaling pathways as well. This mechanism of atypical angiogenesis accounts for Auspitz sign.[15]

Overall, the pathological mechanism behind psoriasis is complex, but certain immune cells and cytokines, such as IL-17, are clear contributors to the pathogenesis of psoriasis.

Can drugs trigger the onset of psoriasis?

Beta-blockers, both cardioselective and non-cardioselective agents, are the most frequent culprit of drug-induced or exacerbated psoriasis.[17] A common hypothesis for this medication side effect is the blockage of beta-adrenergic subtype 2 receptors on keratinocytes.[18] This prevents the formation of cyclic AMP, leading to increased keratinocyte proliferation.[18] Additional drugs that provoke psoriasis include lithium and tetracyclines. Other drugs with a weak or minimal association with drug-induced or aggravated psoriasis are ACE inhibitors, amiodarone, quinidine, gemfibrozil, progesterone, morphine, acetazolamide, valproic acid, potassium iodide, digoxin, clonidine, carbamazepine, and penicillin.[17]

Table 2
Subtypes of psoriasis.[9,13,14]

Subtype	Clinical Presentation
Plaque Psoriasis	Well defined, salmon colored or erythematous plaques with silvery-white scale
Guttate Psoriasis	Scaly, round, erythematous papules (<1 cm)
Pustular Psoriasis	Localized: several, coalescing sterile pustules Generalized: pustules with widespread erythematous, tender skin Systemic symptoms as well
Inverse Psoriasis	Mildly erosive, erythematous patches and plaques in intertriginous locations No scaling
Psoriatic Erythroderma	Widespread, diffuse erythema Medical emergency (e.g. heart failure)
Nail Psoriasis	Pitting, oils spots, paronychia, onycholysis, onychodystrophy, splinter hemorrhages, and onycholysis

What are the other subtypes of psoriasis besides plaque psoriasis (Table 2 [9,13,14])?

Guttate psoriasis commonly affects children or adolescents and is triggered by Streptococcal infection, viral illness, or life stressors. A family history of psoriasis also increases a child's chance of developing guttate psoriasis. This disease variant presents as somewhat scaly, circular, erythematous papules smaller than 1 cm on the trunk and extremities. Forty percent of patients with guttate psoriasis go on to develop chronic plaque psoriasis.[9,14,15]

Pustular psoriasis presents as several, coalescing sterile pustules in a localized or generalized distribution. The palms of the hands and soles of the feet are commonly affected. Many reports of pustular psoriasis involve pustules forming over both chronic plaques of psoriasis and erythematous skin. Systemic symptoms, such as fever and nausea, have also been documented in these patients. Sudden discontinuation of systemic corticosteroids has been known to cause acute onset of pustular psoriasis.[9,14,15] This form of psoriasis has been associated with the unregulated activity of IL-36.[19]

Inverse psoriasis primarily develops in intertriginous regions, such as the axillary, intergluteal, inframammary, and genital areas. Clinical presentation includes erythematous patches and plaques that lack scaling and can be mildly erosive. This variation of psoriasis is also called flexural psoriasis or intertriginous psoriasis.[9,14,15]

Psoriatic erythroderma is a form of psoriasis that is lethal. Presenting as diffuse erythema with whole-body involvement, this disease can lead to hypoalbuminemia and high-output cardiac failure. Thus, emergency intervention is needed.[9,14,15]

Twenty to fifty percent of psoriasis patients have visible changes in their nails due to their disease. Nail psoriasis includes mild to severe

conditions, such as pitting, oil spots, paronychia, onycholysis, onychodystrophy, splinter hemorrhages, and onycholysis. Eighty percent of patients with psoriatic arthritis have some form of nail psoriasis.[9,14,15]

What diseases are associated with psoriasis?

Psoriatic arthritis is a classical comorbidity associated with psoriasis. The exact prevalence varies based upon the population studied, but the clinical manifestations include edema, pain or stiffness of the joints, enthesitis, and dactylitis. Skin lesions usually occur before the symptoms of psoriatic arthritis and 90 % of psoriatic arthritis patients have nail changes. Additionally, an increased CD4:CD8 ratio is found in the synovial fluid.[20]

There is also an association with psoriasis and inflammatory bowel disease, specifically Crohn's disease. It has been found that individuals with psoriasis have a threefold risk of developing Crohn's disease, and Crohn's disease patients have a sevenfold risk for developing psoriasis. Dermatologists must also be vigilant for signs of anxiety, depression, and other mental health disorders as well as obesity, diabetes, and hypertension in their psoriasis patients as these diseases affect patients physically and emotionally.[20]

What are the treatment options for psoriasis?

Obesity, dyslipidemia, hypertension, and insulin resistance must be taken into account when treating psoriasis. Studies have shown these risk factors can increase the severity of psoriasis in patients.[20–22] Moreover, these comorbidities can decrease the efficacy of biologic treatment for psoriasis. Diabetes decreases the response of IL-17 inhibitors in psoriasis patients, with obesity lowering the response of both TNF alpha inhibitors and IL-17 inhibitors.[23] Thus, an interdisciplinary team is needed to achieve optimal care in managing the treatment of both psoriasis and other comorbidities.

There are several treatment options available for psoriasis, including topical agents, oral systemic medications, phototherapy and biologic agents. Corticosteroids, calcineurin inhibitors, vitamin D analogues, and tazarotene are examples of topical agents used to treat this disease.[24] Oral systemic drugs, such as methotrexate, acitretin, ciclosporin, deucravacitinib and apremilast, are also used.[25,26] In addition, light sources, such as UVB, PUVA, and Pulse Dye Laser, are a few of the many effective phototherapies for psoriasis.[27] Phototherapy also spares the patient from enduring systemic side effects seen in oral and biologic therapy.[27]

Finally, biologic agents are specific immunomodulators that help control the dysregulation of the immune system seen in the pathogenesis of psoriasis. There are four different classes of biologic agents: TNF alpha inhibitors (e.g. infliximab, etanercept, adalimumab, certolizumab pegol), IL-17 inhibitors (e.g. secukinumab, ixekizumab, brodalumab, bimekizumab), IL-23 inhibitors (e.g. guselkumab, tildrakizumab, risankizumab) and IL-12/23 inhibitor (e.g. ustekinumab).[28] Since biologic medications have a very targeted attack on the immune system, they often leave most of the immune system unaffected. However, patients have a rare risk of infection. As such, tuberculosis (TB) testing is done as a baseline for patients starting biologic medications and only repeated if a patient has a high risk of TB exposure.[29]

Teaching points

- Plaque psoriasis is a chronic, inflammatory skin disease that presents as erythematous or salmon pink, well-demarcated plaques with slivery-white scale on the extensor surfaces of the elbows, knees, scalp, and lower back.
- Other subtypes of psoriasis include pustular psoriasis, inverse psoriasis, guttate psoriasis, psoriatic erythroderma, and nail psoriasis.
- When psoriasis is widespread, a broad differential must be considered, including but not limited to atopic dermatitis, lichen planus, secondary syphilis, mycosis fungoides, and psoriasis. Differentiation is possible with a skin biopsy and additional staining.
- On histology, psoriasis is characterized by hyperkeratosis, regular acanthosis, confluent parakeratosis, neutrophilic microabscesses/pustules (of Munro and Kogoj), hypogranulosis, perivascular lymphocytes, thinning of the suprapapillary plates, and dilated papillary dermal capillaries.
- The pathogenesis of psoriasis involves plasmacytoid dendritic cells mainly activating the Th17 pathway, with a lesser role of the Th1 pathway, to increase epidermal hyperplasia and other inflammatory processes.
- Beta-blockers are the most common cause of drug-induced or exacerbated psoriasis.
- Classic comorbidities associated with psoriasis include psoriatic arthritis, inflammatory bowel disease, depression, and anxiety as well as obesity, diabetes, and hypertension.
- Current treatment options for psoriasis are topical agents (e.g. corticosteroids, calcineurin inhibitors, vitamin D analogues, and tazarotene), oral systemic agents (e.g. methotrexate, acitretin, ciclosporin, apremilast), phototherapy (e.g. UVB, PUVA, PDL), and biologic agents. Biologics are divided into four classes: TNF alpha inhibitors, IL-17 inhibitors, IL-23 inhibitors, and an IL-12/23 inhibitor.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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