Psoriasis: Pathogenesis and Evaluation Options

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Abstract

Background: Psoriasis is an immune-mediated inflammatory disease with unknown etiology that may be associated with the defect in proliferation and differentiation of keratinocytes associated with inflammatory cell infiltration particularly consisting T-lymphocytes, macrophages, and neutrophils. Psoriasis affects 1–3% of the adult population with various extra cutaneous manifestations. In the United States, psoriasis affects approximately 3.2% of adults, 0.13% of children and the incidence is approximately 80 new cases per 100,000 person-years. Worldwide, approximately 125 million people have psoriasis, and psoriasis prevalence is highly variable across regions, ranging from 0.5% in parts of Asia to as high as 8% in Norway.

Keywords: Psoriasis

Psoriasis
Psoriasis is a non-contagious inflammatory disease. The main symptoms are reddish, scaly patches of skin that may itch. It is a chronic condition that is typically associated with periods of more severe skin problems (flare-ups) followed by periods of milder skin problems or none at all. Various treatments can relieve the symptoms, but there is no cure for psoriasis. Its severity can vary quite a lot. In some people it is bothersome more than anything else, and they can cope with it quite well. Others feel that it has a major effect on their quality of life, since the treatment and skin care can take a long time. Many people are also unhappy about having visible reddened and scaly skin patches especially if they are on exposed areas of their body. Sometimes the inflammation that is causing the psoriasis affects other parts of the body too, such as the joints or nails (1).

Epidemiology:
In most regions, women and men are affected equally. While psoriasis can manifest at any age, a bimodal age distribution exists for psoriasis presentation at ages 18 to 39 years and also at ages 50 to 69 years. Genetic and environmental factors may influence the age at onset of psoriasis. For example, the presence of the human leukocyte antigen (HLA)-C*06 allele is associated with earlier onset age of psoriasis (2). According to a 2013 systematic review of published population-based studies, it was found that psoriasis was more frequent in Caucasian populations compared to non-Caucasians. Furthermore, East African countries have higher reported prevalence of the disease compared to West African countries. The reported prevalence in Egypt varies from 0.19% to 3% (3).
In an epidemiological report in a dermatology clinic in Egypt from November 2015 until November 2018, the percentage of patients with psoriasis among all dermatology patients by was 1.3%, which was higher than that reported from clinics in several West African countries (0.05%-0.9%), almost half that reported in a Nepali dermatology clinic (2.9%), and much lower than that reported in a Turkish clinic (5.5%) (4).
Pathogenesis
Psoriasis is a hyperproliferative skin disease with increased rate of epidermal turnover. The pathogenesis of psoriasis is linked to various cellular mechanism and the role of T cells, antigen presenting cells (APCs), keratinocytes, Langerhans cell, macrophages, natural killer cells, an array of Th1-type cytokines, as well as certain growth factors like vascular endothelial growth factor (VEGF), keratinocytes growth factor (KGF), etc., have been suggested to play a key in the pathogenesis of psoriasis (5).
Psoriasis is an immunologically mediated disease; the activation of T lymphocytes leads to the inflammation in the dermal component and secondary to the inflammatory events there is also that epidermal hyperproliferation (6).

Various mechanisms are hypothesized to be involved in the pathogenesis of psoriasis (7):

- T cell function
- Role of dendritic cell
- Hyperproliferation of keratinocytes
- Angiogenesis
- Cytokine mediators
- Reduced apoptosis
- Genetic factors
- Role of oxidants and antioxidants in psoriasis

1. T cell function
T lymphocytes consist of a functionally distinct population of helper T cells and cytolytic T cells. The principal function of T cells is to recognize the processed peptide antigens that are attached to proteins encoded by the MHC class II genes. Therefore, for activation, T cells need APCs to process and present peptide fragments on the APC cell surface. T cells secrete various lymphokines (8).
T cells may also inhibit immune responses; in this role, these are known as suppressor T cells. Distinct cell membrane proteins are expressed by different populations of T cells. CD4 positivity is shown by most of the helper T cells while cytolytic and suppressor cells are CD8 positive. Activation of T cells requires three steps: a. Binding b. Antigen-specific activation (signal 1) . non-antigen-specific cell-cell interaction (signal 2) (6).

2. Role of dendritic cells
Dendritic cells serve as a major class of antigen presenting cells found in increased abundance in psoriatic skin lesions. Langerhans cells are a type of immature dendritic cell (iDC) found in normal epidermis and can also be found in psoriasis lesions. IDCs are derived from blood monocytes or other myeloid precursors and have an immunostimulatory role. These iDCs are further stimulated to become mature DCs (mDCs). Psoriasis lesions show a marked increase in dermal DCs. XIIIa and CD11c are expressed by myeloid DCs or iDCs, and CD83 and DC-LAMP proteins are positive for mDC (9).

3. Hyperproliferation of keratinocytes
The skin provides a protective mechanism through its multilayered structure. The epidermis consists of five layers, stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum. Mainly the keratinocytes are formed in the stratum basale and further they migrate towards the stratum corneum. As cells move toward the surface, their organelles disappear and are filled with keratin. The topmost layer of keratin provides a protective feature (10).
In normal conditions the epidermal cell cycle is completed in about four weeks. But in psoriatic skin, the epidermal cell cycle is accelerated. Cell division in the basal layer occurs every 1.5 days, and the migration of keratinocytes to the stratum corneum occurs within approximately 4 days. This results in hyperproliferation of keratinocytes (11).

4. Angiogenesis
Keratinocytes produce proangiogenic cytokines (VEGF, IL-8), but the precise mechanism for angiogenesis in psoriasis is still unknown. In psoriasis the endothelial cells swell and become activated these activated endothelial cells migrate, sprout, and lay down a basement membrane with pericytes for structural support to form novel vessel networks. This results in widening of the intercellular spaces, and hence, dermal blood vessels dilate thus making it easier for leukocytes to migrate into the skin (12).

5. Cytokine mediators
In psoriasis, the production of cytokines results in epidermal hyperproliferation, vascular dilatation, and dermal inflammation. The cytokines involved in the development of psoriasis include granulocyte–macrophage colony stimulating factor (GMCSF), epithelial growth factor (EGF), IL-8, IL-12, IL-1, IL-6, IFN-γ, and TNF-α. These cytokines result in keratinocyte proliferation, neutrophil migration, potentiation of Th1 type of responses, angiogenesis, upregulation of adhesion molecules, and epidermal hyperplasia (6).

6. Reduced apoptosis
In order to maintain a constant thickness of the epidermis proliferation of keratinocytes in normal epidermis is regulated by apoptotic cell death. The epidermal hyperplasia characteristic of psoriasis is suggested to be due to P53 overexpression and these proliferating cells typically express Bcl-2 that protects them against apoptotic stimuli, while terminally differentiated cells lose Bcl-2 expression (13).

Skin–Gut Axis and Intestinal Dysbiosis in Psoriasis
The adult intestine hosts a number of diverse bacterial species, collectively referred to as the microbiome that reside mainly in the lower gut, where they maintain a symbiotic relationship with their host. Psoriasis, like many other systemic inflammatory diseases, likely involves inappropriate activation of various immune pathways leading to elevations in pro-inflammatory cytokines (14). The gut microbiome is believed to be involved in the development of pro-inflammatory Th17 cells, allowing it to modulate inflammation in diseases such as inflammatory bowel disease and obesity. Like the skin microbiota, the composition of the gut microbiota and its association with psoriasis are unclear (15). Tan et al. compared the gut microbiota in patients with psoriasis with those without the disease and found that those with psoriasis had a significant decrease in A. muciniphila, a species believed to strengthen the integrity of the gut epithelium and protect against systemic inflammatory diseases, such as inflammatory bowel disease, obesity, and atherosclerosis (15). Scher et al. found that the diversity and abundance of the gut microbiota were altered in patients with psoriasis and arthritis compared with healthy controls; microbial diversity was decreased, with the main characteristic of reduced relative abundance of Akkermansia, Ruminococcus, and Pseudobutyryrivibrio (16).

Conversely, psoriatic exacerbation was deemed to be associated with increased colonization of Staphylococcus aureus, Candida albicans, and Malassezia in the skin and gut. Thus, the association between the gut and skin is strong and bidirectional, and gastrointestinal health is associated with skin homeostasis and allostasis (17).
An imbalanced gut microbiome, a pathological state named intestinal dysbiosis, has a negative impact on skin function and integrity. O’Neill et al. found that the gut microbiome can influence skin homeostasis via regulating the coordinate epidermal differentiation and immune system, although the mechanism is not yet fully elucidated (17).

Furthermore, studies provide new evidence to clarify the effect of the gut microbiome on dermatologic physiology, pathology, and immune response, which rely on the dissemination of intestinal microbiota and their metabolites from the gut to the skin (18).

Certain pathogenic bacteria can produce certain metabolites, such as phenol and p-cresol. These metabolites can disrupt the skin barrier integrity and epidermal differentiation, reduce skin hydration, and impair keratinization, which are associated with entry into the bloodstream and accumulation in the skin (18).

In fact, except for skin health, gut microbial metabolite production can significantly impact the health and disease states of the host. This is demonstrated in the examples of short-chain fatty acid and trimethylamine production via bacterial metabolism of dietary complex carbohydrates and choline, respectively. In addition to its role in cardiovascular disease and chronic kidney disease, the gut microbiota impacts the development of inflammatory bowel disease (IBD) and so on (19).

Furthermore, certain gut microbes may recruit regulatory T cells and lymphocytes to promote anti-inflammatory response by certain metabolites, such as retinoic acid and polysaccharide A. Short-chain fatty acids (SCFAs), a type of metabolite, are involved in the activation and apoptosis of immune cells (19).

Accumulating evidence in animals showed that chronic systemic inflammation is the main consequence of intestinal dysbiosis, due to the imbalance between increased epithelial permeability and the activated effector T cells, resulting from the secretion of pro-inflammatory cytokines; this leads to a vicious circle of chronic systemic inflammation. This may be one of numerous mechanisms by which the gut microbiome induces skin impairment (20).

The “skin–gut axis” concept provides a new insight to investigate the association between the intestinal flora and the skin. Modulated aberration of gut microbes leads to a wide variety of inflammatory dermatologic disorders, such as acne vulgaris, seborrheic dermatitis, and psoriasis. Increasing evidence shows the existence of the gut–skin axis, and that an imbalanced gut microbiome can induce inflammatory skin diseases. This offers a feasible approach for improving skin conditions, by the modulation of the gut microbiota (20).
Figure (1): Inflammatory and microbial influences between the gut and skin for a healthy state (left) and a dysbiotic state (right). The intestinal and epidermal barriers are connected through the systemic circulation (blood and lymph) and are visualized here together in a simplistic manner. The dysbiotic state is characterized by an impaired gut barrier (imbalance in gut microbiome, reduced mucus layer, reduced IgA secretion, barrier disruption, intestinal permeation into the bloodstream, and gut inflammation) and an impaired skin barrier (imbalance in skin microbiome, reduced human and microbial antimicrobial peptides (AMP) production, skin rashes/ thickening/ lesions, and skin inflammation). Gut and skin dysbiosis are connected through an immune imbalance, whereas crosstalk can be bidirectional (20).

Clinical Presentation
Psoriasis presents as well-defined erythematous plaques covered with silvery scales commonly over the scalp, extensors of extremity particularly over knees and elbows and lumbosacral region. Psoriasis is classified into two types. Type 1 psoriasis, which has a positive family history, starts before age 40 and is associated with HLA-Cw6; while type 2 psoriasis does not show a family history, presents after age 40, and is not associated with HLA-Cw6 (21).

Psoriasis can present with different morphology in the form of plaque, guttate, rupioid, erythrodermic, pustular, inverse, elephantine, and psoriatic arthritis. Variation in a site is seen with the involvement of scalp, palmar plantar region, genitals, and nails. Any injury to the skin in patients with psoriasis in the form of either mechanical, chemical or radiational trauma induces lesions of psoriasis at that site which is called Koebner phenomenon. It indicates the activeness of disease (21).

Plaque psoriasis typically presents as erythematous plaques with silvery scales most commonly over extensors of extremities, i.e., on the elbows, knees, scalp, and back (Figure 2). It is the most common type of psoriasis which affects 85% to 90% patients. On successive removal of psoriatic scales pinpoint bleeding points are seen. This is called Auspitz sign which is used to confirm the diagnosis clinically (21).
Guttate psoriasis also called as eruptive psoriasis is commonly seen in children after an upper respiratory tract infection with the streptococcal organism. It presents with erythematous and scaly raindrop-shaped lesions mainly over trunk and back. It is the type of psoriasis having the best prognosis (21).

Pustular psoriasis presents with small non-infectious pus-filled lesions with erythema surrounding it. It is of two types localized and generalized. Generalized pustular psoriasis is associated with hypocalcemia and presents with sterile pustules on an erythematous plaque involving the whole body (22). Erythrodermic psoriasis presents with widespread inflammation in the form of erythema and exfoliation of the skin covering more than 90% of the body area. It is associated with severe itching, swelling, and pain. It is the result of an exacerbation of unstable plaque psoriasis, following the abrupt withdrawal of systemic steroids. Complications of erythroderma include impairment in barrier functions of skin, disturbance in basal metabolic rate, increased cutaneous circulation in turn affecting the heart with cardiac failure (23). Nail changes in psoriasis are seen as pitting, oil spots, subungual hyperkeratosis, nail dystrophy, and anchylosis. Fissured tongue is the most common finding of oral psoriasis and has been reported to occur in 6.5% to 20% of people with psoriasis affecting the skin (23).

Inverse psoriasis is also called as flexural psoriasis or intertriginous psoriasis. It appears as smooth, erythematous and sharply demarcated patches affecting intertriginous areas like groins, armpits, intergluteal region, and inframammary region. The skin may be moist, macerated, may contain fissures which may be malodorous, pruritic, or both. It needs to be differentiated from dermatophyte infection affecting these sites, which presents with central clearing and the active border with scales, vesicles, and pustules at the margin (24).

Sebopsoriasis is a form of psoriasis which typically manifests as red plaques with greasy scales. It commonly affects areas with increased sebum production such as the scalp, forehead, nasolabial folds, sternum, and retro-auricular folds (24).
Psoriatic arthritis is a form of chronic inflammatory arthritis which affects 30% patients with psoriasis. It commonly occurs in association with skin and nail psoriasis. It typically involves painful inflammation of the joints and connective tissue commonly affecting the joints of the fingers and toes. It leads to sausage-shaped swelling of the fingers and toes known as dactylitis. Psoriatic arthritis can also affect the hips, knees, spine presenting as spondylitis and sacroiliac joints with sacroiliitis.

Ocular features: psoriasis also affects the eyelid, conjunctiva, and cornea giving rise to trichiasis, ectropion, conjunctivitis, and corneal dryness. The most common eye feature is blepharitis which can lead to cicatricial ectropion, madarosis, and trichiasis. In some cases, anterior uveitis may be seen.

**Diagnosis**

Usually, diagnosis is made by clinical morphology and site of lesions. Histopathology is rarely necessary but may help to differentiate psoriasis from another dermatosis if the diagnosis is not easy. Characteristic changes in biopsy show parakeratosis, micro-abscess, the absence of granular lesions, regular elongation of ridges in the form of camel foot appearance, spongiform pustules of Kogoj with dilated and tortuous capillaries in the dermal papilla.

**Laboratory studies**:

- One should order complete CBC, renal and liver function tests
- Rheumatoid factor
- ESR may be elevated in erythrodermic and pustular psoriasis
- Uric acid levels are high in psoriasis
- If only hand and feet are involved, obtain scrapings for fungal studies
- Pregnancy test
- Hepatitis serology
- PPD

**Treatment**

Psoriasis Area Severity Index (PASI) is the most widely used measurement tool which assesses the severity of the condition and allows to evaluate the treatment efficiency. Topical therapy is used in mild to moderate psoriasis. Emollients and moisturizers may help in improving barrier function and retain the hydration of stratum corneum. Topical agents used are coal tar, dithranol, corticosteroids, vitamin D analog, and retinoids.

- The drug of choice is methotrexate and should be used as long as it remains effective
- Cyclosporine can be used to induce a clinical response but its use should be intermittent.
- When patients fail to respond to methotrexate, switch to biological agents; in some cases, combine with methotrexate

Phototherapy includes PUVA therapy which combines psoralen with exposure to ultraviolet light (UVA), as well as NBUVB (Narrowband UVB light) with a range of 311 nanometers to 313 nanometers. NBUVB is equally effective without the side effects of psoralen like gastrointestinal upset, cataract formation, and carcinogenic effect. It can safely be given to children, pregnant and lactating females and even elderly. Guttate psoriasis has been known to respond best to phototherapy.

Systemic drugs are used in extensive cases, the involvement of nails and psoriatic arthritis. Methotrexate, retinoids, cyclosporine, and fumarates are possible options. Routine blood, liver functions, and renal functions should be monitored in patients on systemic therapy.

Biologicals are manufactured proteins that interrupt the immune process in psoriasis which are infliximab, adalimumab, etanercept, and interleukin antagonists. Before starting any biological agent, the patient should be worked up for tuberculosis and hepatitis. There is a serious risk of infections in these patients and all precautions should be taken that the patient is not severely immunocompromised.
Prolonged use of steroids and other immunosuppressives may delay wound healing. Ocular psoriasis requires aggressive treatment with topical corticosteroids (33). Patients with psoriasis should avoid all skin trauma for fear of inducing the Kobner reaction. In addition, psoriatic patients should avoid the use of beta-blockers, chloroquine or NSAIDs. They should also avoid alcohol because of the risk of developing fatty liver (33).

**Prognosis**

Psoriasis is a chronic condition which is known to have a negative impact on the quality of life in patients as well as a family member. Psoriasis is a life long illness marked by relapses and remissions. About 10% of patients develop severe deforming arthritis. Remissions are experienced in 10-60% of patients (34). Over the course of the disease, psoriasis has been associated with depression, suicide, alcoholism, smoking, substance abuse, metabolic syndrome and a variety of skin cancers. In addition, patients with psoriasis tend to have major medical comorbidities like kidney disease, heart disease, and joint problems. Several studies have noted a link between psoriasis and adverse cardiac events (35). Pustular psoriasis and erythrodermic psoriasis may be life-threatening, while psoriatic arthritis affects the functional prognosis negatively (36).

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