Review Article

Psoriasis - Recent Advancement on Immunopathogenesis and Immunotherapy – A Comprehensive Review

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ABSTRACT

Psoriasis is a chronic hyperproliferative inflammatory skin disease that is primarily caused by T cells. It is characterized by aberrant T-cell-dominated dermal inflammatory infiltration, intra-epidermal neutrophil granulocyte buildup, and hyperproliferation of keratinocytes. It's possible that some of the cytokines generated by activated T cells encourage psoriatic keratinocyte growth. It has recently become evident that chemokines originating from endothelial cells or activated keratinocytes are essential for drawing T lymphocytes to the skin and initiating the neutrophilic infiltration that results in the development of subcorneal pustules (also known as Munro's microabscess). Psoriatic arthritis can be effectively treated with several conventional psoriasis medicines, including methotrexate and cyclosporine. However, these medications are frequently insufficiently beneficial, have short half-lives, and raise serious safety issues. Determining the severity of the cutaneous condition is the first step in managing psoriasis. Nonetheless, a comprehensive, contractual approach to therapy is advised, paying special attention to problems pertaining to psychosocial impairment and quality of life. When thinking about treatment alternatives, it's also crucial to take into account the existence of psoriasis on the palms, soles, body folds, genitalia, face, or nails, as well as any concurrent joint diseases. Biological therapies for the treatment of psoriasis and/or psoriatic arthritis fall into three categories based on how they work: T-cell modulating agents (e.g., alefacept and efalizumab); TNFα blockers (e.g., adalimumab, certolizumab, etanercept, golimumab, and infliximab); and inhibitors of interleukin (IL) 12 and IL–23 (e.g., ustekinumab and briakinumab).

Keywords: Keratinocytes, T-cell, Munro's microabscess, cytokine, angiogenesis.

INTRODUCTION

Treatment for psoriasis, an immune-mediated skin illness that is persistent, can last a lifetime. Due to their inability to treat their psoriasis, side effects, or detrimental effects on quality of life, many patients express unhappiness with conventional non-biologic therapy. The hyperproliferation of the epidermis, conspicuous, elongated blood vessels, and thick perivascular lymphocytic infiltration are histological characteristics of psoriasis. It is currently believed that psoriasis is an auto-immune condition[7]. There is obviously a need for innovative medicines, even with the wide range of therapies now accessible. A long-term condition that affects the skin and joints is psoriasis. Silvery scaling covering erythematous plaques and a chronic, recurring history are clinical features.[1-6]

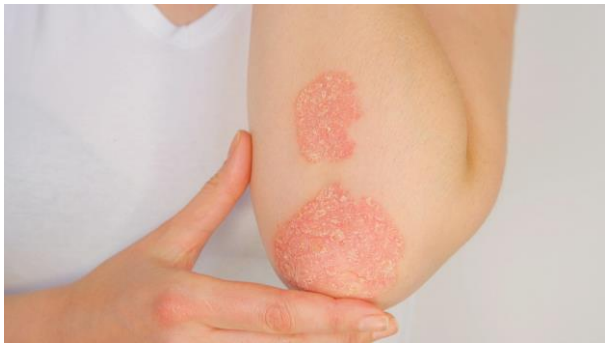

Figure 1: Psoriasis[8].

Epidemiology:

It's believed that psoriasis affects 2- 3% of people worldwide. It's well known that the complaint is more common in the world's polar areas, but the impact it has on a tropical or tropical nation like India cannot be understated. Due to varying environmental and inheritable factors, the frequency of psoriasis can differ from region to region in a country as different as India. There has been substantiation of an advanced prevalence in men, with a peak age at onset in the third and fourth decades of life[12]. Psoriatic arthritis can develop at any age between 35 and 50, with no perceptible coitus bias. In around 70% of cases, psoriasis develops prior to articular involvement; 15% of cases witness arthritis further than a time before psoriasis begins, and the remaining 15% of cases witness both ails within a time of one another[13].

Etiology:

You have an increased chance of developing psoriasis if you have a parent, grandmother, family, or family who has it. Psoriasis is not transmissible, unlike the common cold wave or chickenpox.

Substantially the vulnerable system is responsible for the spreading of psoriasis. T- T-cells, or white blood cells, are an element of the vulnerable system in the mortal body. By combating pathogens like bacteria and contagions, these cells help keep us healthy. T- T-cells assault the body's skin cells when a person has psoriasis because the vulnerable system is conking. The body produces new skin cells more

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constantly as a result of this assault. Psoriasis results from an accumulation of redundant skin cells on the skin's face. After T- T-T-cells begin attacking skin cells, they frequently do so for the remainder of an existent life. One case isn't the same as the others. A subset of children with guttate(guttate) psoriasis never develops it again[9].

Types of psoriasis:

There are 5 different types of psoriasis

1. **Plaque psoriasis:** The most current type manifests as elevated, red skin patches carpeted in argentine-white scales. The patches generally form on the crown, torso, and branches, particularly the knees and elbows, and they typically develop symmetrically over the body.
2. **Guttate psoriasis**: This form resembles little red blotches and generally affects the casket or branches. It generally manifests in youths or youthful grown-ups. Upper respiratory tract infections, similar to strep throat, can set off outbreaks.
3. **Pustular psoriasis:** This kind is characterized by papules, which are pus-filled lumps encircled by red skin. Although the hands and bases are generally affected, there's a variant that affects the maturity of the body. Stress, certain substances, conditions, and medicines can all beget symptoms.
4. **Inverse psoriasis:** This variety manifests as red, smooth patches in skin crowds, similar to those under the guts, in the crotch, or under the armpits. Sweating and rubbing may complicate it.
5. **Erythrodermic psoriasis:** This is an uncommon but severe kind of psoriasis that covers much of the body in red, with scales on the skin. It can be brought on by taking certain specifics, including corticosteroids, or by getting a terrible sunburn. When another kind of psoriasis is inadequately managed, it might lead to erythrodermic psoriasis, which can be relatively dangerous.[10]

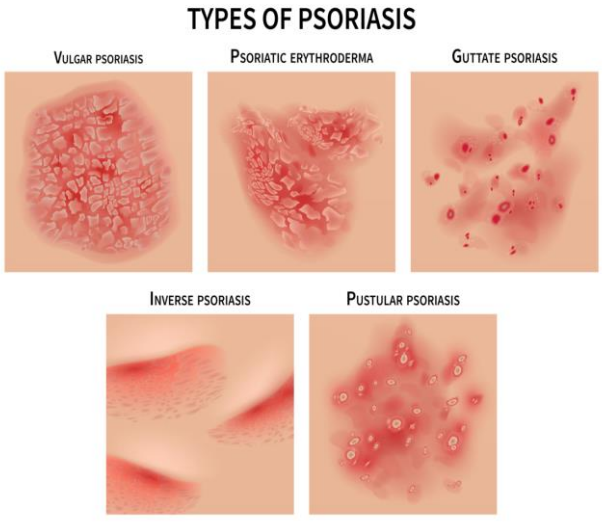

Figure 2: Types of psoriasis[11]

Immunopathogenesis:

The current models used to describe the pathology of psoriasis show changes in inflammatory mediators and cell composition when comparing skin with and without the condition. Regarding cell composition, non-lesional skin contains few immature Langerhans and dendritic cells, few CD4+ lymphocytes, and seldom CD8+ lymphocytes while lesional skin has a high concentration of these and other cell types[14].

1. T cell activation

It is generally accepted that the pathophysiology of the disease involves aberrant T-cell regulation in conjunction with keratinocyte-complex cytokine network interaction. Any physical or chemical harm to the faulty keratinocytes, if the underlying problem is in the keratinocytes, may trigger the production and release of cytokines, which would activate T lymphocytes without the need for an antigen. More cytokines would be released as a result, and keratinocytes, T lymphocytes, and inflammation would then proliferate[15]

2. Hyperproliferation of keratinocytes

When the T cells get activated that results in the release of various mediators like cytokine which leads to hyperproliferation of keratinocytes Hyperproliferating psoriatic keratinocytes have a short cell cycle. The psoriatic epidermis experiences keratinocyte maturation and shedding in 4 days, whereas normal epidermis takes 26 days. It is believed that the increased proliferation is controlled by growth factors, which come from various cell types[15].

3. Angiogenesis

It is still unclear how angiogenesis occurs in psoriasis, however, keratinocytes are believed to be a significant source of pro-angiogenic cytokines. The Golgi apparatus is clearly visible as endothelial cells inflate and become active in a growing psoriatic plaque. Dermal blood arteries expand, and intercellular gaps widen as a result of endothelial cell activation and swelling. Lesional capillary loops express E-selectin and take on a venous phenotype, including bridging fenestrations, which facilitate leukocyte migration into the skin. That results in psoriatic lesions[15].

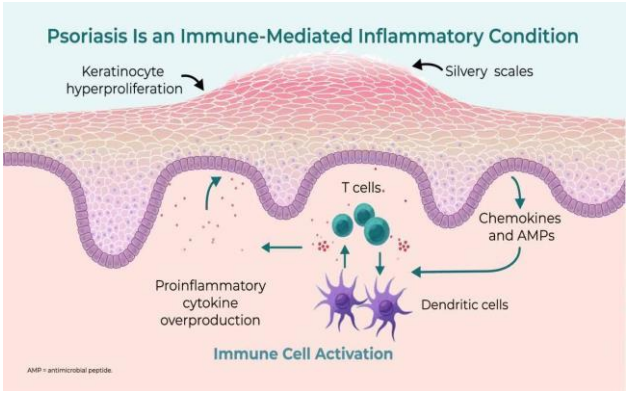

Figure 3: Immunopathogenesis of psoriasis[16]

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Cytokine mediators involved:

1. TNF-α:

The production of GM-CSF, PAI2, β-defensins, TGF-α, ICAM-1, and IL-8 is induced in keratinocytes. Improvement of macrophages' ability to secrete pro-inflammatory cytokines. Endothelial cells are stimulated to release VEGF. Increased proliferation of keratinocytes.

2. IFN-γ:

The inhibition of normal keratinocyte proliferation in vitro. ICAM-1 expression on endothelial and keratinocyte cells is increased, which affects lymphocyte trafficking into the lesional epidermis. Increased TNF-α receptors and phagocytes' stimulation of APC activity and TNF-α release

3. GM-CSF:

Enhances the growth of keratinocytes and stimulates neutrophils. It also encourages endothelial cell migration and proliferation.

4. IL-1:

Fibroblast KGF and GM-CSF expression and keratinocyte E-selectin, VCAM-1, and ICAM-1 induction. Following that, these fibroblast-derived substances promote the growth and development of keratinocytes. A mitogen that directly affects keratinocytes and promotes angiogenesis.

5. IL-2:

It serves as a growth factor and chemoattractant for T cells. Causes cytotoxicity in T cells. Increases the activity of NK cells. In those who are predisposed, high doses of IL-2 may cause psoriasis.

6. IL-6:

Increases T cell activation, proliferation, and chemotaxis in dermal infiltration. B-cell and macrophage proliferation and activation. In vitro stimulation of keratinocyte growth.

7. IL-8

T-cell and neutrophil migration into the epidermis T cell activation, proliferation, and angiogenesis promotion.

8. IL-12

Increases T cell differentiation and activation while promoting the maturation route of type 1 T cells.

9. IL-17

Increases fibroblasts' surface expression of intracellular adhesion molecule-1 (ICAM-1).

10. IL-22

Together with IL-17, it stimulates the production of defensins, MMPs, and other molecules, such as S100A7, which increases keratinocyte motility. Additionally, IL-22 raises TNF-α mRNA expression.

11. IL-23

It stimulates nuclear STAT-3 transcription and is a major inducer of Th-17 cells. Results in the rise of IL-17 and IL-22 levels. Produces mixed infiltration and noticeable acanthosis.

12. Endothelin

It is chemo-attractive to neutrophils and mitogenic to keratinocytes. PASI (Psoriasis Area and Severity Index) scores are correlated with serum levels of endothelin-1.

13. VEGF

When psoriasis causes erythema, it is up-regulated. Controls the development and remodeling of vascular tissue in psoriasis lesions. The connection between angiogenesis and cell-mediated inflammation in psoriasis may be explained by VEGF, as leukocytes exhibit enhanced adherence to selectins and VCAM expressed on new capillaries in the skin.

14. FGF

It is found both suprabasally and basally in psoriasis and has angiogenic and mitogenic properties.

15. NGF

Psoriatic lesion over-expressed. It encourages keratinocyte and endothelial cell proliferation and the production of adhesion molecules.

Diagnosis:

A dermatologist usually looks for tell signs of psoriasis, such as red, scaly plaques, on the skin, nails, and scalp. They might ask about joint pain, recent stressors, and family history because these can be signs of psoriatic arthritis[23].

Sometimes the diagnosis may require skin biopsy if symptoms are not clear.

By offering a conclusive microscopic analysis of skin cells, a skin biopsy helps diagnose psoriasis[21]. The majority of physicians can identify psoriasis by visual examination, but when symptoms mimic those of other skin disorders, such as lupus or eczema, a biopsy can be helpful[22].

Usually completed quickly, this process entails taking a tiny sample of skin, which a pathologist will subsequently examine to provide a precise diagnosis[24].

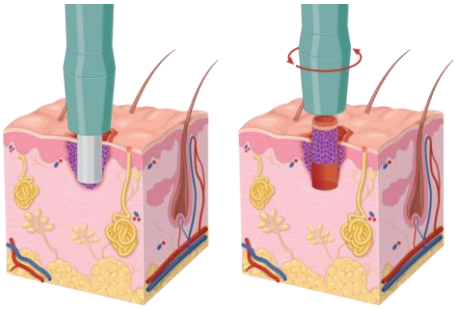

Figure 4: Skin biopsy[25]

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Immunotherapy:

Psoriasis can be treated in a number of ways, from topical medications for less severe cases to phototherapy and systemic medications for more severe cases. The arsenal has recently been expanded to include biologics, which are bioactive substances that function at the cellular level.

The use of biologics that target particular inflammatory pathways has transformed immunotherapy for psoriasis.

Treatments currently in use include:

1. Biological therapy

   By blocking pro-inflammatory cytokines, medications such as etanercept, adalimumab, and ustekinumab successfully treat moderate to severe psoriasis.

   For moderate to severe psoriasis, biologic therapy is a targeted treatment that targets particular immune system pathways that contribute to inflammation. These treatments fall into a number of types, including IL-12/23 inhibitors (ustekinumab), IL-17 inhibitors (ixekizumab, secukinumab), and TNF-alpha inhibitors (adalimumab, etanercept)[27,28]

2. Histotubulin

   According to a case study, its anti-inflammatory and anti-autoimmune properties may cause mild to moderate instances to go into remission[17].

3. Immune-checkpoint inhibitors

   The majority of flares may be controlled with conventional therapy, albeit they can make psoriasis worse[20].

4. Non-biological therapy

   Adalimumab and infliximab are more effective treatments for cutaneous psoriasis than methotrexate, which is advised for people with moderate to severe psoriasis[29].

   Patients with severe, resistant psoriasis are advised to take cyclosporine[29].

CONCLUSION

Inflammatory cells, keratinocytes, and antimicrobial peptides are among the cell types involved in the pathophysiology of psoriasis. Further basic research on the pathophysiology will advance the creation of psoriasis therapeutic drugs. Psoriasis is currently thought to be a chronic immune-mediated condition, with T lymphocytes serving as the main pathophysiological modulator. With the growing understanding of the T-lymphocyte's function, new methods for managing the inflammatory process have been developed. Biologic drugs in psoriasis will examine the novel biologic treatments that seek to specifically inhibit the immunological processes described in this research that are implicated in the pathophysiology of psoriasis.

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