Research Article

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Is a reversible autocephalous medication reaction or is paradoxical psoriasis the opposite of idiopathic psoriasis?

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ABSTRACT

Common chronic skin disease psoriasis is primarily caused by the intricate interaction of T cells, dendritic cells, and inflammatory cytokines such as TNF-α, IL-17, IL-12, and IL-23. The significance of these important cytokines, particularly TNF-α, has been demonstrated by successful anti-cytokine antibody therapy. A tiny percentage of patients experience the development of new psoriasiform lesions while receiving anti-TNF-α medication for classical idiopathic psoriasis.

This contradictory condition, known as paradoxical psoriasis, has separate immunological processes and overlapped histology patterns, hence clinically resembling idiopathic psoriasis. We go over the distinctions between idiopathic and paradoxical psoriasis in this review, focusing primarily on innate immunity since paradoxical psoriasis is characterized by type I IFN-mediated immunity without the activation of memory and autoreactive T cells. Additionally, we posted a useful algorithm for the treatment of paradoxical psoriasis. The severity of lesions and the state of underlying disorders should be taken into consideration when deciding whether to switch biologics or stop taking a medication.

Keywords : Paradoxical psoriasis, Tumor necrosis factor inhibitors, biological products,immunity, innate

INTRODUCTION

In people who are genetically susceptible, psoriasis is a common chronic inflammatory skin disease that is mostly brought on by the interaction of multiple environmental risk factors. One of the main contributing factors is persistent inflammation.

harmful function. Its global prevalence is from 2% to 3%, with a small predilection for adults over children and a similar prevalence in both genders [1]. Extrinsic risk factors for psoriasis include infections, mechanical stress, air pollution, vaccinations, smoking, alcohol, and smoking [4–6]. Significant intrinsic risk factors include mental stress, obesity, diabetes mellitus, metabolic syndrome, and hypertension.

The clinical variations of idiopathic psoriasis include pustular, erythrodermic, guttate, plaque, and inverse psoriasis, based on morphologic characteristics. The most common form of plaque psoriasis is characterized by erythematous, scaly patches or plaques over the body, scalp, and surface extensor muscles. According to histopathology, it is characterized by prominent epidermal acanthosis, hyperkeratosis, parakeratosis, and rete ridge extension. It also shows persistent inflammatory infiltration, primarily of T cells, neutrophils, macrophages, and mast cells in the skin's outer layer.

Early on, host DNA binds with antimicrobial peptides (AMPs) produced by the epidermis, such LL-37, activate plasmacytoid dendritic cells (pDCs). Subsequently, interferon (IFN)-α is secreted by pDCs, and this helps activate CDs, or conventional dendritic cells. TNF-α, IL-12, IL-23, and other pro-inflammatory cytokines generated by CD4+ cells subsequently trigger the activation of T lymphocytes that may be autoreactive, including Th17, Th22, and T helper (Th) 1 cells (Fig. 1).

TNF-α is a pleiotropic cytokine that has the ability to increase inflammation via several mechanisms. Activated CD4+ cells and many immune cell types, such as macrophages, lymphocytes, keratinocytes, and endothelial cells, release TNF-α. TNF- The Th17/IL-23/α axis is primarily involved in plaque psoriasis. Th17 cells can produce several mediators, including IL-17 and IL-22, once they are activated. These cytokines enhance the in vivo chronic immune response and keratinocyte growth.

Over the years, a growing comprehension of the part TNF-α and other cytokines play in the aetiology of psoriasis has led to the clinical introduction of several biologic medicines. Anti-TNF-α medication has demonstrated extraordinary success when used as a combined treatment for patients with moderate-to-severe psoriasis. However, between 2% and 5% of the patients get psoriasis for the first time or worsen pre-existing conditions.lesions with psoriasis while receiving biologics, particularly TNF-α inhibitors. Paradoxical psoriasis (PP) is the term for this immune-mediated, non-infectious inflammatory side effect of biological agents. TNF-α inhibitors

are not the only biologics available. Ustekinumab, an IL-12/23 inhibitor; Secukinumab, an IL-17A inhibitor; Dupilumab, an IL-4/13 inhibitor; Tocilizumab, a Siltuximab inhibitor; and IL-23 It was reported that inhibitors (such as guselkumab and risankizumab) had caused PP. Even though PP and traditional idiopathic psoriasis have comparable clinical presentations, their immune systems work very differently.

Psoriasis without a cause

Adaptive and Innate Immunity

According to new research, patients with active, severe psoriasis are primarily affected by adaptive immunity, whereas those with chronic stability are primarily affected by innate immunity. Innate immunity in psoriatic lesions begins with the production of endogenous AMPs and the activation of pDCs. The natural immunological effectors known as AMPs include skin and are frequently created by neutrophils or keratinocytes that have invaded the skin in pathological situations such wounds or infections [7,8]. Neutrophophil gelatinase-associated lipocalin, cathelicidin, β-defensins, S100 proteins, lysozyme, RNase 7, elafin, and other AMPs are shown to be abundantly expressed in psoriatic lesions [9]. As a catalyst molecules against microbes, the continuous expression of AMPs in psoriatic lesions activates keratinocytes and innate immune cells, mostly in a pattern recognition receptor (PRR)-dependent way, including neutrophils, macrophages, and DCs. AMPs attach themselves to nucleic acid fragments to create a complex that is resistant to breaking down [10,11]. The complex enters endosomes and triggers the toll-like receptor (TLR), which draws in neutrophils and macrophages, forms a neutrophil extracellular trap (NET), and produces IFN-α. IFN-α produced from pDCs encourages cDC maturation, which allows autologous reactive T cells—particularly CD8+ T cells—to concentrate into the dermis [12,13].

The continuous overactivation of the immune system following DCs activation and activated T cell stimulation are the primary pathways involved in the pathogenesis of chronic psoriasis. The two main psoriatic cytokines secreted by activated CD4+ cells are IL-12 and IL-23. It was discovered that the development of psoriasis was associated with a mutation of TYK2, one of the intracellular tyrosine kinases of the JAK-STAT superfamily [14]. The downstream signal transduction of receptors for the IL-12, IL-23, and type I IFN family was started by the combination of TYK2 and JAK2 [15, 16]. When this signal transduction was inhibited, IL-12, IL-23, and type I IFN signaling all but stopped functioning [17].

Neural T lymphocytes develop into Th1 cells and encourage IL-12 release, which is notably elevated in psoriatic lesions. Psoriatic plaques attract Th1 cells through chemokines produced by myeloid cells. as well as keratinocytes (CXCL9, CXCL10, and CXCL11). The overproduction of TNF-α and IFN-γ is the result of the Th1-biased profile. IL-12 and IL-23 differ in the second subunit, p35, but share the subunit p40. The p40 subunit and elevated IL-12 have been linked in earlier research, which has drawn more focus on the IL-23/Th-17 immunological axis and IL-17A, the primary downstream effector.

The IL-23 receptor expressed on naive T cells recognizes IL-23 produced from myeloid cells, which is thought to be crucial for the differentiation and maintenance of Th17 cells [18]. The intricate of IL-23R and IL-12Rβ1 causes a rise in IL-17 and retinoid-related orphan receptor (ROR)-γt after activating STAT3, a signal transducer and activator of transcription 3 [19]. Innate immune cells like macrophages and DCs release inflammatory cytokines (e.g. The differentiation of naive T cells into Th17 cells is dependent on ROR-γt, which is facilitated by TGFβ1, IL-1β, IL-23, and IL-6 [20]. Additionally, it has been found that mast cells and neutrophils significantly trigger the accumulation of IL-17 and the transcription factor ROR-γt through the development of NETs in pustular and plaque psoriasis [21, 22]. The Th17 phenotype is mostly maintained and expanded with the help of IL-23. IL-17A and IL-17F induction were totally inhibited in animals lacking IL-23p19 [23]. Clinical studies have demonstrated that psoriatic lesions exhibit elevated levels ofmessenger RNA for IL-23p19 in comparison to normal skin. Additionally, the IL-23 receptor is overexpressed on dermal DC and Langerhans cells in psoriasis patients.

Th17 cells, CD8+ T cells, and innate immunity neutrophils produce IL-17A, the most functional isoform of the IL-17 family [24]. Furthermore, independent of IL-23, natural killer cells and γδT cells can generate IL-17A [24, 25]. The primary IL-23 downstream effector cytokine is IL-17. Through the production of pro-inflammatory cytokines, AMPs such LL-37, and chemokines, it stimulates the proliferation of keratinocytes and contributes to the subsequent inflammatory process. This, in turn, amplifies the aggregation of neutrophils, Th17 cells, and DCs in a circular manner [26]. A positive feedback loop is created by all of these processes combined [27]. The recruitment process benefits from the use of CXCL-1, CXCL-2, and CXCL-8 (IL-8). of white blood cells [28]. Psoriasis patients have higher levels of IL-17, which is linked to vascular alterations in psoriatic lesions. Through the expression of VEGF, IL-8, endothelial cell migration, and its heterodimeric relationship with IL-17F, IL-17A plays a role in angiogenesis.

cytokine [29]. Five different IL-17 isoforms (IL-17 B to F) are all implicated in the pathogenesis of psoriasis to varying degrees, despite the fact that IL-17A is believed to be the essential effector cytokine of Th17 cells [30–32].

The main isoforms that are overexpressed in psoriasis are IL-17A, E, and F [32, 33]. Furthermore, exogenous

stimuli including UV light, 12-O-tetradecanoyl phorbol-13-acetate (TPA), and other cytokines like IL-9 can cause Th17-mediated inflammation [34–36]. More than ever, the IL-23/IL-17 pathway's pathogenicity is widely acknowledged with a superior knowledge of psoriasis's innate and adaptive immunity. Ultimately, the activation and multiplication of Th1 and Th17 cells are caused by the cytokines they generate together of keratinocytes as well as the appearance of outbreaks with psoriasis.

Features of the histology

Idiopathic psoriasis's classic histology characteristics match the condition's clinical manifestation. An increased stratum corneum, the emergence of nuclei in the higher layers and stratum corneum, and the loss of the usual granular layer are indicative of an inflamed epidermis caused by a lack of normal differentiation. Neutrophils are referred to as Munro's micro-abscesses and Kogoj pustules, respectively, and assemble in the stratum corneum and epidermis. There are lots of mononuclear cells in the dermis. The erythema associated with psoriasis is brought on by dilation of blood vessels.

PSORIASIS WITH PARADOXES

The cause of paradoxical psoriasis pathogenesis

There is a substantial correlation between gene polymorphisms and the anti-TNF-α medication response. Different polymorphisms in single nucleotides (SNPs) have been linked to paradoxical psoriasiform in the following genes: FBXL19, CTLA4, SLC12A8, TNFR1B, TNFAIP3 [37], IL23R [38], and TAP1 [39]. A genetic predisposition to polyposisive illness (PP) may be the TNF-α rs1799964 uncommon C allele in patients with inflammatory bowel disease, particularly those receiving adalimumab treatment. A genetic predisposing factor for classical psoriasis, but not for PP, is the HLA-C w 06 rs 10484554 [40]. Psychological stressors, tobacco use, and a family history of psoriasis were identified as risk factors for the development of PP in a recent case-control research involving 97 individuals [41, 42].

Similar immunological processes underlie PP and the early stages of idiopathic psoriasis, which are characterized by macrophages, neutrophils, mast cells, pDCs, and monocytes are among the cellular components of innate immunity [43, 44]. The main mechanism of PP is the overexpression of pDCs-derived IFN-α. Unlike traditional psoriasis, it undergoes an immunologic process that is independent of T cells [45]. Lesions of PP had a higher concentration of pDCs than lesions of traditional plaque psoriasis and normal, healthy skin [46]. When compared to the level of pDCs in classical plaque psoriasis, this rise was noteworthy [45].

pDCs are generally invisible in peripheral tissues, but in the event of an infection, wound, or aberrant autoimmunity, they may be drawn to the skin.

When nucleic acid sensors TLR7 and TLR9 are present, pDCs respond by producing high concentrations of type I IFN. Intracellular antimicrobial defense is activated by type I IFN. processes and has an impact on immune response mechanisms. Previous research in autoimmune illnesses such juvenile arthritis and systemic lupus has shown an increase in IFN-α following anti-TNF-α medication.

skin disease [47–50]. TNF-α is released by DCs in response to IFN-α, and this ultimately promotes DC maturation and gradually reduces DCs' capacity to produce IFN-α. Thus, in conventional psoriasis, early transitory upregulation of IFN-α is later replaced by TNF-α-dominant inflammation. The use of TNF-α inhibitors causes abnormalities in DC maturation and permits continuous type I IFN production. PP thus fails to elicit an adaptive immune response, whereas classical psoriasis progresses to become an autoimmune disease mediated by T cells. This fits with their clinical histories in that there are no recurrences. Following regression, classical psoriasis in PP patients typically manifests as chronic and recurrent.

Apart from the prominent function of IFN-α in the development of PP, multiple investigations have disclosed the polarization skewing of immune cell subtypes in PP. Th1- and Th17-type cytokine infiltrates were the main characteristics of PP linked with anti-TNF-α drugs [51, 52]. In the PP lesions, it was found that the expression of morbific cytokines, such as IL-17A and IL-22, was elevated [53]. Anti-TNF-α-related psoriasiform dermatitis was also significantly associated with higher levels of β-Defensins and IL-36, a hallmark of the psoriasis-like/IL-17 pathway phenotype [54]. A recent study found that the severity of psoriasiform skin lesions was correlated with the amount of T cells expressing IL-17A, and anti-IL-12/IL-23 therapy was successful in these cases [51]. Furthermore, the anti-TNF-α medication facilitates the communication between monocyte membrane TNF and TNF-RII expressed on Treg cells, hence promoting their interaction with monocytes and Tregs. Thus, the inhibition of TNF-α Through an IL-2/STAT5-dependent mechanism, functional Foxp3 (+) Treg cells were increased, and Th17 cells were inhibited [55, 56]. Following infliximab treatment, a negative connection was observed between the percentage of Tregs and the percentage of Th1 and Th17 cells in RA patients [57]. Nonetheless, the outcome of blocking TNF-α varies among autoimmune disorders with distinct underlying types, biological agents, and treatment-responsive groups. For instance, it was discovered that following anti-TNF-α therapy, Th17 cells and IL-17 production were increased in rheumatoid arthritis (RA) [58]. In a different study, the Th1 frequency in RA patients receiving etanercept or infliximab had greater than baseline values, although it remained consistent in Th17 prevalence was at baseline in all

three groups, including the adalimumab-treated group [56]. Application of infliximab led to a reduction in the quantity of Th1 cells, whereas an entirely unfavorable occurrence was noted in the group of ankylosing spondylitis patients receiving etanercept [59].

The inflammatory cytokines and chemokines of PP are obviously in disarray. TNF-α inhibitor treatment was shown to downregulate IL-6, IL-8, IL-1β, CCL13, and MCP-1. According to a recent publication [60], the suppression of TNF-α can lead to an increase in TIMP-3, which is regulated by levels of miR-21. This suggests that additional inflammatory cytokines, in addition to TNF-α, may also play a role in the pathogenesis of the PP.

It has been reported that RA patients' increased peripheral Th17 cells are correlated with a decline in the expression of CCR6, a distinctive surface marker associated with the recruitment of Th17 cells [58]. CX3CL1 and its receptor CX3CR1 were found to be significantly reduced in the responding RA patients receiving treatment with infliximab [61]. Comparable CCL18, CXCL10, CXCL13, and CCL20 phenomena were noted. Treatment with anti-TNF-α causes IFN-α to build up, which can trigger the development of CXCR3, a chemokine receptor that is strongly expressed on effector CD8 (+) T cells and Th1-type CD4 (+) T cells [62]. CXCR3 was required for the recruitment of memory CD4 (+) T cells and activated Th1 and T cytotoxic cells to the inflammatory regions of the skin [63, 64]. These transitional chemokines and cytokines have the opposite effect on immune cell subtypes. As an illustration, moving from core memory T utilizing golimumab, cells to effector memory T cells proceeded in RA patients. Simultaneously, TNF-α, IL-2, and IL-17 were observed to be upregulated, maybe due to memory T cells' compensatory production of TNF-α [65]. The limited samples and research to date have left the precise activities of these alterant cytokines and chemokines unclear.

Characteristics of the histology and clinical

Many cases have been reported since the initial report in 2003 [66]. The articles that have been published state that women make up 72.2%–73.5% of the PP [67]. Just 11.8% of these individuals had a family history of psoriasis, and the age of onset spans from 7 to 83 years old [68]. Children with chronic illnesses were reported to have a higher incidence rate of PP. compared to juvenile idiopathic arthritis or inflammatory bowel disease, nonbacterial osteomyelitis [69].

After using biologics, PP typically develops one month [70] to three years [71], with an average of 11 months [67]. It frequently regresses when therapy is stopped. The most typical provoking There are two anti-TNF-α inhibitors: adalimumab and infliximab.

Inhibitors of IL-12/23 p40, IL-17, IL-4Ra, and IL-23 p19 are among the others [72]. PP presentations can be varied and combined. Plaque, pustular, guttate, erythrodermic, and inverse psoriasis are the most common clinical forms [67]. Palmoplantar or scalp involvement is also common, and in more severe cases, scalp involvement can progress to alopecia. Less frequently, nails are affected, and symptoms including onycholysis, discolouration, and pitting may appear. [62].

While the histological characteristics of PP and classical psoriasis are comparable, PP's histological patterns typically overlap [45]. There exist primarily three patterns: lichenoid reaction with focal interface dermatitis; psoriasis-like dermatitis (with infiltration of intraepidermal or subcorneal neutrophils); and eczematiform spongiotic pattern. According to a recent retrospective study, idiopathic psoriasis was more likely to exhibit confluent parakeratosis, neutrophils in the stratum, and papillary plate thinning, whereas PP was more likely to exhibit total lack of parakeratosis, neutrophils in the epidermis, and ≥3 eosinophils in the dermis. The tendency to have acanthosis was more evident in specimens of infliximab-induced psoriasis than in those of etanercept- or adalimumab-induced PP, however this could be the result of sampling bias. There was no discernible difference between those who responded to topical medicines and those who did not [73]. The following characteristics allow us to differentiate PP from the worsening of the initial psoriasis. First, before PP manifested, the patient's psoriasis showed a period of noticeable or total improvement, although Original psoriasis typically has a long clinical course, and some conditions—such as using beta-blockers, antimalarial medications, lithium, or glucocorticoids improperly—can cause exacerbation. Second, as previously noted, PP may exhibit certain unusual symptoms that are rarely observed in the histology of original psoriasis, such as spongiosis and eosinophils. Thirdly, PP typically goes away when biologics are stopped, but original psoriasis is unlikely to go better or may even worsen in the same situation if further therapy is not taken.

According to the findings in, laboratory testing may offer some hints to confirm PP. a few case reports, but the lack of large sample data makes the practical significance uncertain. For instance, PP might exhibit assessed IFN-α expression in the lesion and blood [46]. It was shown that the quantity of T cells producing IL-17A correlated with the the degree of PP [51].

PP MANAGEMENT

The management of the underlying illness and the reduction of skin symptoms are part of the PP outline treatment. When the offending medication is stopped, half of the patients spontaneously regress, but the other half experience permanent lesions. Drug discontinuation without conditions

may worsen underlying medical conditions [74].

It is now thought that when an eruption is mild to moderate, individuals with controlled underlying diseases should continue receiving their present medication. It is advised to use topical steroids, vitamin D3 substitutes, and calcineurin inhibitors. Additional UV therapy and systemic medication (such as steroids, methotrexate, cyclosporine, mycophenolate mofetil, and acitretin) should be used for moderate-to-severe skin eruptions.

sometimes topical therapy is not enough. Among them, cyclosporine should only be used when absolutely required for temporary bridge therapy. Interestingly, stopping biological therapy at this point is not necessary [75].

In patients with uncontrolled underlying disorders, topical and/or systemic therapy, as well as the suspension or substitution of anti-TNF-α medication, are the mainstays [72]. According to reports, cyclosporine applied in excess had a greater impact on PP than methotrexate or steroids [67,76]. A high dosage of methotrexate (greater than 15 mg/week) is preferable to a dosage of under 10 mg per week. Although adalimumab showed a small advantage over other TNF-α inhibitors, switching to another TNF-α inhibitor was beneficial in less than 50% of the cases [67]. Furthermore, topical In a pustular psoriasis instance linked to infliximab, corticosteroids were successful [75]. A few cohort studies came to the conclusion that PP would benefit from the substitution of a different biologic, namely ustekinumab, for the TNF-α inhibitor [77,78]. In patients with Parkinson's disease (PP), moderate-to-high anti-nuclear antibody titers and widespread pustular presentations may be detrimental prognostic factors [79]. Variations in DNA copy number may be a potential marker to predict the development of PP and the response to adalimumab [80,81].

PP therapy remains a difficult task. Recently, a few algorithms for the management of PP were proposed. However, there are differences between them [67, 82–84]. Maintaining equilibrium between the underlying illness and the cutaneous side effects is crucial to management.

Carefully consider whether to keep taking the TNF-α inhibitor, stop taking it, or switch it out. Generally, for moderate or severe eruptions, replacing the TNF-α inhibitor is recommended in patients with well-controlled underlying illness. Replacement with alternative biologics is advised in cases of uncontrolled underlying disease and/or intractable lesions, such as severe genital lesions, palmoplantar involvement with a handicap, or scalp psoriasis with alopecia. Various disorders determine which biological agent substitute to use. For instance, ixekizumab, ustekinumab, and brodalumab [85] are suitable for psoriasis; ustekinumab and vedolizumab are optional for inflammatory bowel disease [77,83]; tocilizumab and rituximab are appropriate for RA; in cases of pyoderma gangrenosum, and secukinumab [86].

CONCLUSION

The mechanism behind PP is still unknown at this time, particularly with regard to IFN-α's downstream immunological response. First of all, variations within a Numerous genes have demonstrated the function of host factors. Second, the occurrence of PP depends on pDCs. When skin is wounded, pDCs can identify nucleic acids that are dependent on TLR7 and TLR9 and temporarily create type I IFN. To help with nucleic acid recognition, cathelicidin peptides are enough to produce pDCs, type I IFN, IL-17A, and IL-22 [87]. Furthermore, in response to TLR7 stimulation, pDCs can enhance Th17 cells' effector function and encourage Th17 cell development [88]. It makes sense that sustained pDC activation and increased IFN-α would function similarly to mediate Th17 cell activation and differentiation. Not only is the current research problematic due to a paucity of samples and analysis, but we have also seen an innate immunity-biased pathway of psoriasiform lesion initiation in addition to the conventional Immune response dominated by Th17/Th1 cells. Th17 cells are thought to play a significant role in bridging innate and adaptive immunity, as was previously indicated. Different from the traditional route, it appears that recruited Th17 and Th1 cells mediate the pathophysiology of psoriasis. Prior research indicates that TNF-α acts in a time-dose-dependent manner, although The pattern of TNF-α inhibition is not clear. If comparable, this could represent the fundamental process behind spontaneous regression in the absence of TNF-α inhibitor discontinuation.

Even though there is still much to learn about PP, we have gained a great deal of expertise managing it as more and more study is done. If we can better identify the cytokines involved and their biological sources, then other potential targets for therapeutic intervention of PP, idiopathic psoriasis, and other inflammatory illnesses may be just around the corner.

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