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CASE REPORT

Abrocitinib Treatment for Localized Type of Generalized Pustular Psoriasis: A Case Report

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Abstract: Generalized Pustular Psoriasis (GPP) is a recurrent dermatological condition characterized by widespread erythematous plaques, scaling, and sterile pustules. Notably, in a subset of patients, these lesions manifest exclusively in localized areas. We report a case where abrocitinib was used to treat the localized type of GPP, achieving relatively good clinical efficacy and without obvious side effects. To date, there are no published reports on the use of abrocitinib for GPP treatment, either domestically or internationally, making this case a valuable reference for clinicians and researchers.

Keywords: generalized pustular psoriasis, abrocitinib, JAK inhibitor

Introduction

Generalized pustular psoriasis (GPP) is a rare and periodically occurring autoinflammatory skin disease, Clinically, it is mainly manifested by erythema and aseptic pustules, with or without systemic inflammatory responses. The main histological manifestation is neutrophil infiltration.[1] Besides skin manifestations, this disease also encompasses symptoms such as fever, electrolyte imbalance, arthralgia, and may involve multiple organs. In severe cases, it can be life-threatening.[2] The global incidence of GPP is estimated to be 2–7 million,[3] and the prevalence rate in China is approximately 1.403 per 100,000 individuals.[4] This disease can occur at any age, being most common in middle-aged and elderly people, but it can also occur in children and pregnant women.[5] The classification of GPP has no unified standard as yet. At present, it is mainly classified into the following five categories:[6] acute generalized pustular psoriasis, sub-acute annular circinate pustular psoriasis, generalized pustular psoriasis of pregnancy, infantile pustular psoriasis, and juvenile pustular psoriasis. The etiology of this disease remains undefined. Nevertheless, a plethora of literature reports suggest that the abrupt cessation of systemic and topical glucocorticoids constitutes a common precipitating factor.[7] Infections, medications, hypocalcemia, emotions, seasonal alterations, pregnancy, and menstruation can all incite the onset of GPP.[8] Concurrently, studies imply that its onset is also related to genetic factors and immunity.[9] The principal therapeutic agents for GPP encompass acitretin, cyclosporine, methotrexate and various biological agents targeting diverse targets.[6] In recent years, the widespread application of small molecule JAK inhibitors (Tofacitinib) in rheumatoid arthritis and psoriatic arthritis has emerged as a novel therapeutic modality for psoriasis,[10] featuring notable clinical efficacy and attributes such as lower production costs, rapid onset, and favorable tolerance.

Herein, we report a case of treating the localized type of generalized pustular psoriasis with abrocitinib, which achieved relatively good clinical efficacy and no obvious side effects. The patient is still under follow-up treatment at present.

Clinical Data

A 48-year-old female patient presented with the complaint of "repeated emergence of erythema accompanied by pruritus on both lower legs for 3 years". The patient indicated that 3 years ago, erythema emerged on both lower legs without discernible triggers, accompanied by a sensation of pruritus. She had consulted multiple hospitals and was diagnosed with eczema. She was treated with halometasone cream and tacrolimus cream externally, prednisone tablets and acitretin capsules orally. The

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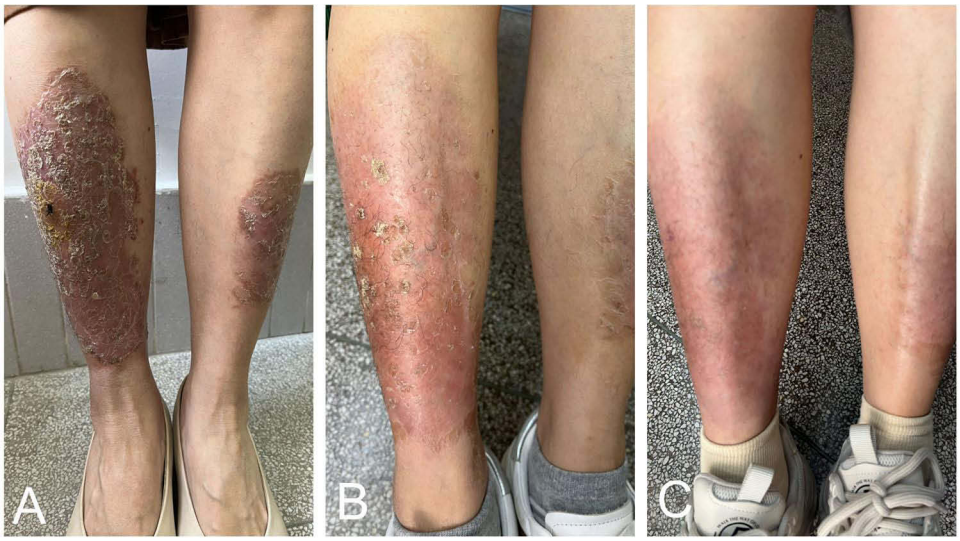

Figure 1 Clinical photographs of patient before and after abrocitinib treatment. Prior treatment (**A**), 2 weeks after treatment with abrocitinib (**B**), 4 weeks after treatment with abrocitinib (**C**).

condition fluctuated between improvement and deterioration, and the area of the skin lesion gradually expanded. Nearly 1 year, pustules manifested on the surface of the erythema on both lower legs. In October 2023, the patient visited Xuanwu Hospital in Beijing and was diagnosed with atopic dermatitis. She was treated with abrocitinib tablets 100mg once daily, and the rash ameliorated. Nevertheless, the rash relapsed after drug discontinuation, thus she visited our hospital. She was diagnosed with pustular psoriasis, and a histopathological examination was conducted on the skin lesion.

Specialized examination revealed diffuse palm-sized red patches on the anterior tibia of both lower legs, with needle-sized pustules on the surface and thick yellow crusts covering them (Figure 1A).

Laboratory examination outcomes demonstrated that immunoglobulin E was 147.8 IU/mL (reference range 0–100IU/mL). The complete blood count, C-reactive protein, erythrocyte sedimentation rate, urinalysis, liver and kidney functions, seven items of blood lipid, five items of immunity, two items of rheumatism, six items of female tumor, and tuberculosis infection T-cell spot test were all normal. Antibodies for hepatitis B, hepatitis C, human immunodeficiency virus (HIV) and Treponema pallidum particle assay were all negative. The electrocardiogram shows normal findings. The thoracic computed tomography (CT) discloses no remarkable abnormalities in the lungs.

The outcome of the histopathological examination of the skin tissue indicated a confluent parakeratosis, Munro microabscesses and Kogoj spongiform pustules were detectable The epidermis exhibited hyperplasia and thickening of the stratum spinosum, moderate-to-severe intercellular edema, as well as the formation of epidermal blisters. The epidermal rete ridges were regularly descending, while the dermal papillae were significantly ascending. A considerable quantity of inflammatory cells infiltrated the epidermis. The superficial dermal vessels were dilated and hyperemic, with a large number of lymphocytes, neutrophils, and eosinophils infiltrating around the vessels (Figure 2A and B). The diagnosis was pustular psoriasis.

In the treatment aspect, the patient was administered abrocitinib 100mg twice daily for 2 weeks. The pustules and scales on both lower legs of the patient largely subsided (Figure 1B). Proceed with the oral administration of abrocitinib 100mg twice daily for a half-month, the pustules and scales on both lower legs completely disappeared and the color of the erythema became light (Figure 1C). Currently, the patient still continues to take abrocitinib 100mg once daily. The disease is well controlled and no adverse reactions occur.

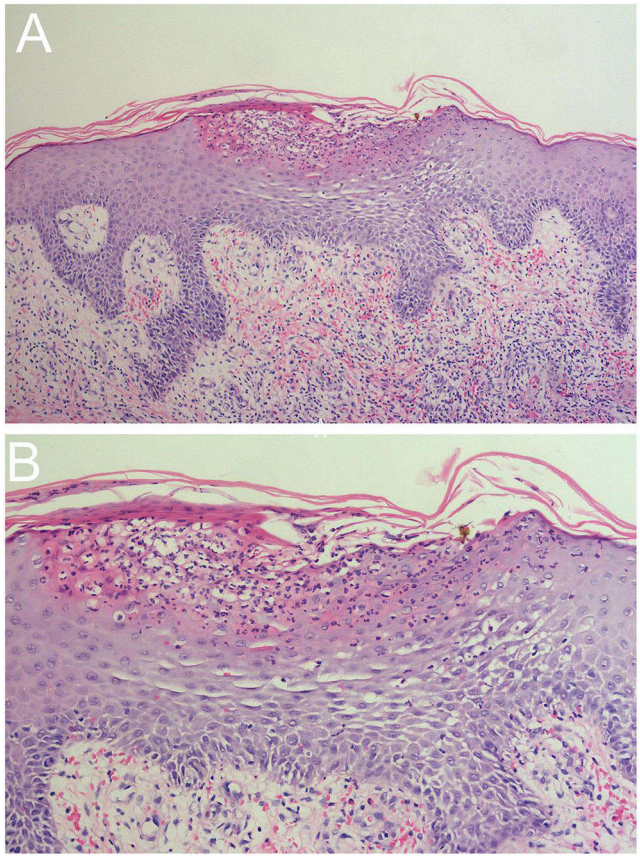

Figure 2 Pathological examination of skin tissue: indicated a confluent parakeratosis, Munro microabscesses and Kogoj spongiform pustules were detectable. The epidermis exhibited hyperplasia and thickening of the stratum spinosum, moderate-to-severe intercellular edema, as well as the formation of epidermal blisters. The epidermal rete ridges were regularly descending, while the dermal papillae were significantly ascending. A considerable quantity of inflammatory cells infiltrated the epidermis. The superficial dermal vessels were dilated and hyperemic, with a large number of lymphocytes, neutrophils, and eosinophils infiltrating around the vessels. ((**A**) ×10, (**B**) ×20).

Discussion

GPP is a recurrent disorder characterized by generalized erythema, scales, and aseptic pustules all over the body. Nevertheless, in certain patients, the skin lesions merely arise in local regions, such as the genital, elbows, or lower legs, and are inclined to be misdiagnosed as eczema at an early stage. In 1968, Baker and Ryan put forward four disparate types of GPP: Zumbusch, annular, localized, and exanthematic types.[11] The middle-aged woman described in this article exhibited diffuse erythema on both lower legs, accompanied by pustules on the surface and covered with thick yellow crusts. Based on the integration of clinical and pathological manifestations, she was diagnosed with the localized type of GPP. Some scholars abroad have also reported GPP restricted to the genital area.[12]

The pathogenic mechanism of GPP remains incompletely elucidated. A plethora of studies suggest that it might be correlated with genetic and immune factors. It has been identified that the majority of GPP patients carry mutations in the IL36RN, and it has also been validated that the abnormalities of IL-36, IL-36 receptor, and the natural antagonist IL-36Ra constitute crucial mechanisms for the initiation of GPP.[13] When IL-36Ra fails to antagonize and restrain the pro-inflammatory effect of IL-36, it will give rise to the upregulation of the IL-36 signal, subsequently activating downstream pathways such as MAPK and NF-κB, thereby facilitating the secretion of inflammatory cytokines such as IL-1, IL-8, IL-36, and activating relevant immune responses.[14,15] The pathogenesis of GPP incorporates intricate immune factors, where the innate immune system cytokines IL-1, IL-36, and IL-17 assume a crucial role, and TNF-α and IL-17A are also implicated.[2] A burgeoning number of researchers assert that neutrophils exert a substantive pathogenic impact in GPP, with neutrophil chemokines CXCL1, CXCL2, and CXCL8 being highly expressed in GPP.[16] The neutrophils of patients can secrete a more copious amount of exosomes, activate the NF-κB and MAPK signaling pathways, and induce the upregulation of diverse inflammatory cytokines such as IL-1β and IL-36γ in keratinocytes, giving rise to a more

vehement autoinflammatory response.[17] Consequently, some scholars classify GPP as an autoinflammatory keratinization diseases.

The first-line systemic therapeutic regimens for GPP incorporate acitretin, cyclosporine, methotrexate and infliximab,[18] while second-line treatments consist of TNF-α inhibitors, topical therapeutics, and phototherapy. Genetic studies have manifested that the functional deficiency of IL36RN resides at the core of the pathogenesis of GPP. Thus, Japan has sanctioned the IL-36 inhibitor (Spesolimab) for the treatment of adult GPP.[19] Other biological agents, such as IL-1 inhibitors, IL-17 inhibitors, IL-12/23 inhibitor, IL-1R and IL-1β inhibitors are extensively utilized in clinical practice. Although biological agents boast the attributes of being targeted, having a swift onset, and presenting fewer adverse events, they may potentially trigger or aggravate GPP and give rise to drug resistance. In our case report, the patient had previously been treated with acitretin capsules, but the extent of skin lesions continued to increase. The patient was misdiagnosed with atopic dermatitis by other clinicians. Following the administration of abrocitinib, a significant improvement in clinical outcomes was observed. Therefore, for patients with intractable, recurrent, localized GPP who are unresponsive to conventional treatments, the application of JAK inhibitors can be contemplated.

Abrocitinib is a small-molecule oral Janus kinase (JAK) 1 inhibitor that is capable of blocking the JAK/STAT signaling transduction pathway, thereby reducing the generation and release of multiple cytokines and is used for the treatment of moderate to severe atopic dermatitis (AD) in adults.[20] The JAK-STAT signaling pathway mediates the transduction of cytokines such as IFN-γ, IL-4, and IL-2.[21] Our findings demonstrate that IL-2 induces the expression of the IL-36R gene in a JAK/STAT-dependent manner.[22] Therefore, JAK inhibitors can effectively suppress the IL-2-induced upregulation of IL-36R, thereby mitigating the symptoms associated with GPP. In the pathogenesis of GPP, the innate immune system's IL-36 and IL-17 also exert extremely important roles, After IL-17 binds to the receptor, it induces the gene expression of downstream inflammation-related factors through multiple signaling transduction pathways such as MAPK and STAT, thereby recruiting inflammatory cells such as T cells and neutrophils, triggering an inflammatory response.[23] Moreover, IL-36 and IL-17 are involved in the differentiation and metastasis of neutrophils, as well as in the primary immune response, stimulating the production of various cytokines. Therefore, the use of JAK inhibitors can effectively block these signaling pathways and treat related immune-mediated diseases. However, research has revealed that elevated levels of IL36A, IL36G, and IL36RN are observed in the skin lesions of atopic dermatitis. Epidermal Staphylococcus aureus can increase in serum IgE by generating IL-36, and the IL36/IL-36R axis causes the transformation of AD from acute to chronic by regulating T cells responses,[24] Therefore, IL-36 plays a crucial role in the pathogenesis of AD, which explains the reason for the effectiveness of abrocitinib in the treatment of GPP. Wang et al[25] reported favorable clinical outcomes in the treatment of GPP using tofacitinib. Tofacitinib primarily inhibits JAK1 and JAK3, thereby suppressing the JAK-STAT signaling pathway and reducing the production of multiple inflammatory cytokines, including IL-1, IL-17, and IL-23. This potent anti-inflammatory effect makes it suitable for treating GPP. In contrast, abrocitinib selectively inhibits JAK1 and predominantly targets cytokines such as IL-2, IL-4, and IL-13, with relatively weaker effects on IL-17, IL-23, and IL-36. Therefore, abrocitinib may be more appropriate for the treatment of localized type of pustular psoriasis. The major adverse reactions associated with abrocitinib include thrombocytopenia, nausea, vomiting, infections, malignancies, and thrombotic events. In this case report, the patient did not exhibit any significant adverse effects during the one-year treatment period.

Summary

Presently, no reports exist both domestically and internationally concerning the utilization of abrocitinib in the treatment of GPP. Through this case report, we assert that abrocitinib has the potential to be an efficacious therapeutic agent following the limited success of acitretin in treating the localized type of generalized pustular psoriasis. This report has some constraints, Owing to the intricate mechanism of GPP pathogenesis, more comprehensive research is necessary to ascertain the precise therapeutic effect of abrocitinib. Furthermore, the long-term safety of abrocitinib still requires verification through additional clinical data.

Patient Consent

The patient provided written informed consent for publication of clinical information and photographs. This case study does not need institutional approval.

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Disclosure

The authors declare no conflicts of interest in this work.

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