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CASE REPORT

Generalized Pustular Psoriasis with Cushing's Syndrome: A Case of Effective Spesolimab Treatment

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Abstract: Generalized pustular psoriasis (GPP) is a rare neutrophilic skin disease characterized by persistent symptoms and sudden onset of painful, sterile pustules. These pustules may be accompanied by systemic inflammation and can be life-threatening in severe cases. Presently, there is an absence of standardized guidelines for treatment, and the majority of conventional treatments employed by clinicians are predicated on the utilization of glucocorticosteroids, immunosuppressants, and retinoids to attain anti-inflammatory and immune-suppressing effects. However, the therapeutic effect is often unsatisfactory and patients are prone to side effects. The IL-36 receptor monoclonal antibody, Spesolimab, signifies a novel therapeutic modality that has received approval from both the National Drug Administration (NMPA) of China and the US Food and Drug Administration (FDA) for the management of acute exacerbations of GPP. We report a case of a 40-year-old male patient diagnosed with GPP who had no significant improvement in symptoms and development of Cushing's syndrome after up to six months of treatment with glucocorticoids, immunosuppressants, and retinoids. The patient was treated with Spesolimab, a monoclonal antibody, resulting in a substantial improvement in symptoms. This development offers novel treatment options and provides a reference for clinical medication for patients with this particular type of GPP.

Keywords: generalized pustular psoriasis, spesolimab, biologic agents, case report

Introduction

Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening variant of psoriasis, characterized by the recurrent emergence of sterile, neutrophil-rich pustules on painful, erythematous patches. It may also involve the formation of "lakes" of sterile pus.[1] In addition to skin manifestations, GPP can also be accompanied by systemic symptoms such as fever, general malaise, fatigue, and disabling edema.[2] The exact etiology and pathogenesis of GPP have not been fully elucidated. The treatment guidelines established by the National Psoriasis Foundation (NPF) in 2012 suggest that the current first-line treatments mainly include the combination of drugs such as acitretin, methotrexate, cyclosporine, and phototherapy, although the results are not satisfactory.[3] Moreover, although these pharmacologic approaches to treatment have demonstrated efficacy in patients with GPP, there is a risk of toxicity associated with the use of these drugs that limits their clinical effectiveness.[4,5] Over the past few years, researchers have uncovered that the interleukin-36 receptor antagonist gene (IL-36RN) is likely the most prevalent causative gene for GPP.[6] Spesolimab exerts its effect by modulating the molecular pathways related to IL-36,[7] and it has demonstrated marked efficacy, swift action onset, and favorable tolerability, offering a fresh and effective treatment alternative.[8] Building on this discovery, pharmaceutical companies have developed related biologic agents. In September 2022, the US Food and Drug Administration (FDA) approved the first therapy for adult patients with generalized pustular psoriasis: a monoclonal antibody antagonist named Spesolimab, which targets the IL-36 receptor specifically. The medication is currently

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accessible in the United States, the European Union, Japan, China, and various other countries and regions, offering a novel therapeutic approach for the management of GPP.[9] This article summarized a case of GPP with Cushing's syndrome and recurrent rashes in a patient who has been on long-term treatment with glucocorticoids and immunosuppressants with poor response. After being treated with Spesolimab for 2 months, the patient's rash completely subsided. Additionally, this case explored how to manage the gradual reduction and discontinuation of drugs such as glucocorticoids and immunosuppressants after the use of biologics in GPP.

Case Report

A 40-year-old male patient arrived at our hospital exhibiting symptoms of "generalized erythema, scaling, pustules, accompanied by itching and pain, for a duration exceeding six months". The patient is a sewage treatment plant employee, long-term exposure to sewage, need to often stay up late to work overtime, cannot work and rest normally, work pressure led to the patient has a 15-year history of drinking alcohol, drinking more than 1000 mL per week, until the onset of the disease to stop drinking alcohol. Upon examining his medical history, it was revealed that the patient initially developed erythema and pustules on his upper arms and the nape of his neck in December 2023, along with skin itching and pain. The use of hormones, immunosuppressants and retinoids were essentially the mainstay of treatment during the patient's six-month-long quest for medical care, but failed to effectively control the condition, with recurrent episodes of illnesses, bringing a huge physical, mental, and economic burden to the patient (Table 1).

When he came to our hospital for treatment, the patient exhibited extensive patchy erythema across the scalp, trunk, and limbs, which was interspersed with pinpoint-sized pustules and surrounded by scattered small red papules and a few

Table 1 Treatment Timeline in Pustular Psoriasis

Date	Hospital	Diagnosis/Disease Progression	Symptoms	Treatment	Efficacy
Dec 2023	Lufeng County Hospital	Pityriasis rosea (later revised)	Erythema, pustules on upper arms and posterior neck; pruritus and pain	Antihistamines	Rash spread systemically within 3 days
Jan 2024	The People's Hospital of Chuxiong Yi Autonomous Prefecturel	Generalized pustular psoriasis (confirmed)	Generalized pustules coalescing into "lakes"	Adalimumab 40mg SC (not used regularly, full course of treatment not administered for financial reasons) Post-discharge: prednisone acetate tablet 50mg qd + Cyclosporine 100mg qd + Thalidomide 50mg qd + Tripterygium glycosides 20mg tid	Partial remission with frequent relapses
Mar 2024	Chuxiong Yi Autonomous Prefecture Hospital of Traditional Chinese Medicine	Relapse during steroid tapering	Recurrent generalized pustules	Methylprednisolone sodium succinate 80mg IV qd ×7d Cyclophosphamide 600mg IV ×1 Methotrexate 5mg IM qw ×3 weeks Discharge: Methylprednisolone 24mg bid + Acitretin capsules 10mg tid + Mycophenolate mofetil 0.5g bid	Poor disease control
May 2024	Chuxiong Yi Autonomous Prefecture Hospital of Traditional Chinese Medicine	Disease flare	Recurrent pustules with fever, elevated skin temperature, severe pain	Continued prior regimen for 13 days Discharge adjustment: Methylprednisolone 12mg bid + Acitretin 10mg tid + Mycophenolate mofetil 0.75g bid	Persistent recurrence
Jun 2024	The First Affiliated Hospital of Yunnan University of Chinese Medicine	Spesolimab intervention	Recurrent pustules with erythema flare (GPPGA=2, GPPASI=12, DLQI=14)	Pre-treatment labs: WBC 12.29×10^9/L, NEUT 10.36×10^9/L, LYMPH 4.35×10^9/L, NEUT% 84.20%, LYMPH% 10.60%, MPV 8.50fL, CRP 90.45mg/L 2024.6.25: Spesolimab 900mg single IV infusion (under ECG monitoring) Post-discharge: Methylprednisolone 12mg qd + Mycophenolate mofetil 0.75g qd + Acitretin 10mg qd	Fever resolved in 24h; pustules resolved by ~80% in 24h, nearly cleared in 72h with erythema progression

(*Continued*)

Table 1 (Continued).

Date	Hospital	Diagnosis/Disease Progression	Symptoms	Treatment	Efficacy
Jul-Aug 2024	Follow-up at The First Affiliated Hospital of Yunnan University of Chinese Medicine	Complete remission	Complete resolution of erythema and scales; no pustule recurrence (GPPGA=0, GPPASI=0, DLQI=2)	Post-treatment labs: WBC 4.8×10^9/L, NEUT 2.05×10^9/L, LYMPH 2.35×10^9/L, NEUT% 42.40%, LYMPH% 48.70%, MPV 8.8fL, CRP 2.31mg/L Tapering to discontinuation: discontinued Methylprednisolone on July 19; discontinued Mycophenolate mofetil on August 7; discontinued Acitretin on August 11	Sustained remission with normalized scores

dry scales, with the waist area being the most severely affected. The skin surrounding the rash was tender to the touch, and the hair-tourniquet sign was present. Following prolonged exposure to glucocorticoids, the patient developed pronounced Cushing's syndrome, characterized by facial swelling and discomfort, dry eyes, and an elevated body temperature, peaking at 39°C. The GPPGA score was 4, the GPPASI score was 32, and DLQI score was 26 points (Figure 1). The patient indicates no further special medical background, no past of psoriasis, and no sensitivities to food or medication. The family history does not reveal any particular medical concerns. According to the European Network of Experts on Rare and Severe Psoriasis (ERASPEN) our institution has provided a precise diagnosis of GPP.[10] We conduct thorough screening to exclude contraindications for patients before using biologics. Upon obtaining the patient's informed consent, on June 25, 2024, a single intravenous infusion of 900mg of the Spesolimab monoclonal antibody was administered under continuous electrocardiographic monitoring. Within 24 hours post-administration, the patient's body temperature normalized, pustules diminished by approximately 80%, and skin discomfort was significantly reduced. Upon Completion of 72 hours of treatment, his skin, previously almost pustule-ridden, had largely cleared up. However, it was observed that the erythema on his skin had progressively intensified, with the affected areas being predominantly on his limbs. The GPPGA score was 2, the GPPASI score was 12, and DLQI score was 14 points (Figure 2). We advised the patient to persist with the oral administration of methylprednisolone tablets at a dosage of 12mg daily, along with Mycophenolate Mofetil Tablets at 0.75g once daily, and acitretin capsules at 10mg once daily, while monitoring the evolution of his skin lesions. After two months of treatment, the patient's erythema and scaling on the trunk, limbs, and scalp completely subsided, and no new pustules recurred during the treatment process. The GPPGA score was 0, the GPPASI score was 0, and DLQI score was 1 points (Figure 3). It is noteworthy that within two months of initiating Spesolimab therapy, patients reported substantial amelioration of symptoms, including obesity resulting from prolonged corticosteroid use, rough skin, and ocular discomfort, following a gradual tapering of the medication.

Discussion

GPP is a rare, chronic, and severe autoinflammatory skin disorder that can manifest with or without systemic inflammation, impacting a diverse population that spans children, adults, pregnant women, and the elderly.[11] The pathogenesis of GPP is not yet fully understood, with most research focusing on the biological and genetic mechanisms of autoinflammation and autoimmunity, ultimately zeroing in on the critical role of gene mutations. Notably, IL36RN mutations have been identified in both sporadic and familial cases of GPP from around the world in recent years.[12–15] This highlights the pivotal role of IL-36RN mutations and IL-36 receptor ligands in the development of GPP, suggesting that the hyperactivation of IL-36 signaling may underlie the immunopathological manifestations of GPP. In this context, germline mutations that disable the anti-inflammatory receptor antagonist encoded by IL36R emerge as a critical contributor to the onset of GPP.[16] IL-36 cytokines can induce both innate and adaptive immune responses by acting on parenchymal cells, stromal cells, and specific subsets of immune cells. In humans, when the gene encoding the IL-36R antagonist undergoes inactivating mutations, the regulation of IL-36R signaling becomes uncontrolled, leading to autoinflammation. A deficiency in IL-36R antagonists can induce downstream inflammatory cascades and recruitment

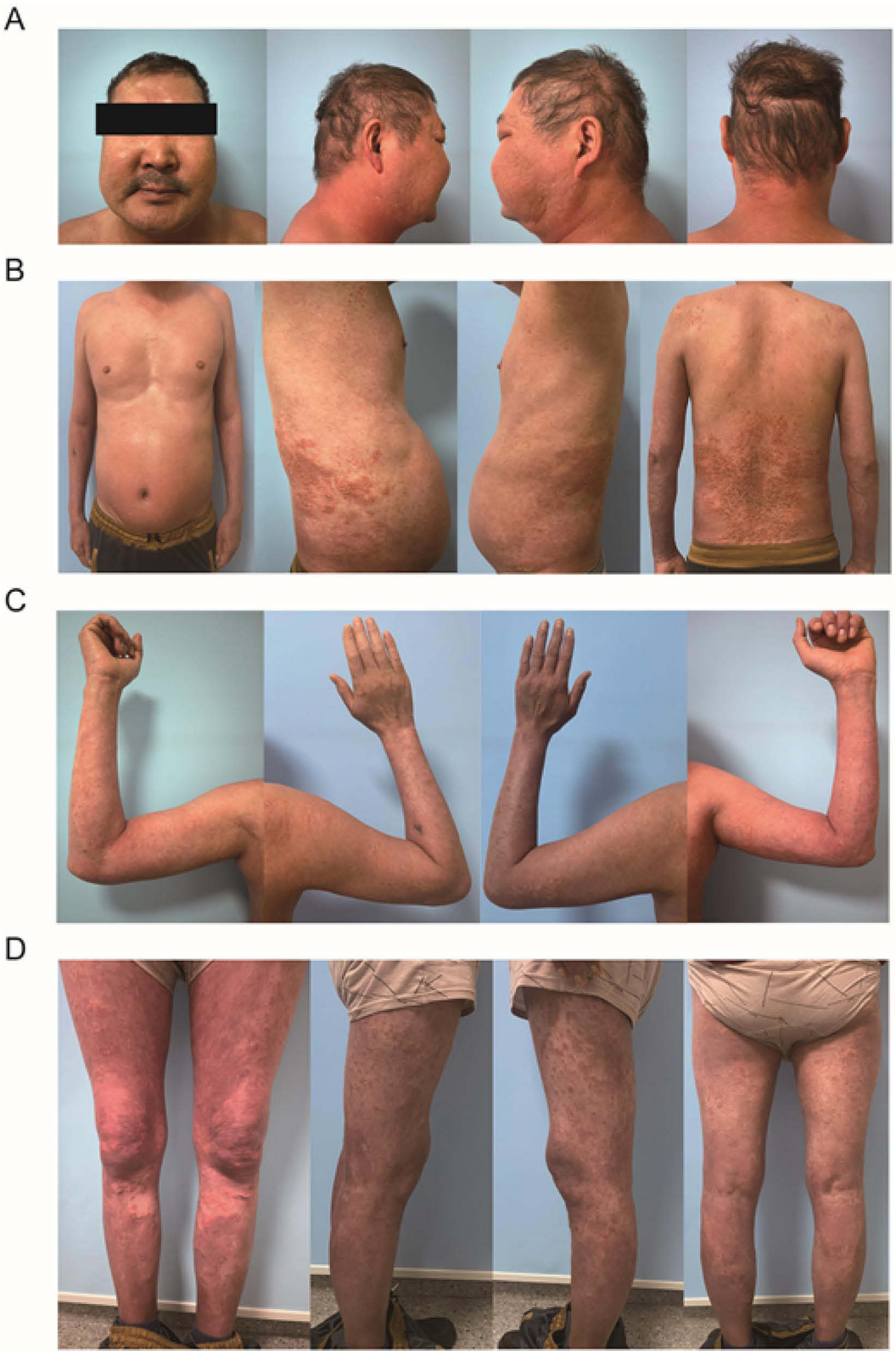

Figure 1 The patient's condition before receiving spesolimab treatment. (**A**) Scattered erythema on the head and face, facial swelling presenting a "moon face" appearance, hair showing "tufted hair" changes. (**B**) Extensive edematous erythema and numerous pustules on the trunk. (**C** and **D**) Scattered erythema on the limbs.

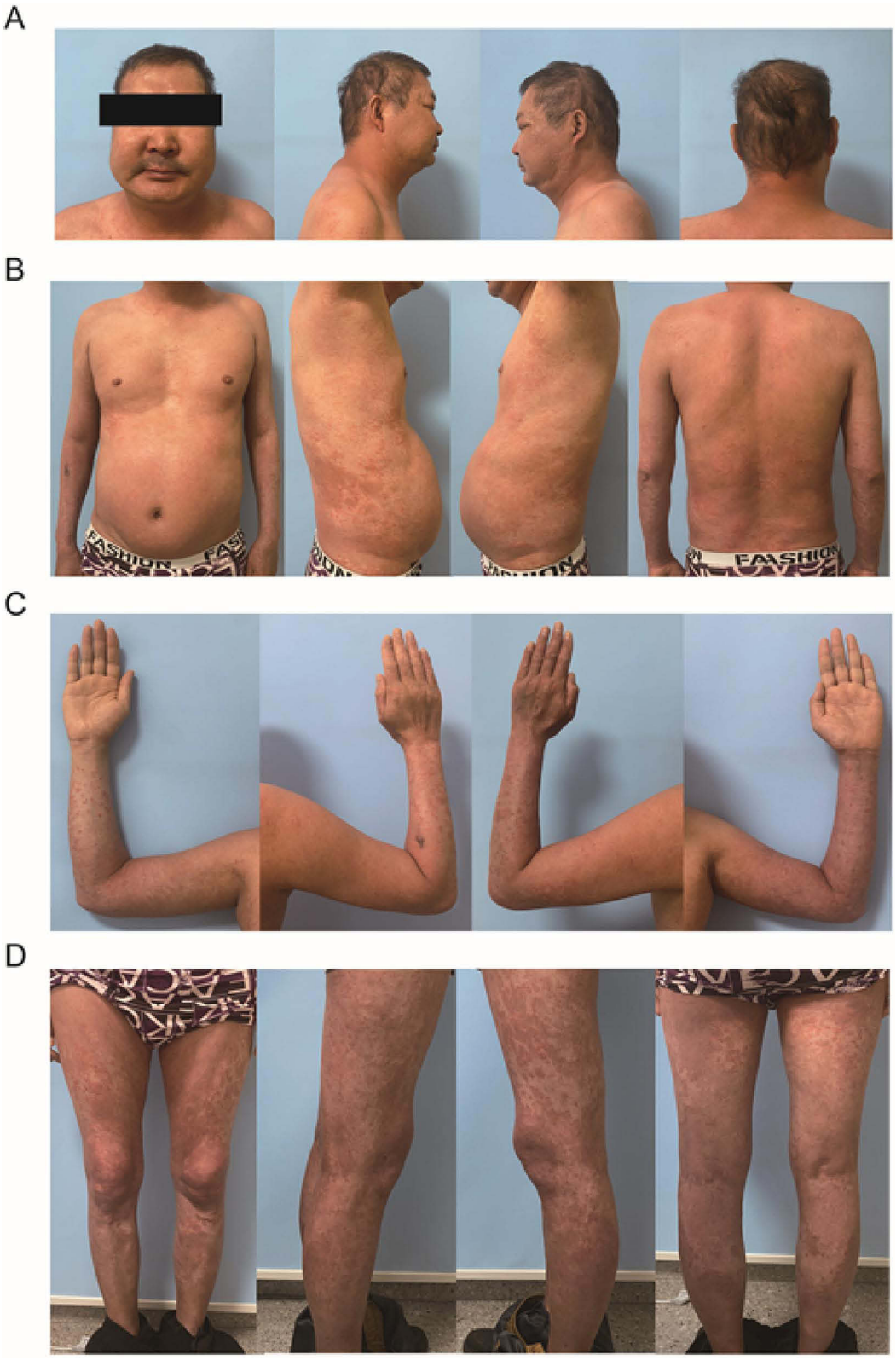

Figure 2 The patient's condition 72 hours after receiving spesolimab treatment. (**A**) Erythema on the head and face has basically subsided with mild improvement in swelling on both sides of the face, (**B**) Pustules on the trunk have completely resolved, with the erythema becoming lighter and darker, (**C** and **D**) Scattered erythema on the limbs has increased compared to before.

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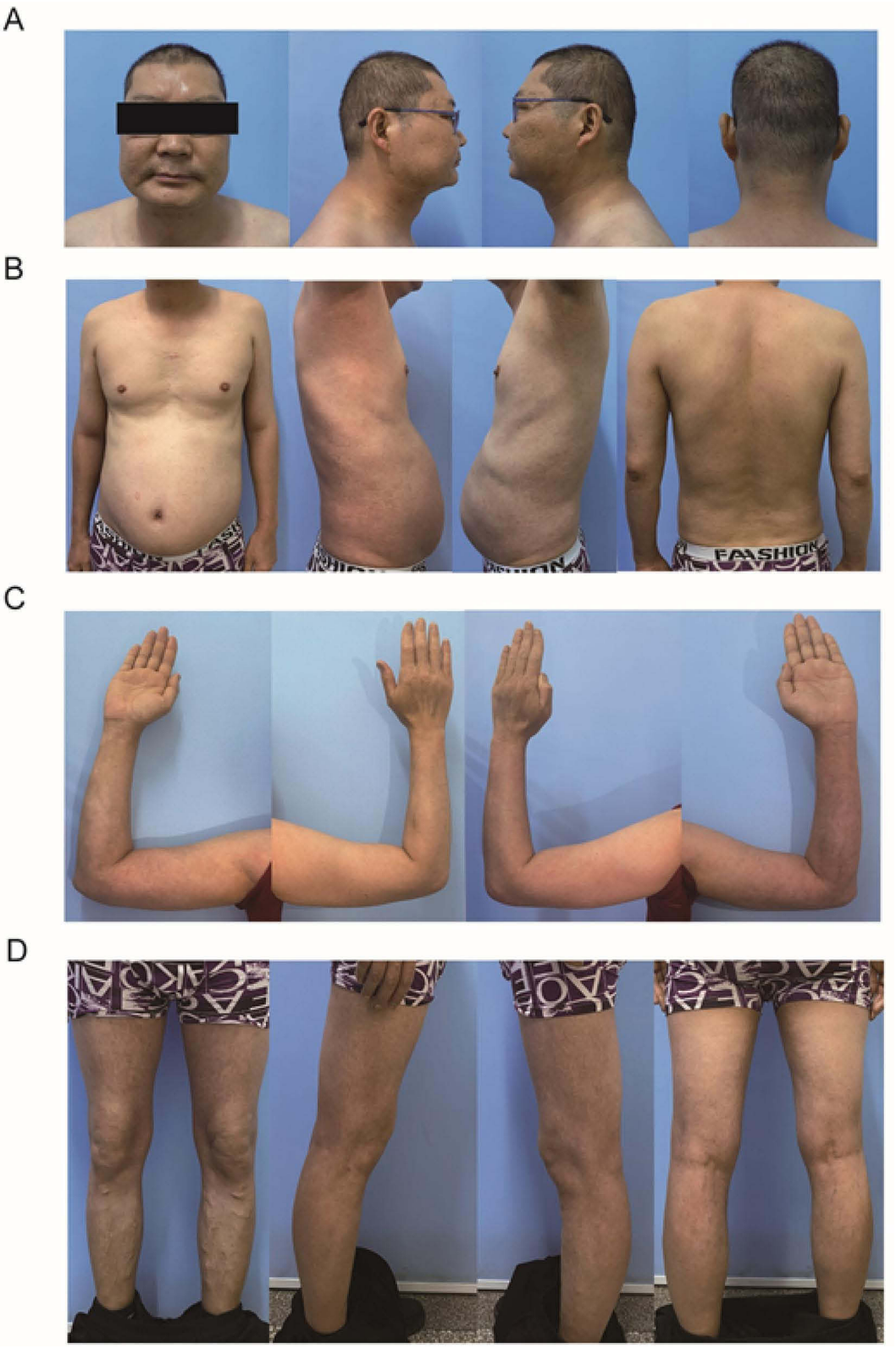

Figure 3 The patient's condition 2 months after receiving spesolimab treatment. (**A**) Erythema on the head and face has completely subsided, with no swelling on the face and hair returning to normal, (**B**) Pustules on the trunk have completely subsided, leaving the skin smooth, (**C** and **D**) Scattered erythema on the limbs has mostly subsided.

of neutrophils, as well as activation of other innate and adaptive immune cells, ultimately resulting in pustular psoriasis characterized by extensive neutrophilic and monocytic inflammatory infiltrates in the epidermis, forming widespread sterile pustules.[17] Therefore, biologics targeting the IL-36 pathway, represented by Spesolimab, will become a new dawn for the treatment of GPP, and clinical case reports and analysis of efficacy are of significant importance for guiding subsequent treatments.

As illustrated in the present case, the patient was unable to control recurrent pustules and erythema with a long-term combination of glucocorticoids, immunosuppressants, and acitretin. Moreover, the patient exhibited Cushing's syndrome (characterized by central obesity, dorsal cervical and supraclavicular fat pads, and a moon face) secondary to prolonged exogenous steroid use.[18] Following Spesolimab monotherapy, temperature normalization, 80% pustule regression, and pain relief were achieved within 24 hours, with complete pustule resolution by 72 hours. However, erythema on the extremities persistently worsened during this period. Based on clinical experience, traditional medications (hormones/immunosuppressants) need to be tapered off to avoid the risk of rebound, so the original regimen was maintained with simultaneous monitoring. Laboratory parameters (CRP decreased from 90.45 mg/L to 2.31 mg/L and neutrophil ratio recovered from 84.2% to 42.4%) were consistent with clinical improvement (Table 1). Literature reports have shown that Spesolimab cleared pustules within 24–48 hours (54% complete remission vs 6% placebo group at 1 week),[19] and erythema subsided with treatment in some cases.[20,21] Therefore, it is reasonable to assume that a stepwise strategy combining a biologic agent (Spesolimab) with conventional drugs can be effective in inducing and maintaining remission. However, the persistent exacerbation of erythema in this case suggests that there may be a mechanism for the differential efficacy of Spesolimab on pustules versus erythema, and in particular, the role of the IL-36 pathway in both lesions needs to be explored in depth.

This case study revealed that the patient exhibited several detrimental lifestyle habits, including alcohol consumption, stress, and nocturnal disturbances. These factors were found to exacerbate the severity of the patient's skin symptoms. Research has demonstrated that the patient's lifestyle (including alcohol intake, smoking, stress, sleep disorders, and sedentary habits), diet, and single nutritional intake may influence the clinical manifestations, severity, and course of psoriasis.[22] Consequently, the patient was thoroughly educated on the proper diet and lifestyle practices during the treatment period and for a period of six months following the conclusion of treatment. There were no relapses observed.

Although this case is valuable, there are still many problems: First, as a single-case study, the rapid efficacy of Spesolimab and delayed erythema resolution require validation in larger cohorts. Second, the 2-month follow-up period precludes assessment of long-term relapse risks and cumulative drug toxicities. Third, while dose consistency and temporal association argue against conventional agents as primary contributors, potential synergism with corticosteroids/immunosuppressants cannot be fully excluded. Finally, the absence of IL-36 pathway-specific biomarkers (eg, IL-36Ra, CXCL8) limits mechanistic insights into treatment response. Extended follow-up and multi-omics profiling are needed to strengthen the evidence.

Conclusion

In summary, this study documents a case involving a 40-year-old Chinese male with a history of GPP spanning over six months. Following two months of treatment with a 900mg intravenous infusion of the Spesolimab monoclonal antibody, the patient's pustules completely vanished, resulting in a GPPGA score of 0, a GPPASI score of 0, and a DLQI score of 2. This real-world case demonstrates Spesolimab potential efficacy in achieving rapid pustule clearance and systemic inflammation control in a Chinese GPP patient, while highlighting the need for further investigation into its heterogeneous effects on erythema resolution. These observations contribute to the evolving strategies for integrating biologics into GPP management in China. We eagerly anticipate future large-scale, long-term follow-up randomized controlled, double-blind clinical trials to offer valuable insights for the long-term management of patients. Furthermore, additional research is warranted on larger sample sizes to explore the duration of treatment effect post Spesolimab therapy and the reduction patterns of hormones, immunosuppressants, retinoids, and other medications.

Ethics Statement

This study does not require institutional approval.

Patient Consent Form

The patients provided written informed consent for the publication of the patients' clinical data and accompanying images.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare that they have no conflicts of interest that relate to the research described in this paper.

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