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CASE REPORT

Successful Treatment of Upadacitinib in Prurigo Nodularis: A Case Report and Review of the Literature

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Background: Prurigo nodularis (PN), while rare, presents significant clinical challenges due to its diverse pathogenesis and presentation. Effective therapy recommendations for PN remain limited. Upadacitinib, an oral highly selective type 1 Janus-associated kinase (JAK, Intracellular tyrosine kinases that phosphorylate cytokine receptors). Inhibitor plays an excellent role in alleviating itching in atopic dermatitis (AD). This is a report on the treatment of PN with upadacitinib, which offers a new option for refractory PN.

Case Presentation: We share our successful treatment experience of upadacitinib on a 43-year-old female patient with refractory PN failing to conventional therapies. She showed significant improvement at the follow-up visits and no obvious adverse effects happened. We also reviewed published case reports of PN patients and PN-related review researches and made a comprehensive discussion of the potential mechanism of JAK1 inhibitors in treating PN.

Conclusion: Upadacitinib may be a safe and potent alternative for patients with refractory PN.

Keywords: prurigo nodularis, upadacitinib, janus kinase inhibitor, immunotherapy, dermatology

Introduction

Prurigo nodularis (PN) is a chronic, recurrent inflammatory skin condition featuring with recalcitrant pruritus and hyperkeratotic nodules symmetrically distributed throughout the body especially favoring the extensor surfaces of the extremities and the trunk. Till now, PN remains a clinical diagnosis, and skin biopsy is of little value.[1] PN is relatively rare. In the United States, the estimated prevalence is 72 per 100,000 individuals, without inclusion of the susceptible population.[2] However, with more than 50% of patients not satisfied with their therapy, it causes a profound detrimental burden on the life quality of patients and an economic burden.[3–5]

The lack of an effective strategy for therapy is partially due to the unclear acknowledgment of the etiology and pathogenesis of PN. Immunological dysfunction and neural dysregulation might play important roles. Recent studies suggest that PN might be predisposed to having an atopic disposition similar to atopic dermatitis (AD).[6] Conventional therapeutic strategies for PN including topical agents, phototherapies and photochemotherapies, neuromodulating therapies, antiepileptics and antidepressants, and conventional systemic immunomodulating therapies like oral corticosteroids, immunosuppressions, are currently off-labeled but experienced options for PN treatment, and none of these have sufficient clinical evidence.[1] Therefore, to date, treatment recommendations for PN remain controversial.

Emerging biologics and small molecule drugs in clinics bring new treatment options for PN, and the inhibitors of Janus kinase are one of the most promising choices. The Janus kinase-signal transducers and activators of transcription (JAK-STAT, The canonical signaling cascade where cytokine binding activates JAKs, which subsequently phosphorylate

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STATs). Pathway play an important role in the expression of proinflammatory signaling pathways by a variety of cytokines. Thus, the inhibition of this pathway could suppress multiple kinds of inflammation caused by different cytokines. Upadacitinib is an oral, highly selective type 1 Janus-associated kinase (JAK1) inhibitor.[7] It was approved the indication of moderate to severe rheumatoid arthritis refractory to biologic disease-modifying antirheumatic drugs in adults by the US Food and Drug Administration and European Medicines Agency in 2019 first. Then it was approved the use on moderate-to-severe AD in patients 12 years of age or older by the China National Medical Products Administration in February, 2022. In clinical practice, upadacitinib has also been tried to treat alopecia areata, and especially allergic asthma.[8–10] However, the application of upadacitinib in PN with an atopy background has not yet been reported.

Case Report

A 43-year-old woman farmer complained of intensive skin pruritus with widespread nodules for 9 months at our clinic. It was initialized with symmetric diffuse rashes on both lower limbs without obvious triggers 9 months ago, which then spread to the whole body, including the scalp, face, trunk, and upper limbs. The rashes were hard and nodular, symmetrically distributed on the skin, accompanied by severe itching, which deteriorated especially at night. The skin between nodules was dry and rough. Her work and quality of life were severely impacted by the rash and itching. She had an atopic background of seasonal attacked allergic rhinitis (AR) for 3 years and chronic spontaneous urticaria (CSU) for 4 years. Her concomitant medical conditions were under stable control at the time of presentation. She denied family history of allergy and PN.

Physical examination revealed extensive symmetrically grouped erythematous, keratotic nodules on her scalp, face, trunk, and extensor surfaces of extremities, and there were multiple scratches. The keratinized nodules were surface exfoliated and measured between several millimeters up to 1cm in diameter (Figure 1). Her nasal mucosa was pale and swollen. The skin scratch sign was positive. There was no palpable lymphadenopathy. Blood tests showed an eosinophil count of 0.13×10^9/ L (normal range $<1.0\times10^9$/L), and a basophil count of 0.02×10^9/ L (normal range $<0.1\times10^9$/L). Tuberculosis and hepatitis markers showed negative results. The result of serum liver function was within the normal range. Serum total immunoglobulin E (IgE) was 180 IU/mL (normal range <100.0 IU/mL). 100 items of food-specific IgG4 including common fruits, vegetables, meat, and eggs were all within the normal range (<250.0 U/mL). Clinical diagnosis of PN was determined based on her typical manifestations and the ancillary tests described above ruled out secondary causes of her pruritus. We used different scoring systems to evaluate the change in her different diseases, which were described in detail (including assessment methods and interpretation of each scoring system) in the Supplementary Table 1.

Scoring Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), and Body Surface Area (BSA) were used for the skin lesion, which was 55, 22.5, and 80% pretreatment, respectively. Pruritus Numerical Rating Scale (NRS) was used for itch intensity, which was 9 at baseline. Dermatology Life Quality Index (DLQI) was used for the influence of life, which was 9 at baseline. Total Nasal Symptom Score (TNSS) for AR, which was 0 during the whole treatment. Urticaria control test (UCT) for her CSU, which was 14 at baseline. Previous treatment focused on the relief of pruritus with topical steroids like dexamethasone acetate cream, oral anti-histamines like ebastine, Chinese herbal medicine, and even thalidomide, which only showed mildly alleviation of itch and minimal impact on rashes. The patient came to our clinic seeking a full remission. Based on the comprehensive examination of the patient's condition, we suggested the strategy of upadacitinib treatment. With the patient's consent, treatment with upadacitinib was administered orally at a dose of 15 mg once a day together with the antihistamine medicine ebastine used as needed to relieve pruritus due to CSU or PN. Since the symptoms were under full control, there was no medication for her AR. She was followed up at weeks 8, 12, and 24 with the evaluation of symptom scores and serum tests.

During her follow-up, she achieved continuous improvement of the symptoms. At week 8, the first follow-up visit, the patient experienced a close to 60% improvement in skin lesions and marked resolution of itching. The density of nodules was reduced, and the skin lesions were flattened. Her quality of life improved significantly (DLQI decreased 5 points from pretreatment). The intuitive lesion changes can be seen in Figure 1. The quantified reductions in PN lesions, pruritus resolution, improvement in quality of life, and symptom control in AR and CSU are shown in Figure 2. At week 12, the

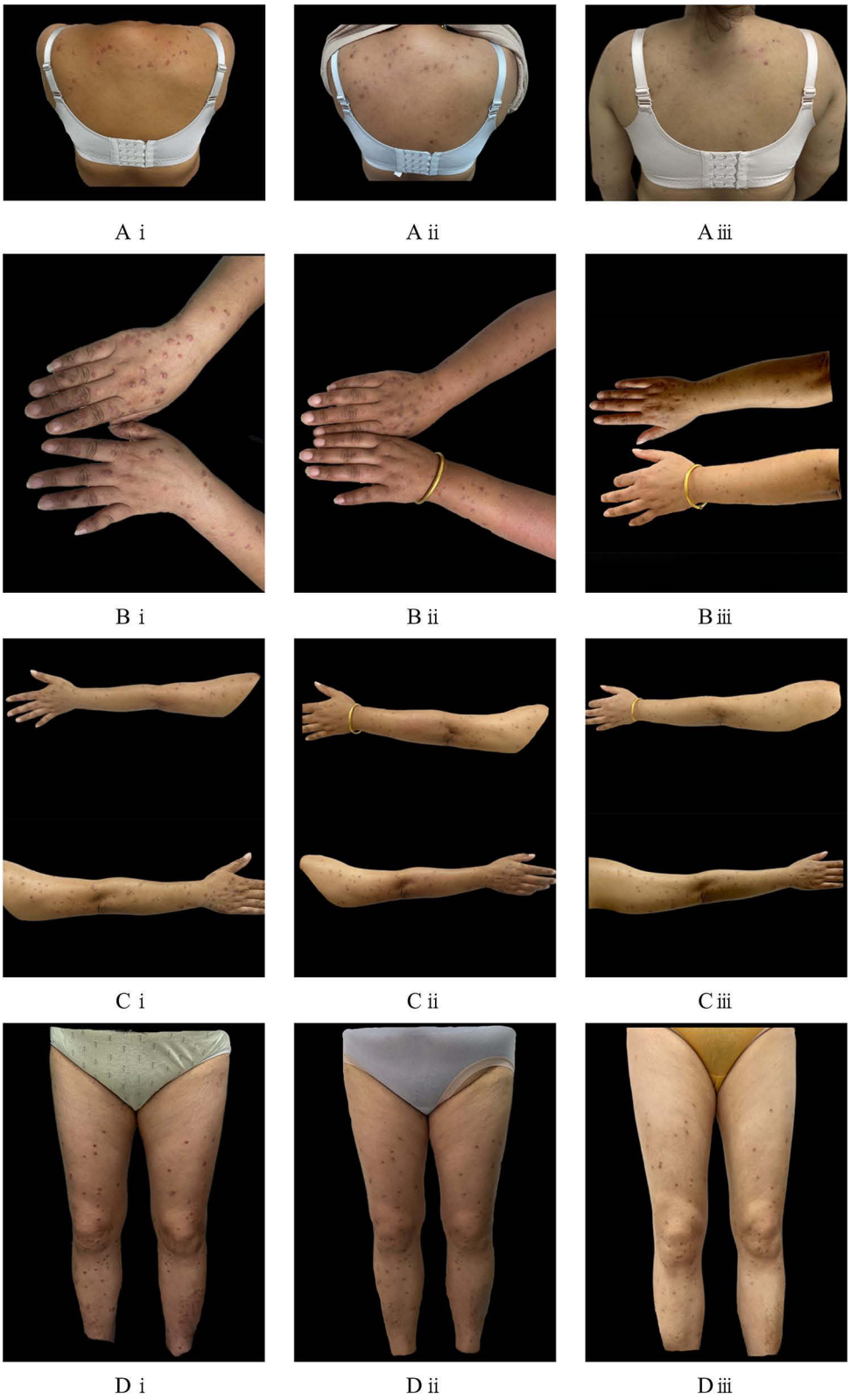

Figure 1 Manifestation of the skin lesions at baseline, week 8, and week 24 during the upadacitinib treatment: (Ai-Aii) lesions on the back; (Bi-Bii) lesions on the hands; (Ci-Cii) lesions on the upper extremities; (Di-Dii) lesions on the lower extremities.

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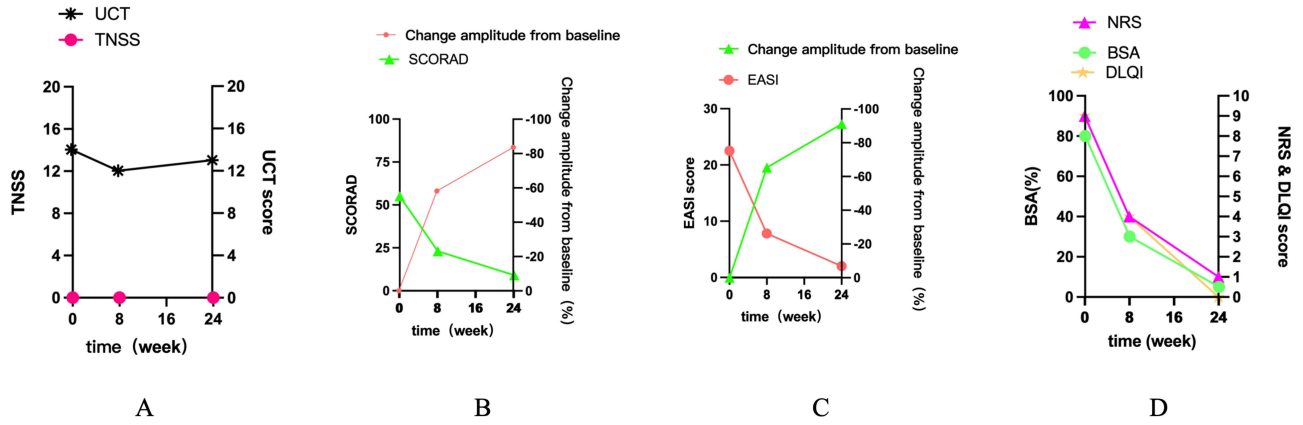

Figure 2 The evolution of the symptom profile during the administration of upadacitinib. (**A**) Control of comorbid conditions (TNSS+TNNSS for allergic rhinitis, and UCT for chronic urticaria). (**B**) SCORAD score and its corresponding variation in magnitude. (**C**) EASI score and its corresponding variation in magnitude. (**D**) Alterations in NRS, BSA, and DLQI score.

patient's reexamination of serological tests revealed that the patient's basophil count was 0.01×10^9/L and eosinophil count was 0.12×10^9/L, both of which were within the normal range and lower than pretreatment. Serum IgE was 62.5 IU/mL (normal range <100.0 IU/mL). Food-specific IgG4, immunoglobulin, and complement were still within the normal range. The serum index of liver, kidney function, and blood lipid were within the normal range.

During the treatment, the patient complained of decreased menstrual volume at week 8, which returned to normal level at week 12 and kept normal since then. The treatment regimen and follow-up are still in progress. No significant adverse effects (AEs) were reported.

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (approval number 20230275). The patient has given written consent for this case report to be published and for all details and images shown in it.

Discussion

In the current presentation, we reported the successful treatment of upadacitinib for a refractory PN with an atopy background. The patient demonstrated significant improvements in skin lesions, pruritus, quality of life, and complete control of pre-existing atopic diseases.

PN or chronic prurigo of nodular type, a main subtype of chronic prurigo, is a chronic, recurrent inflammatory skin condition.[11] The characteristic clinical manifestation of PN was first reported by Hyde and Montgomery in 1909.[2] Given the heterogeneous nature of the etiology of PN, most current treatments for PN are off-label and ineffective. PN patients always undergo numerous medications, both topically and systemically, known as the stepwise-treatment approach.[12] Topic corticosteroids, oral steroids, and immunosuppressors are the most common medications. Brown et al comprehensively reviewed the clinical trial data on both topical and systemic therapies for PN, including their respective efficacy profiles and adverse effects.[13] However, clinical practices revealed that these therapies are not only insufficient in efficacy but often induce worry about adverse effects of long-term administration.[14] There is an urgent need for new agents to resolve this problem.

Profound understanding of its underlying immune mechanism and inflammatory pathway and the development of precise immunotargeting therapies are helpful for this. Skin inflammation is crucial for pruritus' activation. The T helper type 2 (Th2) type immune response was proposed given that PN frequently coexists with AD.[6,15] Garcovich et al also found that PN, like AD, shows typical type 2 immune tilt pathological manifestations, and may have a direct impact on itch fibers.[16] Previous studies have found cutaneous overexpression of interleukin (IL)-4, IL-13, and IL-31, which are typical Th2-associated cytokines and are crucial to the pathophysiology of chronic itch and nodular lesions in PN.[17,18] Therefore, strategies targeting the Th2 pathway have been tried in clinical work and achieved some merits. Dupilumab, an IL-4 /IL-13 inhibitor, was approved by the US FDA as the first and only treatment indication for PN in adults on

September 28, 2022.[19] However, this patient declined dupilumab due to a phobia of injections and difficult access to transportation. Nemolizumab as a humanized IL-31RA monoclonal antibody, shows a great reduction in pruritus and severity of skin lesions in patients with PN.[20,21] However, at the time of writing, nemolizumab is not available in China, and no registration filings have been checked, nor was it accessible to the patient during treatment selection.

Emerging studies reveal that the Signal Transducer and Activator of Transcription (STAT, Proteins recruited to activated receptors, then dimerize and migrate to the nucleus to regulate gene transcription). Pathway plays a key role in PN. Fukushi et al showed that Th2 cytokines associated STAT6 activation together with some unknown stimuli activating STAT3 in 22 cases of PN.[22] And Agrawal et al found elevated expression of STAT 1, 3, 6 in PN lesions.[23] The molecular components of the JAK-STAT pathway were identified for over 30 years.[24] Among them, JAK1 in the family was shown to play a dependent role in signaling chronic pruritus.[25] IL-4 and IL-13 activate JAK1 and JAK3, mediate the activation of the STAT6 signaling pathway, and up-regulate the expression of IL-31 through binding to the receptors. IL-31 activates JAK1, JAK2, and STAT3 signaling pathways and induces pruritus through binding to the heterodimeric IL-31 receptor A and oncostatin M beta receptor.[26,27] These findings reveal the potential role of JAK inhibitors in the treatment of PN by interfering with Th2-type immune response.

Upadacitinib is a highly selective JAK1 inhibitor, indications in China include moderate to severe AD, rheumatoid arthritis, and psoriatic arthritis in adults and adolescents over 12 years old. The therapeutic principle of JAK inhibitors in rheumatic diseases is to inhibit IL-6 and interferon γ related signaling pathways.[28,29] By targeting JAK1, upadacitinib blocks the signal transduction of itch-inducing cytokines such as IL-4, IL-13, IL-31, and thymic stromal lymphopoietin, thereby relieving pruritus and treating AD.[30] In particular, Betancor et al reported a case of a middle-aged male patient with AD and allergic asthma who not only showed improvement in AD but also induced remission of allergic asthma during the treatment with upadacitinib, the result of JAK1 inhibition and disruption of Th2 differentiation by upadacitinib, which in line with our patient, whose symptoms of AR and CSU got completely controlled.[10] Some researchers indicated that the blockade of the JAK-STAT signaling pathway was effective in improving symptoms in the AR mice model.[31–33] Some small scale controlled human studies have also shown that Th2-related cytokines, especially IL-31 and IL-9, were up-regulated in patients with CSU, suggesting that the JAK-STAT pathway may play a role in the pathogenesis of CSU.[34,35] In a review of the literature, many case reports supported the efficacy of JAK inhibitors in PN whether with an atopy background,[36–40] and CPG Phase II trials for the JAK1 inhibitors abrocitinib and povorcitinib are ongoing.[41]

It's worth mentioning that in this case of the patient, blood tests showed that the blood eosinophil and basophil count was decreased after treatment with upadacitinib, accompanied by pruritus and rash significant relief. This alteration could be explained by the eosinophilic aggregation that is typically boosted by IL-4, IL-5, and IL-13.[42] Whether blood eosinophil count can be used as a biomarker of PN condition changes remains to be studied.

Conclusion

Here, we report a patient with refractory PN and an atopic background benefited from the treatment of upadacitinib, as indicated by anti-pruritus, lesion-clearance effects, change of immunological parameters, full control of concomitant diseases, and discontinuation of symptomatic medicines. Putting together the findings of earlier research, JAK inhibitors appear to be a safe and potent alternative for the treatment of patients with refractory PN. Our case adds new evidence for its potential clinical application. In all, there is an unmet need for clinical research on large numbers of patients to validate the efficacy and comprehend the function of the JAK-STAT pathway in PN.

Abbreviations

PN, prurigo nodularis; JAK, Janus-associated kinase; AD, atopic dermatitis; JAK-STAT, Janus kinase-signal transducers and activators of transcription; AR, allergic rhinitis; CSU, chronic spontaneous urticaria; IgE, immunoglobulin E; SCORAD, Scoring Atopic Dermatitis; EASI, Eczema Area and Severity Index; BSA, Body Surface Area; NRS, Pruritus Numerical Rating Scale; DLQI, Dermatology Life Quality Index; TNSS, Total Nasal Symptom Score; UCT, Urticaria control test; AEs, adverse effects; Th2, T helper type 2; IL, interleukin; STAT, Signal Transducer and Activator of Transcription.

Data Sharing Statement

Data sharing is not applicable to this article.

Ethical Approval

This study involving human participant was reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (Approval No. 20230275). The patient/participant provided her written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article. This article was approved for publication by the Scientific Research Department of the Second Affiliated Hospital of Zhejiang University School of Medicine.

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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

The authors have no potential conflicts of interest to disclose for this work.

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