MEDS Clinical Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2023.040105
ISSN 2616-1907 Vol. 4 Num. 1

Dupilumab for Recurrent Prurigo Nodularis: A Case Report and Review of the Literature

Wei Jiang[1,a,*], Xueyong Wang[1,a], Nan Li[1,a], Zhiguo Xu[1,a]

[1]The 78th Group Army Hospital of Chinese PLA, Mudanjiang, Heilongjiang, 157000, China
[a]570963755@qq.com
[*]Corresponding author

Keywords: Prurigo nodularis; Dupilumab

Abstract: Prurigo nodularis (PN) is a chronic inflammatory skin disease that affects the quality of life of patients and is classified in the ICD-10 as a group of chronic lichen simplex and itchy skin diseases (ICD-10/L28) with an incidence of approximately 36.7-148.53 per 100,000 people. The pathogenesis of PN is closely related to type 2 inflammatory response. There are no standardized treatment guidelines for this disease, and traditional anti-pruritic treatment regimens often fail to control the vicious pruritic-scratch cycle in PN and have a poor safety profile. Traditional treatment options for PN include oral antihistamines, thalidomide, and topical hormones, calcium phosphatase inhibitors, and other treatments. However, traditional treatment options often suffer from poor pruritus control and high side effects. A patient with prurigo nodularis was admitted to our hospital who responded poorly to routine topical glucocorticoids and other drug therapies and relapsed after discharge from treatment. After readmission, the patient was successfully treated with dupilumab, a biological agent targeting interleukin-4/13. The patient's rash was significantly flattened, and the pruritus NRS score was significantly decreased. In this case, successful treatment of refractory PN with dupilumab could provide new ideas for treatment.

1. Introduction

A 22-year-old man was admitted to our hospital due to nodules and severe itching on the back and extremities for 1 year, aggravated for 2 months. One year ago, the patient developed red papules with itching after being bitten by mosquitoes on both upper limbs, which was not significantly improved after self-medication, and the rash gradually generalized and progressed to local skin reddish-brown nodules with significant itching affecting nocturnal sleep. Six months ago, he was hospitalized in our hospital and given oral thalidomide tablets, antihistamines, and topical halomethasone cream encapsulation for about 1 month for treatment of PN. After the above treatment, the patient was discharged with better condition. Two months ago, the nodules on the back and extremities recurred and worsened again, and red pustules appeared on skin with pain. According to the patient's intractable PN and secondary skin infection, our outpatient clinic admitted him to the hospital again. Physical examination on admission revealed brown skin nodules on the patient's trunk as well as extremities. Some skin rashes result in red pustules and pus head

formation due to repeated scratching, and local skin temperature increases with painful compression. Pruritus NRS score was 9 on admission. Laboratory findings at baseline revealed an absolute eosinophil count of 0.5×10^9/L (reference range $<0.5\times10^9$/L), a percentage value of 1% (reference range 0.5% ~ 5%) and total Serum IgE > 2500 IU/ml(reference range <100IU/ml). Culture result of pustular secretion was Staphylococcus aureus. Considering that the patient's condition recurred in the short term, the treatment regimen for this patient was as follows: 1. Topical moisturizing skin care to enhance skin barrier function; 2. Dupilumab was administered subcutaneously 600 mg for the first time with 300 mg every two weeks; 3. Local nodules were treated with topical glucocorticoids cream encapsulation; 4. Patient was given oral cefaclor capsules for 1 week due to skin infection. After 4 doses of dupilumab treatment, the skin nodules were significantly absorbed with a few residual scars observed locally (Figure 1A and B). All local red pustules disappeared within one week. Pruritus NRS score decreased to 1 after 6 weeks treatment. The patient had no obvious adverse reactions during the treatment, and the condition did not recur during the follow-up for 6 months.

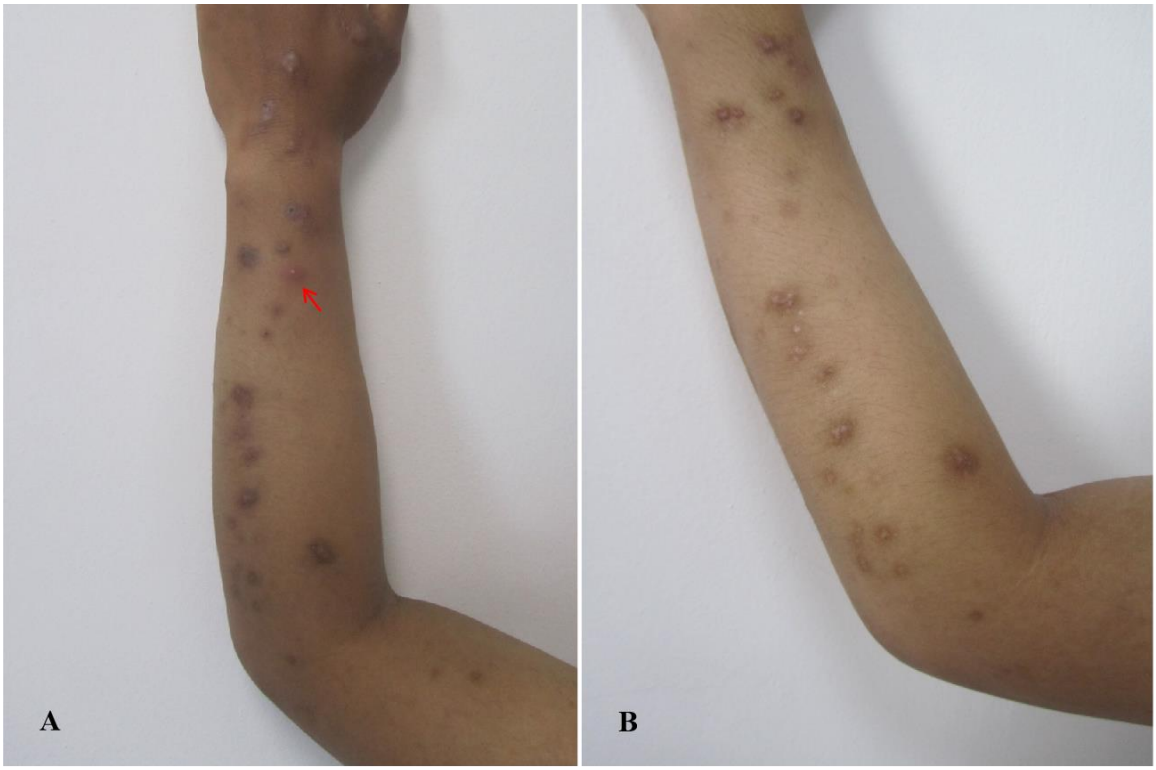

Figure 1 Rapid clinical response of prurigo nodularis (PN) to dupilumab treatment. Clinical images of the left upper limb (A) before and (B) after 6 weeks of treatment with the IL-4/13 antibody dupilumab, demonstrating rapid reduction in nodules and signs of cutaneous inflammation.

2. Discussion and literature review

Current mainstream view suggests that local type 2 inflammation in PN skin is an important mechanism leading to persistent chronic pruritus and pathogenesis[1]. PN and atopic dermatitis have many similarities in terms of onset and chronic lesion characteristics[2], and more than 50% of PN patients have been reported to be atopic disposition[3]. Th2-type cytokines, such as IL-4, IL-13, and IL-31, are closely involved in inflammatory responses and chronic pruritus formation in local skin lesions of PN[4]. There are no standardized diagnostic and therapeutic guidelines for the treatment of PN[5]. For this patient with recurrent disease and poor response to conventional therapy, there is

currently no appropriate treatment[6]. Evidence-based evidence for treatment relies primarily on expert consensus, which may be related to the low number of PN patients due to the low incidence of PN[6]. At the time of our patient admission, the clinical indication for dupilumab is clinically approved for the treatment of atopic dermatitis. Therefore, the use of dupilumab is off-label for this patient[7]. On September 28, 2022, the U.S. Food and Drug Administration officially approved dupilumab for clinical use in the treatment of PN. Although our treatment for this patient was off-label usage of dupilumab, we carefully searched the relevant literature and current cutting-edge findings of PN treatment in combination with the patient's disease characteristics and under the premise that conventional treatment of PN drugs was ineffective. Dupilumab was prescribed for PN and was not started until the patient's consent was obtained and informed consent was signed. The treatment result turned out to be a surprising one. The patient was subjectively very satisfied with the clinical outcome of dupilumab.

Local skin inflammation of PN can stimulate C-type nerve fiber endings to generate electrophysiological impulses that are transmitted to the dorsal ganglion nerve roots of the spinal cord, which transmit pruritic sensations to the cerebral cortex via the spinothalamic tract[1, 2, 8]. In turn, the itching sensation promotes scratching behavior and leads to increased disease progression[9]. Blocking any link in this itch-scratch conduction loop may serve as an effective target for this disease[2].

Dupilumab improves PN pruritus by blocking the pruritic signal pathway primarily through antagonism of IL-4 and IL-13 co-receptors[10, 11, 12]. A phase III clinical trial (N=160; NCT04202679) of dupilumab for moderate-to-severe PN (300 mg once a month, doubling the first dose) demonstrated that it was effective in improving pruritus, anxiety and depression, and quality of life scores in PN patients[13]. Patients admitted to our hospital had recurrent disease after conventional treatment. After the standardized administration of dupilumab, the patient's rash improved, itching was relieved, and he was satisfied with the treatment effect. The pruritus NRS score decreased from 9 to 1. No adverse events were observed during the treatment.

A noteworthy point is that the patient's condition worsened and he was readmitted with a bacterial skin infection. Skin dysbacteriosis (toxic effects such as Staphylococcus aureus) has been reported to be associated with exacerbations in PN patients[2, 13]. Staphylococcus aureus infection and toxic effects in PN patients can be the initiating factor for exacerbation[14, 15], not just secondary bacterial infection following a vicious cycle of itching and scratching. It has been shown that type 2 immune responses can suppress Toll-like receptor expression, thereby reducing local immunity leading to an increased likelihood of infection [16]. The patient in this case may also have achieved an antibacterial infection effect with dupleuximab treatment. The above therapeutic effects may require clinical studies to further elucidate their specific mechanisms.

Interestingly, the patient's serum IgE concentration exceeded 2500 IU/ml both at admission and discharge. This situation also suggested to us that the patient had an atopic tendency. Further questioning revealed that the patient had no past history of atopic tendency however. Current research suggests that about 50% of patients with PN have atopic tendencies[3, 4, 17]. This condition may lead to the existence of predisposition to allergies to exogenous or endogenous allergen-type substances[3]. Whether high levels of serum IgE concentrations in PN patients are associated with disease initiation or relapse needs to be explored in further studies.

PN is one of the most pruritic diseases associated with pruritus in dermatology[2, 18]. Clinical statistics found that the pruritus VAS score of PN can reach to maximum 10 points[7, 19, 20]. Therefore, it is very important to effectively control and treat the pruritus caused by PN. To date, the specific pathogenesis of PN has not been fully elucidated. However, in fact, the current mainstream view is that the pathogenesis of PN or other types of chronic pruritus-related diseases such as atopic dermatitis may have certain common features[1, 21]. Currently, studies targeting the

inflammatory targets of pruritus have revealed that type 2 inflammatory factors are intimately involved in the development of chronic pruritus[22, 23]. In this regard, inflammatory pathways with Th2 type cells as the core are closely involved in the development of PN[24]. Locally in the cutaneous area, keratinocytes (physical skin barrier)[1], immune cells (Type 2 inflammatory pathway)[6], and peripheral nervous fiber endings (pruritoreceptive transmission)[25], are involved in the localized pruritogenesis of PN in terms of structural and functional aspects. Therefore, effective interventions in PN treatment should also revolve around these three important aspects.

The current study found that IL-4, IL-13, and IL-31 are all Th2 cell-derived inflammatory cytokines[2]. They may exert and mediate the activation of downstream inflammatory pathways by binding to the corresponding receptors of keratinocytes, leading to a local chronic inflammatory response in PN lesions[26]. On the other hand, IL-4, IL-13 and IL-31 may also mediate the formation and transmission of chronic pruritus by binding to the corresponding receptors (IL-4RA, IL-31RA/ Oncostatin M) in C-type peripheral nervous fiber endings[3, 27]. These cytokines (IL-4, IL-13, and IL-31) have been found to induce local pruritus in human or in somatic animal models with subcutaneous injections[28, 29, 30]. Recent studies have revealed that IL-4 and IL-13 can exert intercellular inflammatory transduction by binding to IL-4RA, and that IL4-RA can further induce chronic inflammatory and pruritic responses by further activating the JAK1 signalling pathway[31, 32, 33].

The mechanism of dupilumab is primarily targeted to antagonize IL-4/13R. Phase 3 clinical trials on dupilumab for PN have demonstrated that dupilumab is effective in the management of PN patients[13]. In addition, Vixarelimab may combat pruritus by targeting binding to the OSMR β and is currently under Phase 2 clinical trial for PN. In the phase 3 clinical trial for the treatment of PN, Nemolizumab was found to be effective in controlling the onset of pruritus in PN patients 48 h after subcutaneous administration (0.5 mg/kg). Patients' sleep quality improved significantly and pruritus NRS scores decreased by 56% on average after standardized application of Nemolizumab, while pruritus NRS scores decreased by only 22.9% in the control group ($p < 0.001$). The clinical finding also suggests that nemolizumab also has a good effect in PN treatment[27]. Abrocitinib, upadacitinib, baricitinib, and gusacitinib are JAK inhibitors. Clinical trials have found that all of the above drugs have good results in the treatment of moderate to severe AD[17, 34]. However, there are only case reports of JAK inhibitors being effective in controlling the clinical symptoms of PN[33, 35, 36, 37]. Therefore, more clinical RCTs around JAK inhibitors for PN need to be conducted to clarify their efficacy.

3. Conclusions

Currently, there are now an increasing number of case reports about the effective therapy of PN with dupilumab. Among them, a case report by Tahel et al. found that the pruritus of a 9-year-old girl with PN improved significantly after 2 weeks of dupilumab administration, and the local nodules subsided and absorbed significantly after 3 months of standardized treatment[38]. We also found that the pruritus improved and the local rash was significantly improved in a 2-year-old boy diagnosed with AD after subcutaneous injection of dupilumab 300 mg with single dosage. The above findings suggest that dupilumab may be very effective in the treatment of chronic pruritic skin diseases and may have a better safety profile for use in children[16].

The shortcoming of this paper lies in the limited number of cases. We plan to design a standardized RCT trial to validate the efficacy of dupilumab in PN. There are few data on dupleixumab for treatment of relapsed PN all over the world. This article may provide new options and new ideas for the treatment of relapsed PN. Further investigations and randomized clinical trials are needed to evaluate the therapeutic approach of targeting IL-4/13 in PN.

References

[1] Kwatra S.G., Breaking the Itch-Scratch Cycle in Prurigo Nodularis. N Engl J Med, 2020. 382(8): p. 757-758.

[2] Garcovich, S., M. Maurelli, P. Gisondi, K. Peris, G. Yosipovitch, and G. Girolomoni, Pruritus as a Distinctive Feature of Type 2 Inflammation. Vaccines (Basel), 2021. 9(3).

[3] Labib A., T. Ju A. Vander Does, and G. Yosipovitch, Immunotargets and Therapy for Prurigo Nodularis. Immunotargets Ther, 2022. 11: p. 11-21.

[4] Wong L.S. and Y.T. Yen, Chronic Nodular Prurigo: An Update on the Pathogenesis and Treatment. Int J Mol Sci, 2022. 23(20).

[5] Williams K.A., A.H. Huang, M. Belzberg, and S.G. Kwatra, Prurigo nodularis: Pathogenesis and management. J Am Acad Dermatol, 2020. 83(6): p. 1567-1575.

[6] Elmariah S., B. Kim, T. Berger, S. Chisolm, S.G. Kwatra, N. Mollanazar, and G. Yosipovitch, Practical approaches for diagnosis and management of prurigo nodularis: United States expert panel consensus. J Am Acad Dermatol, 2021. 84(3): p. 747-760.

[7] Huang A.H., K.A. Williams, and S.G. Kwatra, Prurigo nodularis: Epidemiology and clinical features. J Am Acad Dermatol, 2020. 83(6): p. 1559-1565.

[8] Stander S., C. Zeidler, M. Pereira, J.C. Szepietowski, L. McLeod, S. Qin, N. Williams, T. Sciascia, and M. Augustin, Worst Itch Numerical Rating Scale for Prurigo Nodularis: A Psychometric Evaluation. J Eur Acad Dermatol Venereol, 2021.

[9] Yang T.B. and B.S. Kim, Pruritus in allergy and immunology. J Allergy Clin Immunol, 2019. 144(2): p. 353-360.

[10] Chiricozzi, A., M. Maurelli, N. Gori, G. Argenziano, C. De Simone, G. Calabrese, G. Girolomoni, and K. Peris, Dupilumab improves clinical manifestations, symptoms, and quality of life in adult patients with chronic nodular prurigo. J Am Acad Dermatol, 2020. 83(1): p. 39-45.

[11] Holm, J.G., T. Agner, C. Sand, and S.F. Thomsen, Dupilumab for prurigo nodularis: Case series and review of the literature. Dermatol Ther, 2020. 33(2): p. e13222.

[12] Husein-ElAhmed, H. and M. Steinhoff, Dupilumab in prurigo nodularis: a systematic review of current evidence and analysis of predictive factors to response. J Dermatolog Treat, 2022. 33(3): p. 1547-1553.

[13] Cunha, I.M., I. Valadao, E. Gomes, and A. Marinho, Dupilumab: A Safe and Successful Treatment in Refractory Prurigo Nodularis. J Allergy Clin Immunol Pract, 2022. 10(5): p. 1365-1366.

[14] Fostini, A.C., G. Girolomoni, and G. Tessari, Prurigo nodularis: an update on etiopathogenesis and therapy. J Dermatolog Treat, 2013. 24(6): p. 458-62.

[15] Hanel, K.H., C. Cornelissen, B. Luscher, and J.M. Baron, Cytokines and the skin barrier. Int J Mol Sci, 2013. 14(4): p. 6720-45.

[16] Munoz-Bellido, F.J., E. Moreno, and I. Davila, Dupilumab: A Review of Present Indications and Off-Label Uses. J Investig Allergol Clin Immunol, 2022. 32(2): p. 97-115.

[17] Langan S.M., A.D. Irvine, and S. Weidinger, Atopic dermatitis. Lancet, 2020. 396(10247): p. 345-360.

[18] Szollosi A.G., A. Olah, E. Lisztes, Z. Griger, and B.I. Toth, Pruritus: A Sensory Symptom Generated in Cutaneous Immuno-Neuronal Crosstalk. Front Pharmacol, 2022. 13: p. 745658.

[19] Huang A.H., J.K. Canner, R. Khanna, S. Kang, and S.G. Kwatra, Real-World Prevalence of Prurigo Nodularis and Burden of Associated Diseases. J Invest Dermatol, 2020. 140(2): p. 480-483 e4.

[20] Inui K., T. Ugajin, T. Namiki, and H. Yokozeki, Chronic prurigo: A retrospective study of 168 cases. J Dermatol, 2020. 47(3): p. 283-289.

[21] Kahremany S., L. Hofmann, A. Gruzman, and G. Cohen, Advances in Understanding the Initial Steps of Pruritoceptive Itch: How the Itch Hits the Switch. Int J Mol Sci, 2020. 21(14).

[22] Beck K.M., E.J. Yang, S. Sekhon, T. Bhutani, and W. Liao, Dupilumab Treatment for Generalized Prurigo Nodularis. JAMA Dermatol, 2019. 155(1): p. 118-120.

[23] Cevikbas F. and E.A. Lerner, Physiology and Pathophysiology of Itch. Physiol Rev, 2020. 100(3): p. 945-982.

[24] Miake S., G. Tsuji, M. Takemura, A. Hashimoto-Hachiya, Y.H. Vu, M. Furue, and T. Nakahara, IL-4 Augments IL-31/IL-31 Receptor Alpha Interaction Leading to Enhanced Ccl 17 and Ccl 22 Production in Dendritic Cells: Implications for Atopic Dermatitis. Int J Mol Sci, 2019. 20(16).

[25] Ringkamp M., R.J. Schepers, S.G. Shimada, L.M. Johanek, T.V. Hartke, J. Borzan, B. Shim, R.H. LaMotte, and R.A. Meyer, A role for nociceptive, myelinated nerve fibers in itch sensation. J Neurosci, 2011. 31(42): p. 14841-9.

[26] Wong L.S., Y.T. Yen, S.H. Lin, and C.H. Lee, IL-17A Induces Endothelin-1 Expression through p38 Pathway in Prurigo Nodularis. J Invest Dermatol, 2020. 140(3): p. 702-706 e2.

[27] Stander S., G. Yosipovitch, J.P. Lacour, F.J. Legat, C. Paul, A. Reich, K. Chaouche, F. Ahmad, and C. Piketty, Nemolizumab efficacy in prurigo nodularis: onset of action on itch and sleep disturbances. J Eur Acad Dermatol Venereol, 2022. 36(10): p. 1820-1825.

[28] Sonkoly E., A. Muller, A.I. Lauerma, A. Pivarcsi, H. Soto, L. Kemeny, H. Alenius, M.C. Dieu-Nosjean, S. Meller, J.

Rieker, M. Steinhoff, T.K. Hoffmann, T. Ruzicka, A. Zlotnik, and B. Homey, IL-31: a new link between T cells and pruritus in atopic skin inflammation. J Allergy Clin Immunol, 2006. 117(2): p. 411-7.
[29] Raap U., K. Wichmann, M. Bruder, S. Stander, B. Wedi, A. Kapp, and T. Werfel, Correlation of IL-31 serum levels with severity of atopic dermatitis. J Allergy Clin Immunol, 2008. 122(2): p. 421-3.
[30] Mashaghi A., A. Marmalidou, M. Tehrani, P.M. Grace, C. Pothoulakis, and R. Dana, Neuropeptide substance P and the immune response. Cell Mol Life Sci, 2016. 73(22): p. 4249-4264.
[31] Matsumura S., M. Terao, H. Murota, and I. Katayama, Th2 cytokines enhance TrkA expression, upregulate proliferation, and downregulate differentiation of keratinocytes. J Dermatol Sci, 2015. 78(3): p. 215-23.
[32] Agrawal D., K. Sardana, S.R. Mathachan, M. Bhardwaj, A. Ahuja, and S. Jain, A prospective study examining the expression of STAT 1, 3, 6 in prurigo nodularis lesions with its immunopathogenic and therapeutic implications. J Cosmet Dermatol, 2022. 21(9): p. 4009-4015.
[33] Ju T., A. Labib, A. Vander Does, and G. Yosipovitch, Topical Janus kinase-signal transducers and activators of transcription inhibitor tofacitinib is effective in reducing nonatopic dermatitis chronic itch: A case series. J Am Acad Dermatol, 2022. 87(2): p. 400-403.
[34] Li H., Z. Zhang, H. Zhang, Y. Guo, and Z. Yao, Update on the Pathogenesis and Therapy of Atopic Dermatitis. Clin Rev Allergy Immunol, 2021. 61(3): p. 324-338.
[35] Peng C., C. Li, Y. Zhou, Q. Wang, P. Xie, T. Li, and P. Hao, Tofacitinib for Prurigo Nodularis: A Case Report. Clin Cosmet Investig Dermatol, 2022. 15: p. 503-506.
[36] Pereira M.P., C. Zeidler, and S. Stander, Improvement of chronic nodular prurigo with baricitinib. J Eur Acad Dermatol Venereol, 2022. 36(6): p. e486-e488.
[37] Yin M., R. Wu, J. Chen, and X. Dou, Successful treatment of refractory prurigo nodularis with baricitinib. Dermatol Ther, 2022. 35(8): p. e15642.
[38] Fachler T., S. Maria Faitataziadou, and V. Molho-Pessach, Dupilumab for pediatric prurigo nodularis: A case report. Pediatr Dermatol, 2021. 38(1): p. 334-335.