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Generalized prurigo nodularis with dramatic response to dupilumab treatment, case report

Boyvadoğlu C et al. Generalized PN with response to dupilumab

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Abstract**BACKGROUND**

Prurigo nodularis (PN) is a chronic condition characterized by a papulonodular pruriginous eruption of unknown aetiology. Currently, there are no medications for PN that the US Food and Drug Administration has approved, which leads to very variable practices in the prescription of off-label treatments. Treatment of PN is based on clinical experience rather than controlled trials. We present our case of generalized PN, in which we had a dramatic response with dupilumab.

CASE SUMMARY

A 58-year-old female patient was admitted to our clinic with severe itchy, erythematous nodular lesions that were widespread all over her body, especially on the legs and back. It was learned that the patient's complaints started 4 years ago, and there was a significant increase in the lesions in the last period. Dermatological examination revealed diffuse firm erythematous excoriated nodular lesions all over the body. In the blood tests of the patient, serum IgE was measured at 9330 IU/mL. The patient was diagnosed with generalized prurigo nodularis together with clinical and histopathological findings. Due to severe clinical findings and the presence of comorbidities, dupilumab treatment was planned for the patient. In the follow-up 4 months later, it was observed that all nodular lesions healed with postinflammatory

hypopigmentation. The IgE value decreased to 1500 IU/mL after 4 months of dupilumab treatment.

CONCLUSION

Dupilumab treatment stands out as an effective and safe systemic treatment agent among existing systemic treatments.

Key Words: Dupilumab, Prurigo nodularis, Pruritus, IgE, Atopic dermatitis

Core tip: Prurigo nodularis (PN) ² is a difficult disease to treat and causes frustration to both the patient and the treating doctor. Treatment of PN is based on clinical experience rather than controlled trials. PN is a disease that negatively affects the quality of life of patients due to severe itching. Patients often receive limited benefit from first-line treatments and require systemic therapy. Dupilumab treatment stands out ²⁴ as an effective and safe systemic treatment agent among existing systemic treatments. In this case, we show how effective and well tolerated treatment with dupilumab is in the treatment of recalcitrant PN.

INTRODUCTION

² Prurigo nodularis (PN) is a chronic condition characterized by a papulonodular pruriginous eruption of unknown aetiology. PN is a difficult disease to treat and causes frustration for both the physician and the patient. Previously, it was reported that there is an association between various systemic diseases and PN. ² The classic lesion in PN is a firm pruritic nodule that is hyperkeratotic, numbers from a few to hundreds, and ranges from several millimetres to 2 cm in diameter ⁷ [1]. PN most frequently affects middle-aged adults and tends to be observed more often in women compared with men. PN is related to psychiatric, cardiovascular, renal, and endocrine disorders, besides malignancy and HIV. ⁷ The burden of systemic comorbidities in PN frequently exceeds that of other inflammatory skin disorders (i.e., psoriasis or atopic dermatitis) [2].

⁸ Immune and neural dysregulation are important in the pathogenesis of PN. Neuropeptides and immune cells are implicated in cutaneous inflammation. ¹⁵ Interleukin (IL)-31, tryptase, eosinophil cationic protein, histamine, prostaglandins, and neuropeptides are only a few of the mediators that immune cells in the skin release to cause a significant inflammatory reaction and severe itching. That immune reaction is critical to the pathogenesis of PN. Additionally, eosinophils play an important role in the cutaneous inflammation and itching related to PN. Eosinophil infiltration is observed in the dermis of PN patients' lesional skin. It is believed that the pathophysiology of PN is a cutaneous reaction pattern brought on by recurrent cycles of chronic itching and scratching [3].

⁸ Therapy for PN is based on topical, intralesional, and systemic neuroimmune modulatory treatments to split a short-circuited itch-scratch cycle. A personalized therapy plan, centered on the comorbidities, patient's age, disease severity, and side effect profile of treatments, is needed [3].

⁴ Dupilumab is a human monoclonal antibody; it blocks interleukin-4 and interleukin-13. Dupilumab has shown efficacy in asthma patients with high eosinophil levels. The blockade by dupilumab of these key drivers of type 2 helper T-cell (Th2)-mediated inflammation could benefit the therapy of Th2-associated diseases, including atopic dermatitis [4]. Emma Guttman-Yassky et al. showed that ¹⁶ dupilumab rapidly and effectively inhibited cellular and molecular cutaneous mediators of inflammation, reversed related epidermal abnormalities, and improved ¹⁰ disease severity scores and symptoms in patients with AD. Dupilumab remarkably inhibited systemic type 2 inflammatory mediators, including the chemokines, periostin, and total and allergen-specific IgEs [5].

Dupilumab treatment has been demonstrated to be an efficacious therapy for PN. Compared to atopic dermatitis, the treatment response to dupilumab therapy initiates later. Two months of treatment are needed until the pruritus is relieved. Complete remission is uncommonly observed before 4 months of treatment. Atopic dermatitis-related PN patients need longer therapy than non-atopic dermatitis-related PN patients [6].

Our patient had persistent and severe generalized PN. In our patient, for whom we started dupilumab treatment, a complete response was obtained in a short time. We present this case to emphasize that dupilumab therapy should be an important treatment agent that should be considered in the treatment of severe generalized PN.

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CASE PRESENTATION

Chief complaints

A 58-year-old female patient was admitted to our clinic with severe itchy, erythematous nodular lesions that were widespread all over her body, especially on her legs and back.

History of present illness

It was learned that the patient's complaints started 4 years ago, and there was a significant increase in the lesions in the last period. She had previously used systemic corticosteroid and oral antihistamine treatments for these itchy lesions, but there was no improvement. Then she was treated with omalizumab 300 mg every 4 weeks for 19 months, but did not benefit and there was a significant increase in nodular lesions, especially in the last period.

History of past illness

She had diabetes, hypertension, and coronary artery disease. She was using sitagliptin, metformin, insulin, telmisartan, acetylsalicylic acid, and trimetazidine for these diseases.

Personal and family history

The patient and her family had a known history of atopy.

Physical examination

Dermatological examination revealed diffuse firm erythematous excoriated nodular lesions all over the body, especially on the anterior surfaces of the tibia (Figure 1) and back (Figure 2).

Laboratory testing

In the blood tests of the patient, serum IgE 9330 IU/mL (normal range: 0-100 IU/mL), WBC $14,8 \times 10^3/\mu\text{L}$ (normal range: $3,39\text{--}8,86 \times 10^3/\mu\text{L}$), eosinophil 7.6% ($1,13 \times 10^3/\mu\text{L}$ (normal range: $0,03\text{--}0,27 \times 10^3/\mu\text{L}$)), lymphocyte 16.10% ($2,38 \times 10^3/\mu\text{L}$), neutrophil 69.30% ($10,25 \times 10^3/\mu\text{L}$ (normal range: $1,5\text{--}5 \times 10^3/\mu\text{L}$)), hemoglobin 10.2 g/dL (normal range: 11,1-14,7 g/dL), hematocrit 32.4% (normal range: 36,9-49,1 %) , mean corpuscular volume 74,5 fL (normal range: 87-102,2 fL), platelet $542 \times 10^3/\mu\text{L}$ (normal range: $158\text{--}374 \times 10^3/\mu\text{L}$), iron 17 ug/dL (normal range: 70-180 ug/dL), total iron binding capacity 421 ug/dL, CRP 7 mg/L (normal range: 0-5 mg/L), ESR 67 mm/h (normal range: 1-30 mm/h), glucose 151 mg/dL (normal range: 74-106 mg/dL), B 12 83 ng/L (normal range: 180-914 ng/L), Anti-HIV (-), Anti-HCV (-), HBsAg (-) were measured.

Imaging examination

Biopsy taken from the nodular lesion on the patient's back: "Focal keratotic, prominent granular layer, and large area of the epidermis with parakeratotic and psoriasiform hyperplasia containing fibrin and neutrophils was observed; increased vascularity in the upper dermis; infiltration consisting of perivascular condensed

lymphocytes, plasmacytes, and eosinophil polymorphs." reported as. It was observed as "IgG, IgA, IgM, C3c, and C1q negative" in immunofluorescence microscopy.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patient was consulted to internal medicine with blood results. No malignancy was found in the further examinations.

FINAL DIAGNOSIS

The patient was diagnosed with generalized prurigo nodularis together with clinical and histopathological findings. The patient was evaluated as having atopic dermatitis related PN because of the pruritus, xerosis, atopy history, and high IgE values. The peak pruritus numerical rating scale was 9 before treatment.

TREATMENT

Oral iron replacement therapy was given to the patient by the internal medicine department, but clinical findings did not improve. Cyclosporine and other immunosuppressive treatment options could not be planned for the patient due to concomitant hypertension and other systemic diseases. Due to severe clinical findings and the presence of comorbidities, dupilumab treatment was planned for the patient. Dupilumab therapy was administered at the standard dose: an initial induction dose of 600 mg followed by 300 mg every 14 days.

OUTCOME AND FOLLOW-UP

In the follow-up 4 months later, it was observed that all nodular lesions healed with postinflammatory hypopigmentation (Figure 3) in the patient whose itching complaint completely resolved in a short time. The IgE value decreased to 1500

IU/mL after 4 months of dupilumab treatment. The peak pruritus numerical rating scale was 0 after 4 months of dupilumab treatment.

DISCUSSION

The mechanisms underlying the development of PN are still not fully known. The pathogenesis of PN involves T cells and their cytokines, particularly IL-31. IL-31 is mainly produced by activated Th2 cells, CD45R0 CLA+ T cells, and mast cells. IL-31 has a significant role in the induction of chronic cutaneous inflammation. It has been shown to have an important role in the etiology of atopic dermatitis and has been accepted as a major dermal pruritogen [7, 8]. In comparison to healthy skin, messenger RNA for IL-31 is found more frequently in PN lesional skin [3]. IL-31 and its receptor have become potential therapeutic targets for a range of pruritic diseases, including PN [9].

Lesional biopsies have shown that IL-4 and IL-13 have critical roles in the development of PN. Hence, there are similarities between PN and atopic dermatitis in terms of the involvement of Th2 activation and the STAT pathway [10]. Therefore, it has been suggested that blocking IL-4/13 with dupilumab could help manage skin inflammation, which leads to itch [11].

Currently, there are no medications for PN that the US Food and Drug Administration has approved, which leads to very variable practices in the prescription of off-label treatments. Treatment of PN is based on clinical experience rather than controlled trials. Studies are limited to case reports and case series. Thus, larger studies with a homogeneous design are required. However, corticosteroids, pimecrolimus, and calcipotriol can be used as topical treatments for PN. However, they have limited efficacy. Phototherapy is recommended as a second-line treatment agent. Phototherapy is an especially useful option for medically complex patients who have comorbidities and drug interactions with other medications. PN patients

most commonly need ¹ treatment with systemic therapies because many patients are refractory to the therapies. Systemic neuromodulating drugs like gabapentin, pregabalin, aprepitant, naltrexone, butorphanol, duloxetine, paroxetine, fluvoxamine, and thalidomide, as well as systemic immunomodulating drugs like methotrexate, cyclosporine, mycophenolate mofetil, azathioprine, and dupilumab, can be used. ^[1,3]

A literature review revealed that all 11 ³ patients with recalcitrant prurigo ³ nodularis treated with dupilumab had a good or perfect response to treatment and tolerated treatment well. Dupilumab seems to be a safe but costly alternative for the therapy of refractory PN ³ patients ^[12]. In our patient, a complete response to dupilumab treatment was obtained within 4 months, which is consistent with the patients previously reported in the literature.

It has been shown that patients with atopic dermatitis-related PN respond more slowly to treatment than patients with non-atopic dermatitis-related PN ^[6]. Although our patient had atopic dermatitis-related PN, she responded very well to the treatment in a short period of 4 months, along with a significant decrease in very high IgE values. It was not possible to comment on whether the dramatic decrease in IgE values was due to dupilumab treatment or whether it was due to the discontinuation of omalizumab treatment.

As a result, complete remission was observed in our patient in a short time after dupilumab treatment. No side effects were observed in the follow-up of dupilumab treatment. No itching was observed in the patient's follow-up. Significant improvements in sleep and quality of life were observed. Based on our case, it can be predicted that dupilumab treatment ⁴ is an effective and safe treatment for patients with refractory generalized PN.

PN is a disease that negatively affects the quality of life of patients due to severe itching. Patients often receive limited benefit from first-line treatments such as topical treatments and phototherapy and require systemic therapy. Dupilumab treatment stands out as an effective and safe systemic treatment agent among existing systemic treatments. There are few cases of PN treated with dupilumab in

the literature, so more studies are needed to evaluate its efficacy. We present our case of generalized PN, in which we had a dramatic response with dupilumab.

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