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LETTER

Severe pemphigoid nodularis successfully treated with dupilumab

To the Editor,

Pemphigoid nodularis (PN) is a variant of bullous pemphigoid (BP) associating clinical features of prurigo and an immunological profile of BP.[1] We present a case of PN successfully treated with dupilumab.

A 76-year-old female patient with a history of hypertension, diabetes, obesity, and atrial fibrillation consulted with a 1-month history of a pruritic eruption. Clinical examination revealed multiple excoriations, severe pruritus (numerical scale of 7/10), erythematous papulonodular lesions of the trunk and extremities involving 15% of the body surface area, and dermographism (Figure 1A,B). The physician's global assessment score was 3/5. Complete blood count showed lymphocytosis (5.0 x 10^9/L) and immunophenotyping revealed a marginal zone B-cell lymphoma. Total immunoglobulin E levels were increased (149 KIU/L). Skin histology was nonspecific, with no blister formation and a discrete lymphohistiocytic infiltrate. Direct immunofluorescence (DIF) showed linear deposition of IgG and complement along the basement membrane zone (Figure 1D). Indirect immunofluorescence (IIF) on salt-split skin showed linear deposition of IgG on the blister roof (Figure 1E). ELISA (Euroimmun®) for anti-BP180NC16A and anti-BP230 antibodies and immunoblotting on normal human epidermal extract were negative. PN was diagnosed. Treatment with 30 g/day of clobetasol propionate 0.05% allowed disease control after a month. However, recurrences occurred systematically during the gradual tapering of corticosteroids and steroid-induced purpura started to develop. Due to her comorbidities and the ongoing Covid-19 pandemic, conventional systemic agents were not proposed. Dupilumab 600 mg subcutaneously followed by 300 mg/2 weeks was introduced off-label leading to a complete resolution of pruritus and skin lesions and no adverse events in 4 months (Figure 1C) and no recurrence in 6 months of follow-up.

PN affects predominantly elderly, female patients. At the onset, PN presents as pruritic, papulonodular, prurigo-like lesions. Blisters can be absent or appear later during PN course.[1] Classic histopathological features of BP such as eosinophilic infiltration can be absent.[1] ELISA anti-BP180NC16A and anti-BP230 is positive in only 57% and 52% of cases of non-bullous variants of BP, respectively.[2] When ELISA is negative, antibodies directed against the ectodomain of BP180, LAD1and LABD97, or against p200 can be identified. Our immunoblotting technique cannot detect anti-LAD1 and anti-LABD97 antibodies and was performed on epidermal extract based on the IIF results.

Dupilumab is a monoclonal antibody binding to interleukin (IL)-4 receptor α. Increased levels of IL-4 and IL-13 have been identified in the sera and skin of BP patients.[3,4] In clinical practice, the Th2 axis has been successfully targeted in BP with dupilumab.[5,6] Abdat et al reported complete clearance in 7 out of 13 patients with refractory BP treated with dupilumab, with a median time-to-response of 2 months and an excellent safety profile.[5] Takamura et al showed that, in a BP patient, clinical response to dupilumab was associated with a decrease in the initially elevated levels of circulating IL-4-, IL-13-producing CD4+ cells suggesting that dupilumab's efficacy in BP could be related to the direct suppression of these Th2 cells.[4]

Dupilumab could act on other components of PN such as pruritus and nodule formation. Chronic itch is a complex neuroimmunological process dependent on neuronal IL-4Ra signaling.[7] IL-4 and IL-13 activate directly itch sensory neurons in mice and humans.[7] A recent study revealed similarities between PN and prurigo in the expression patterns of a6- and b4-integrin, suggesting a similar epidermal hyperproliferative condition.[8] Thus, by analogy to prurigo, IL-4 could be implicated in nodule formation in PN by stimulating keratinocyte proliferation.[9]

We report a case of PN successfully treated with dupilumab. IL-4 and IL-13 inhibition could be a promising therapeutic option in different clinical types of bullous pemphigoid.

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Dr. Jendoubi Fatma and Dr. Konstantinou Maria Polina have been responsible for drafting the manuscript, have made substantial contributions to conception and design, acquisition of data, analysis, and interpretation of data; and have given final approval of the version to be published. Dr. Bost Chloe, Dr. Tournier Emilie, Dr. Paul Carle have made substantial contributions to the analysis and interpretation of data; have been involved in revising critically the manuscript for important intellectual content. All authors have given final approval of the version to be published; have participated sufficiently in the work to take public responsibility for appropriate portions of the content, and have agreed to be accountable for all aspects of the work in

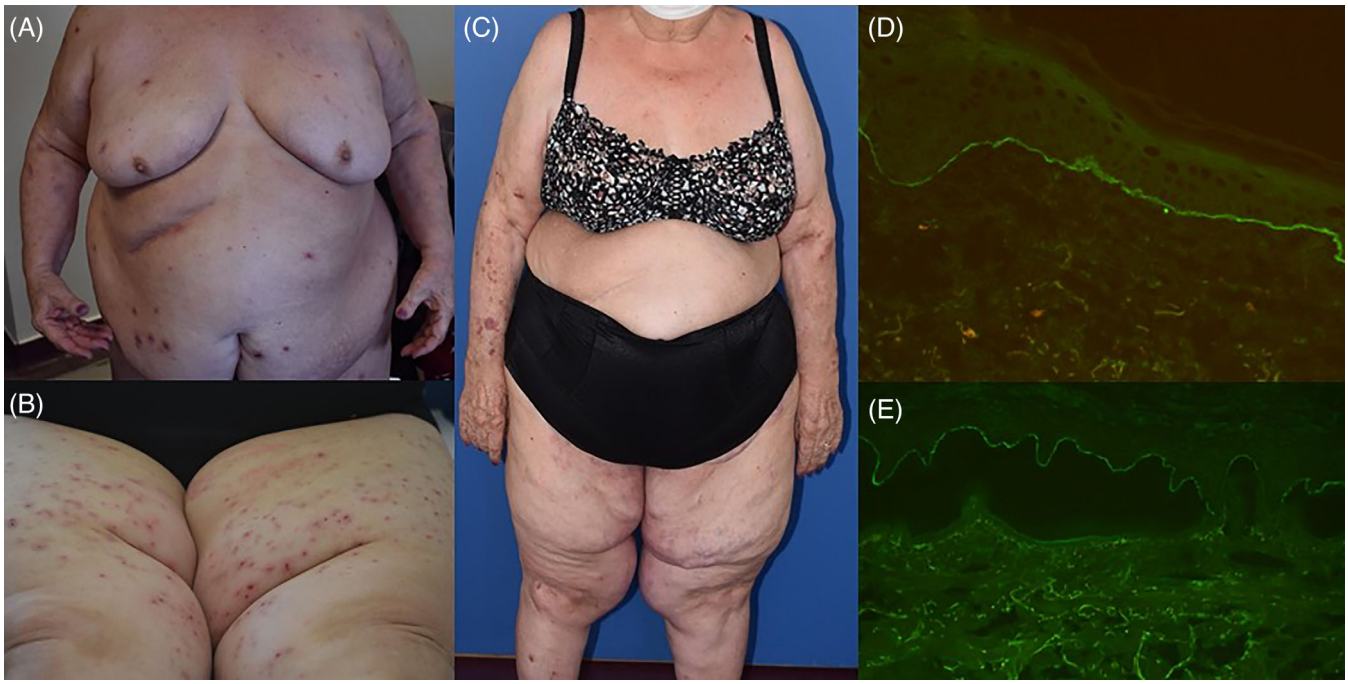

FIGURE 1 (A, B) Pruritic, erythematous, excoriated, papulonodular lesions of the abdomen, upper arms and thighs at initial presentation. (C) Complete response after 4 months of treatment with dupilumab. (D) Direct immunofluorescence showing a linear deposition of IgG and complement at the basement membrane zone. (E) Indirect immunofluorescence on salt-split skin showing linear deposition of IgG antibodies localized on the blister roof.

ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The patient in this manuscript has given written informed consent to the publication of his case details.

CONFLICT OF INTEREST

Jendoubi Fatma has served as a consultant with honoraria for Sanofi Genzyme, Konstantinou Maria Polina and PAUL Carle have served as investigators for Sanofi Genzyme.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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