Exacerbation of clinical manifestations of bullous pemphigoid after treatment with dupilumab

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Dear Editor, Dupilumab is the first approved interleukin (IL)-4Rα inhibitor for the treatment of atopic dermatitis. It is considered an effective and safe drug. When treating atopic dermatitis, the most frequent adverse events reported in adults are conjunctivitis and oral herpes zoster with no significant differences when treating special populations (e.g. history of cancer, severe kidney failure, viral hepatitis, neurological diseases, acquired immunodeficiency syndrome and transplanted recipients) regarding effectiveness and safety.[1] Real-life data seem to confirm the significant improvement in Eczema Area Severity Index score, Pruritus numerical rating scale, Sleep numerical rating scale and Children's Dermatology Life Quality Index scores with a good safety profile also seen in children aged 6–11 years with moderate-to-severe atopic dermatitis, for which dupilumab was recently approved.[2]

Recently, it has been proposed that its use could be extended to a broad range of dermatological conditions driven by type 2 inflammation including bullous pemphigoid. The recruitment process for phase II and III clinical trials (NCT05649579; NCT04206553) is currently underway. Here we report the case of a man diagnosed with bullous pemphigoid who was given dupilumab for compassionate use in another country and who experienced an unexpected adverse event.

A 70-year-old man came to our clinic in June 2023 for an acute exacerbation of bullous pemphigoid. The clinical picture was characterized by bullous lesions on an erythematous–violaceous background affecting the whole body with a predilection for the back, buttocks and the extremities while partially sparing the head–neck region (Figure 1).

The Bullous Pemphigoid Disease Area Index score was 155. The patient was visibly suffering and required admission to hospital. Hypereosinophilia (29.5%, normal value range 1–4%, >1500 cells μL^{-1}, normal value range 50–500 cells μL^{-1}) and electrolytes imbalances (K^+ 2.9 mmol L^{-1}, normal value range 3.6–5.2 mmol L^{-1}; Na^+ 130 mmol L^{-1}, normal value range 135–145 mmol L^{-1}) along with impaired renal functionality (blood creatinine 2.15 mg dL^{-1}, normal value range 0.6–1.3 mg dL^{-1}) were detected.

These alterations probably contributed to the occurrence a few days later of an anterior heart attack, successfully treated. The patient had multiple comorbidities along with ischaemic heart disease, chronic obstructive pulmonary disease and diabetes. The diagnosis of bullous pemphigoid was made in 2022 in Thailand, where he was living at the time. A causative relationship with linagliptin, which he was being treated with for his diabetes, was suspected and drug treatment was stopped. Oral corticosteroids and cyclophosphamide were then introduced with little benefit. For this reason, before returning to Italy, dupilumab was started.

The patient was given an induction dose (600 mg) and then a subsequent dose of the drug (300 mg) 2 weeks later. A week after the second dose, major worsening of the pre-existing bullous pemphigoid was observed. As a result of the close temporal relationship between the two events, a causative role was suspected and dupilumab treatment was interrupted. Systemic corticosteroids were introduced (0.75 mg kg^{-1} daily) with a slowly tapering schedule. Doxycycline 200 mg per day was started in combination with nicotinamide 2 g per day. To our knowledge, this may be the first described case of a patient with bullous pemphigoid exacerbated by dupilumab.

In recent years, an increasing number of paradoxical cutaneous reactions to dupilumab, including psoriasis and psoriasiform manifestations, have been described. The suggested pathogenetic mechanism is that IL-4/IL-13 blockers may lead to the disinhibition of the IL-23/IL-17 pathway.[3] In a similar manner, the blockage of the T helper (Th)1 and Th17 pathways with IL-23/IL-17 blockers may lead to the occurrence of Th2-mediated diseases observed, such as atopic dermatitis and eczematous-like eruptions.[4] These pathogenetic mechanisms do not explain what might have happened in our patient. Regarding the use of dupilumab in bullous pemphigoid, the most common adverse events reported until now have been infections and hypereosinophilia ($>$ 1500 cells μL^{-1}).[5] It has been suggested that blockade of the IL-4/IL-13 pathway may induce hypereosinophilia from the reduction of eosinophil migration.[6] It may be of interest considering whether the hypereosinophilia observed in our patient, and occurring in 4–25% of patients treated with dupilumab,[6] may have caused an exacerbation of bullous pemphigoid. In fact, although it is transient in most patients, persistent cases of patients with symptomatic hypereosinophilia have been reported, including the worsening of asthma symptoms.[7]

In the patient's case reported here, the start of the treatment with dupilumab and the related hypereosinophilia occurred in association with an uncontrolled phase of bullous pemphigoid. Thus, future evaluations concerning this potential adverse event should consider both hypereosinophilia and bullous pemphigoid disease activity at the time of the start of the treatment.

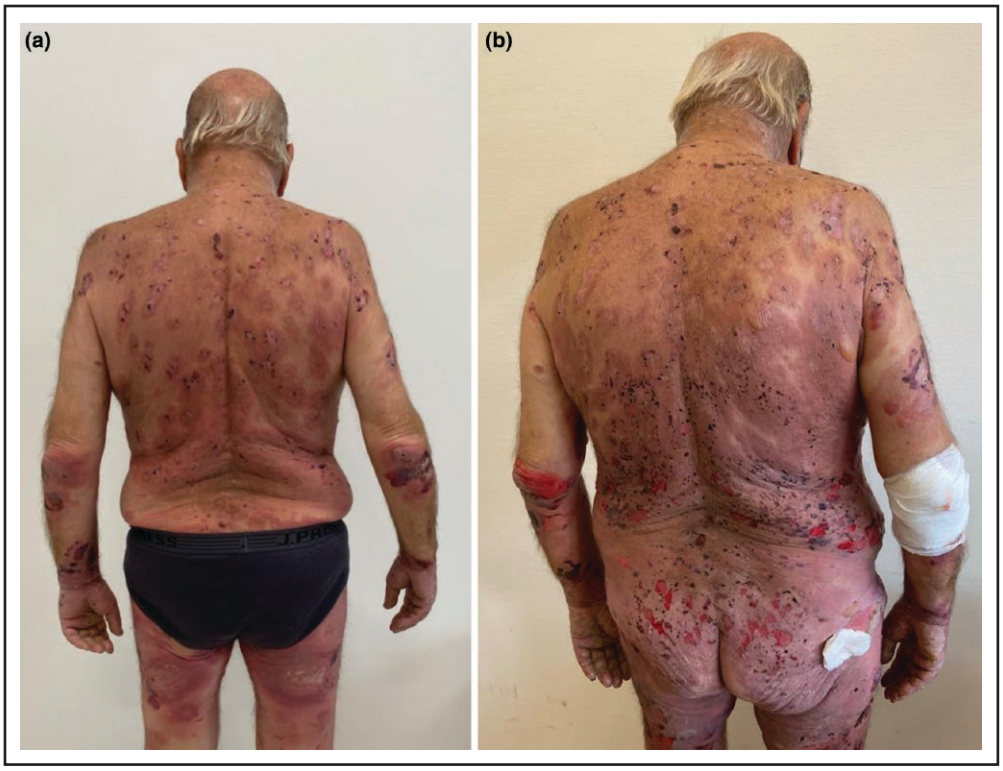

Figure 1 Clinical pictures of the patient affected by bullous pemphigoid showing (a) the involvement of the trunk and the limbs during the induction phase of dupilumab and (b) the rapid deterioration of his conditions after the subsequent dose of the drug 2 weeks later.

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