SHORT COMMUNICATION

Bullous Delayed Pressure Urticaria Responding to Omalizumab

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Accepted Aug 19, 2015; Epub ahead of print Aug 25, 2015

Delayed pressure urticaria (DPU) has been reported to occur in up to 37% of patients with chronic spontaneous urticaria (CSU), but frequently goes unrecognized on account of its delayed onset (1). Lesions are typically painful and persist for up to 72 h. DPU has been shown to cause significantly greater impairment in quality of life than other forms of urticaria (2). The pathogenesis is unclear, but, unlike CSU, eosinophils are thought to play an important pathophysiological role. DPU is generally unresponsive to high-dose antihistamines, and medicaments such as dapsone and corticosteroids are neither consistently effective nor, in the latter case, suited for long-term therapy.

While there are reports of omalizumab (anti-IgE) having a favourable effect on DPU (3, 4) a recent case responded neither to omalizumab nor to tumour necrosis factor (TNF)-α blockade with adalimumab (5). With regard to TNF-α blockade, a case of DPU responding to etanercept without relapse on switching to infliximab has been published (6). In contrast to DPU, bullous DPU is an extremely rare entity, with only 2 cases published to date (7–9). We describe here a rare case of bullous DPU with complete response to omalizumab treatment.

CASE REPORT

A 61-year-old man presented to our department with a 1-year history of recurrent, large, painful swellings following local pressure, associated with general malaise. Swellings occurred on the buttocks, thighs and volar forearms approximately 4–6 h after prolonged sitting or leaning on a hard surface and were repeatedly accompanied by superficial vesicles and blisters that appeared overnight. They resolved over 72 h with minimal scaling. The frequency of blistering was approximately once every 6–8 weeks. Swellings arose with a delay of 4–6 h and blisters appeared somewhat later, between 12 and 24 h after the stimulus. Swellings interfered with activities of daily living and resulted in frequent sick leave. Treatment with cetirizine, and subsequently rupatadine, both at 20 mg/day, had no effect. The patient was otherwise well apart from allergic rhinitis to grass pollen.

Clinical examination revealed large erythematous swellings over areas subject to pressure. Superficial grouped vesicles and blisters filled with serous fluid were noted over a gluteal swelling and on the anterior thigh (Fig. 1).

Full blood count, renal and liver profiles, serum electrophoresis and complement factors were within normal limits. C-reactive protein (CRP) and total IgE were elevated, at 41mg/l and 179 kU/l, respectively, with specific IgE to grass pollen. A skin biopsy from lesional skin on the thigh showed an intra-epidermal blister with an eosinophil-rich dermal inflammatory cell infiltrate (Fig. S1[1]). Direct immunofluorescence of perilesional skin was unremarkable, as were indirect immunofluorescence on salt-split skin, BP-180- and 230-enzyme-linked immunoassays (ELISAs). A pressure challenge with a 10 kg weight, as described previously (9), resulted in a painful erythematous swelling on the affected shoulder at 6 h, persisting for 48 h. Based on these findings, a diagnosis of bullous DPU was made. Step-up treatment with high-dose fexofenadine, 540 mg daily, in combination with montelukast, 10 mg daily, proved ineffective. The patients' disease severity and psychological distress called for a treatment with rapid onset of action. A trial of 300 mg omalizumab was commenced and within 5 days the patient was entirely symptom free. Treatment was continued at this dose once monthly for a half-year period. During this time, neither blisters, nor swellings occurred. Within 8 weeks of discontinuing treatment his symptoms relapsed. Omalizumab was then reintroduced with good effect and 6 months later the patient continues to be symptom free on omalizumab 300 mg given every 4–6 weeks on demand.

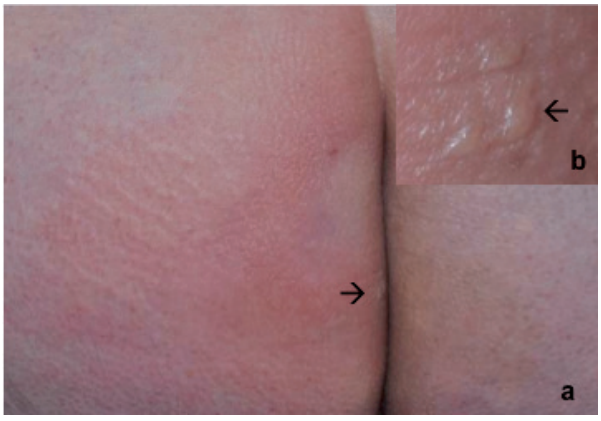

Fig. 1. (a) Erythematous swelling due to delayed pressure urticaria on the left buttock. The arrow shows superficial blistering. (b) Inset showing the blister in close-up.

DISCUSSION

The role of mast cells and mast cell degranulation in DPU is unclear. Histopathological studies document deposition of extracellular neutrophil elastase, but subsequent infiltration with eosinophils and deposition of eosinophil major basic protein appears to be the dominant feature of DPU (10, 11). In early lesions, there is increased expression of E-selectin, vascular adhesion molecule-1 and intercellular adhesion molecule-1 (12, 13), which are responsible for recruiting neutrophils, eosinophils and lymphocytes to the dermis. In addition, increased lesional levels of IL-3 and TNF-α have been detected (14), as has

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2224

IL-6 in suction blisters of DPU lesions (15). The latter is known to co-elute with eosinophil granule proteins, such as major basic protein, on eosinophil degranulation (16).

High numbers of eosinophil cationic protein-releasing eosinophils, together with IL-5 expressing $CD4^+$ and $CD8^+$ T cells were demonstrated recently in a case of bullous DPU (7). Subsequently, large amounts of eosinophil-derived DNA, in association with granule proteins, so-called eosinophil extracellular traps (EET), were detected in lesions of the same case (8). EET are thought to play a role in bacterial defence mechanisms, but also occur in a variety of inflammatory and autoimmune skin diseases. The proportion of EET-releasing eosinophils in bullous DPU was reported to be far greater than in other inflammatory skin disorders, such as Wells syndrome or bullous pemphigoid, and they were entirely absent in CSU (17). It has been proposed that eosinophils, and persisting high tissue concentrations of eosinophil granule proteins in the context of EET may be responsible for blister formation and the prolonged duration of DPU lesions (8).

The efficacy of omalizumab in CSU is based on increased mast cell stability via down-regulation of membrane-bound FcεRI and subsequent cytokine down-regulation. Histological findings in DPU have been likened to late-phase IgE-mediated reactions. Based on data from patients with asthma, treatment with omalizumab resulted in a marked reduction in tissue eosinophilia, but no significant reduction in FcεRII-positive staining cells (18), suggesting that binding of IgE to this receptor is not inhibited by omalizumab. Omalizumab has also been associated with induction of eosinophil apoptosis (19). The case presented here shows omalizumab to be highly effective in the treatment of bullous DPU. The mechanism by which omalizumab leads to improvement in bullous DPU is likely to involve direct inhibition of cutaneous mast cells, resulting in decreased production of eosinophil chemoattractants and activators of eosinophil degranulation.

Conflicts of interest and funding: TJ received research grants and honoraria for serving on the speaker bureau or advisory boards of Novartis GmbH, Nürnberg. SM has received honoraria for serving as an *ad hoc* advisor to Novartis GmbH, Nürnberg. The authors declare that there are no further conflicts of interest.

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