

Clinical Letter

Delayed bullous pressure urticaria: the puzzling role of eosinophils

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Dear Editors,

Delayed bullous pressure urticaria (DBPU) is a rare variant of inducible urticaria characterized by painful deep swellings and blistering following the application of continuous mechanical pressure. It has been suggested that mast cells play a role in the initiation of DBPU, but antihistamines are frequently ineffective and swellings in DBPU follow hours after mechanical pressure [1, 2]. Furthermore, DBPU seems to resemble (clinically and histologically) an IgE-mediated late phase reaction [1, 3, 4].

We investigated levels of eosinophilic cationic protein (ECP) and tryptase in suction blister fluid from a 74-year old patient with DBPU before and five months after introduction of omalizumab. Apart from insulin-dependent diabetes, the patient suffered from coronary heart disease, hypertension depression and prostate hyperplasia. His regular medication comprised clopidogrel, mirtazapine, tamsulosin, irbesartan and hydrochlorothiazide. Clinical diagnosis of DBPU was based on pressure challenge after exclusion of auto-immune bullous diseases. The patient had proved to be refractory to treatment with antihistamines, dapsone and cyclosporine. Before application of omalizumab at four-week intervals, only corticosteroid pulse therapy had led to transient absence of symptoms. During complete remission due to treatment with omalizumab at four-week intervals, the patient developed new (non-bullous) plaques in response to pressure at prolonged treatment intervals (> 4 weeks).

Pressure was applied by suspending a weight of 7 kg from a strap 3 cm in width from adjacent areas of the patient's shoulder for 15 minutes, on one evening and on the next morning. Directly after the second pressure test, a sterile, 8-well skin suction chamber was applied to the shoulder, with four wells covering the pressure test area from 12 hours ago (lesional skin) and four wells on the area tested one hour before (prelesional skin). An urticarial plaque developed in the test area 12 hours after pressure (lesional skin), but not in the adjacent area one hour after pressure (prelesional skin). A vacuum of 350 mmHg was applied for two hours with an aspirator pump. Blister formation was elicited with a heating pad at a temperature of 43°C wrapped over the suction chamber (Figure 1). After blisters had developed, the blister fluid was aspirated with a syringe (needle diameter 27G). The fluid

was centrifuged at 300 g for 5 min and the supernatant was then stored at -80°C until analysis with the ImmunoCAPTM fluorescence enzyme immunoassay (Thermo Fisher Scientific, Freiburg, Germany). Samples were taken before and five months after injection of 300 mg omalizumab. The patient gave his informed consent for this case study. The study was approved by the clinical conference of the Department of Dermatology and Allergy.

Before the introduction of omalizumab ($t = 0$), tissue levels of ECP were high in the suction blister fluid during the initial phases of the disease and then gradually decreased, while tryptase levels tended to increase with time during disease development. Levels of ECP were higher in blister fluid from prelesional skin than in blister fluid from lesional skin (Table 1). However, higher activity of tryptase was seen in blister fluid from lesional skin than in blister fluid from

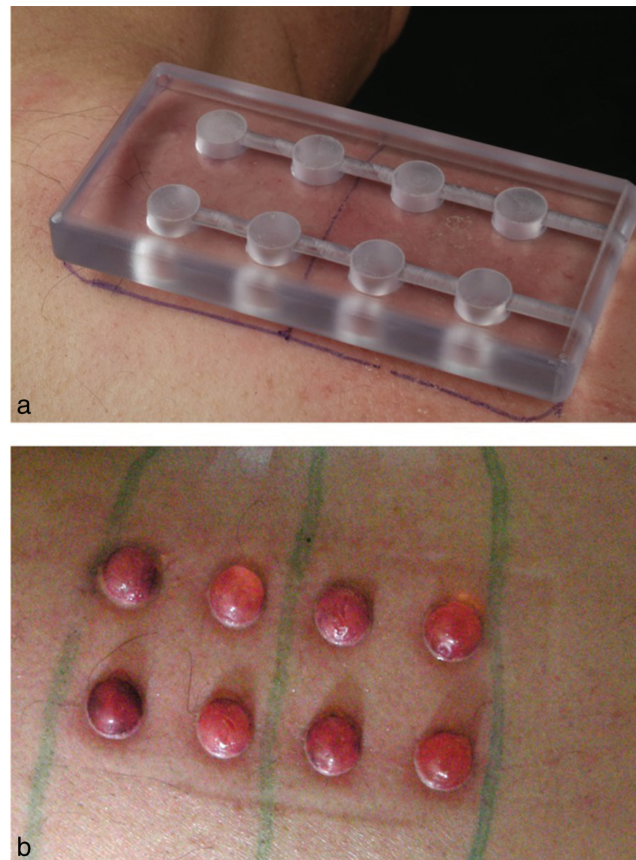


Figure 1 Eight-well skin suction chamber on the pressure-exposed shoulder of a patient with delayed bullous pressure urticaria (DBPU). Four wells covering the pressure test area from twelve hours before (lesional skin) and four wells over the area tested one hour previously (prelesional skin) (a). Blister formation after applying a vacuum of 350 mmHg at a temperature of 43°C for two hours (b).

Table 1 Levels of eosinophilic cationic protein (ECP) and mast cell tryptase in blister fluid.

	Before Omalizumab (t = 0 months)		After Omalizumab (t = 5 months)	
	Prelesional skin	Lesional skin	Prelesional skin	Lesional skin
ECP	185.90 µl	38.23 µl	<2.00 µl	<2.00 µl
Tryptase	21.08 µl	86.57 µl	25.56 µl	22.88 µl

prelesional skin. Interestingly, after introduction of omalizumab (t = 5), ECP levels were below the detection threshold in blister fluid of both early and late phase lesions. However, tryptase remained elevated at a constant level.

Delayed bullous pressure urticaria may be regarded as the most severe form of delayed pressure urticaria (DPU). For the latter, previous studies have already shown an important pathophysiological role of eosinophils [4], which was recently substantiated by observations in DBPU: persistent tissue accumulation of ECP seems to promote pronounced local inflammation at sites of mechanical pressure, which subsequently result in local swelling and blistering [1, 5]. Previous histological examinations in DBPU patients showed eosinophil infiltration of the superficial and deep dermis together with epidermal blisters filled with eosinophils [1, 3, 5]. In contrast to other forms of urticaria, in DBPU eosinophils seem to form extracellular traps (ETs) upon activation. Extracellular traps represent complexes of released cellular DNA and ECP that result in extensive and prolonged tissue inflammation by exerting direct cytotoxic effects [6]. According to this rationale, blistering may be regarded as a result of pronounced and locally restricted tissue injury [1, 5, 6].

Our findings suggest that enhanced eosinophil activity initiates DBPU, since elevations of ECP preceded increases of tryptase. In our patient, introduction of omalizumab already led to complete clinical remission after the first injection. In this context we observed a depletion of ECP but a constantly elevated tryptase level at both test intervals. Mast cells may only act as a promoting and maintaining factor for enhanced eosinophilic inflammation.

Delayed pressure urticaria and its bullous variant are usually unresponsive to antihistamines [3]. Montelukast, dapson, methotrexate and corticosteroids have been reported as alternative therapeutic options in individual cases [7].

Omalizumab has already been shown to be effective in chronic spontaneous urticaria, for some forms of physical urticaria and also in a single case of DBPU [3, 7–9]. There is evidence that omalizumab exerts an inhibitory effect on eosinophils by inducing apoptosis [10].

In summary, our study provides further evidence of a pivotal role for eosinophils in the pathogenesis of DBPU. Increased eosinophil cytotoxic activity seems to initiate

pronounced tissue inflammation with consequent swelling and blistering in response to mechanical pressure.

Conflict of interest

None.

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