Allergology International. 2014;63:495-497
DOI: 10.2332/allergolint.14-LE-0699

Dear Editor

Successful Treatment of a Bullous Urticaria with Omalizumab

Bullous form of urticaria is uncommon; there are only a few case reports in the literature. Bullous lesions can occur as a complication of spontaneous urticaria or delayed pressure urticaria. Despite many clinical and experimental researches in chronic urticaria, the etiopathogenesis of bullous urticaria is still unclear.[1-4] It is thought to result from mechanical pressure of the oedema in the dermis.[4] Treatment of bullous urticaria is a challenge; standard chronic urticaria treatment regimens with antihistamines were used with modest improvement in case report series.[1-4]

Omalizumab is a recombinant humanized, monoclonal anti-IgE antibody that binds specifically to circulating Ig-E molecules and has been approved for the treatment of asthma. However, recent studies suggest that omalizumab might play an important role in the treatment of other potentially Ig-E mediated disease such as atopic dermatitis and there is currently lots of data showing effective results of omalizumab in the management of chronic urticaria.[5-10] EAACI/GA2LEN/EDF/WAO management of urticaria guideline recommend the use of omalizumab for fourth level therapy.[11] Here we present a case with chronic bullous urticaria who was unresponsive to high dose antihistamines and glucocorticosteroids responded very well to omalizumab therapy.

A 76 year old man presented with large erythematous wheals on the different sites of the body. The wheals persisted up to one week and bullous lesions frequently formed on the surface of the wheals. He reported a 4 year history of spontaneous erythematous bullous wheals as well as recurrent attacks. Attacks were recurring every 2 weeks. He had no angioedema. He was receiving angiotensin-converting-enzyme inhibitors because of hypertension. There were many erythematous, edematous plaques with bulla formation on his back and abdomen which healed with crust formation (Fig. 1, 2). Dermographism was not seen. Laboratory findings included normal values for complete blood count with differential, comprehensive metabolic panel including antinuclear antibody, thyroid stimulating hormone level, C4 level, C1 inhibitor function and concentration. Total IgE level was 57 kU/L. Autologous serum skin test was positive. To verify the clinical diagnosis we performed a skin biopsy. Histological examination showed dermal edema with a perivascular mixed infiltrate, consisting of lymphocytes and eosinophils. Histopathological findings were also incuding loss of epidermis because of dermoepidermal separation with extravasated erythrocytes in dermis (Fig. 3). Direct immunofluorescent study was performed to rule out bullous pemphigoid that resulted with nonspecific findings. His signs and symptoms did not improve during administration of different non-sedating H_1-antihistamines, leukotrien antagonists or by increasing up to four-fold of the recommended dose. Emergency treatment with methyl prednisolone and short acting antihistamines did not provide a relief. He had hospitalisations every two weeks. He had no allergy related disease. After high dose corticosteroid therapy (1 mg/kg methyl prednisolone) partial regression was seen. He felt more depressed because of the major reduction in his quality of life. Because of the patient's unresponsive lesions to any treatment, 300 mg of omalizumab every 4 weeks was administered subcutaneously after obtaining written informed consent. His last episode of bullous lesions was seen 1 week before initiation of therapy and he remained free of urticaria during 1 year of omalizumab therapy. He had no longer developed any urticarial symptoms and he had no need of any urticaria treatment.

Bullous urticaria is a rare entity and it should be differentiated from bullous pemphigoid, bullous mastocytosis, insect bite reactions and contact dermatitis. Our patient has been in follow up for two years for recurrent urticaria and two biopsy specimens has been taken showing dermal oedema with eosinophil infiltration. Mastocytosis is characterised by mast cell infiltration in the dermis and bullous pemphigoid is characterised by IgG deposition on the basement membrane in direct immunofluorescent studies. We ruled out mastocytosis by histopathological examination and bullous pemphigoid by direct immunofluorescent study in our patient. Insect bite reactions and contact dermatitis are also ruled out by the history.

The underlying mechanism of bullous urticaria is still unclear. There are cases of bullous delayed pressure urticaria which report that it is characterized by dermal infiltration of activated eosinophils within the lymphocytes.[3,4] Bullous urticaria is considered as an IgE mediated eosinophilic disorder. Therefore omalizumab may be effective in this group of urticaria by binding free IgE and thereby by reducing free IgE in the serum. The reduction in functional IgE leads to a more than 95% down regulation of the IgE receptor.[6] This is seen in mast cells, basophils and dendritic cells, and decreased antigen processing also results in less antigen presentation to Th_2 cells which leads to less stimulation of eosinophils by cytokines. As eosinophils are shown predominant cells in bullous urticaria, omalizumab could decrease the eosinophil accumulation in dermis and can suppress inflammation by this mechanism.

Histamine is known as a selective chemoattractant for eosinophils and pro-inflammatory responses is derived from the histamine-induced activation of eosino-

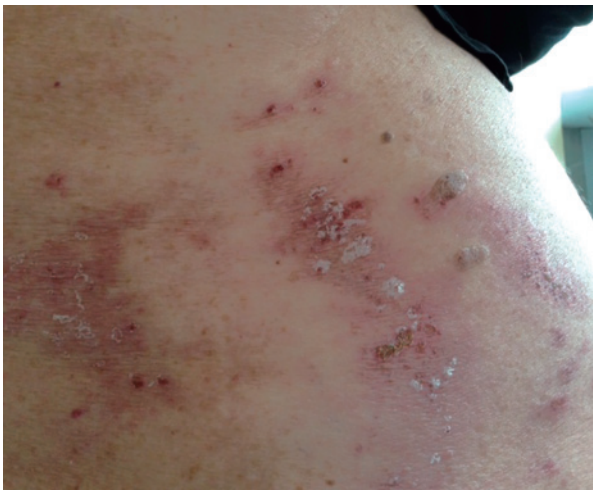

Fig. 1 Back of the patient: Crust formation after healing of bullous lesions.

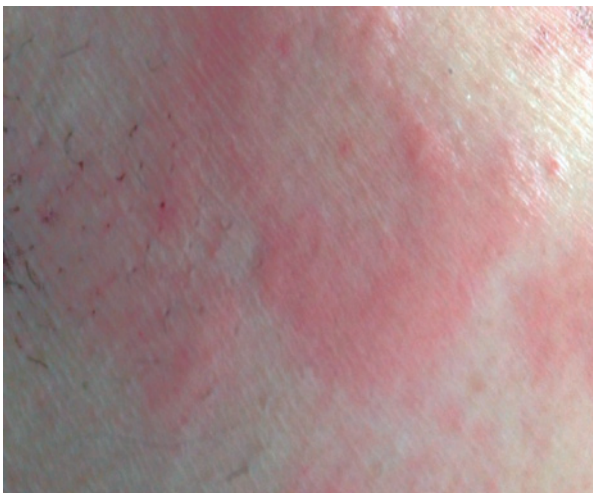

Fig. 2 Wheals on the axilla.

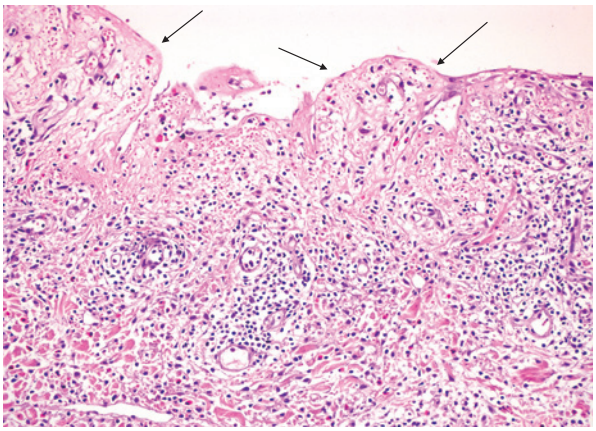

Fig. 3 Histopathological findings by H&E staining (×20). Loss of epidermis because of dermoepidermal separation (arrow), intracellular edema, extravasated erythrocytes, perivascular lymphocytic infiltration in dermis, and increased eosinophils in dermis.

phils. Increased numbers of mast cells, T cells and eosinophils in chronic urticaria can be related to many chemokines such as histamine. Antihistamines are effective in treating 45%-60% of patients with urticaria.[6] However our patient was refractory to antihistamines. Therefore in bullous urticaria we can assume that unknown mechanisms may be responsible for the pathogenesis.

Urticaria is a complex syndrome caused by both immune and non-immune mechanisms. In a subset of patients with chronic urticaria, mast cell degranulation is induced by autoantibodies directed against the α-subunit of the high-affinity IgE receptor, and/or the IgE.[6] Autologous serum skin test was positive in our patient and the bullous urticaria in our case could be autoreactive form of chronic urticaria.

Our patient neither has high values of total Ig-E nor other characteristics of atopy. Recently successful treatment of different forms of urticaria such as cholinergic urticaria, solar urticaria and cold urticaria has also been reported.[8-10] Because of the refractory lesions, omalizumab was administered. The dosage of the drug was calculated based on the IgE levels and bodyweight as it is suggested for severe asthma treatment. The initial intervals between the drug applications were every 4 weeks as recommended in Büyüköztürk S, *et al*..[7] Within a week after the first injection of omalizumab dramatic improvement was seen. The patient experienced major improvement in his quality of life because of the rapid resolution of his symptoms.

In conclusion, we report a rare case of urticaria treated with omalizumab successfully. This report shows that omalizumab may provide a rapid clinical response in patients with severe bullous chronic urticaria.

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Conflict of interest: No potential conflict of interest was disclosed.

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