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Successful treatment of mastocytic anaphylactic episodes with reduction of skin mast cells after anti-IgE therapy

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Key words

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Summary

Mastocytosis is a clonal disease derived from hematopoietic bone marrow progenitor cells. Clinical manifestations of the disease vary greatly depending on tissue involvement. Omalizumab is a recombinant humanized monoclonal anti-IgE antibody licensed in the treatment of asthma with increasing reports of clinical efficiency in other allergic diseases. We describe a case of a patient with mastocytosis responsive clinically and patho-physiologically after anti-IgE treatment.

Introduction

Mast cell disease or mastocytosis is a heterogeneous group of clinical disorders characterized by clonal proliferation and accumulation of mast cells in a variety of tissues. It appears in multiple forms, including urticaria pigmentosa (UP), mastocytomas, diffuse cutaneous mastocytosis (CM), telangiectasia macularis eruptiva perstans (TMEP), and systemic mastocytosis. Although mast cell disease is most commonly identified in the skin, involvement of the skeletal, hematopoietic, gastrointestinal, cardiopulmonary and central nervous systems may be seen (1). Depending on the extent of the disease, these disorders may present with symptoms resulting from mast cell degranulation including flushing, diarrhea, vomiting, cramping, syncope or anaphylaxis. Cutaneous mastocytosis in pediatric patients appears before their first birthday in 80% of affected individuals. Typically, it is not associated with systemic disease and only few of the patients continue later on and present with systemic symptomatology (2).

Case

We present a 25-year-old Caucasian with recurrent episodes of anaphylaxis for the last two years. The patient was first diagnosed in infancy with urticaria pigmentosa without any symptoms associated with systemic disease. As a child, he was never further investigated for mastocytosis. His clinical course remained benign until two years ago when he started experiencing one episode of anaphylaxis almost every month with flushing, hypotension, diarrhea and in some cases dyspnea. These episodes were increased in severity over the previous six months, during his military service. He identifies abrupt temperature changes, stress and alcohol consumption as triggering factors.

Clinical examination revealed numerous brownish-reddish pigmented macules (4 to 10 mm) and papules on the trunk and extremities which urticated in response to physical irritation (positive Darier's sign). Serum tryptase baseline levels were 15 ng/mL and skin biopsy revealed diffuse mast cell

infiltrates with >20 cells per power field. Bone marrow biopsy was not performed due to prolonged Activated Partial Thromboplastin Time (aPTT) without any other abnormal findings in blood tests. He has no other significant medical and family history background. However, an atopic predisposition was documented based on positive skin prick tests to parietaria pollen and elevated serum IgE levels [180KU/L], without any consistent seasonal symptoms from the upper or lower respiratory tract. Skin prick tests and RAST to food allergens were negative. Apart from the skin lesions and the prolonged aPTT, thorough physical examination did not reveal any abnormal findings and the rest of the blood tests were unremarkable.

The patient was initially started on combination treatment with antihistamines and H_2-antagonists. However, the clinical response over the next two months was poor, as he continued having anaphylactic episodes with the same frequency.

It is almost two years since he was started on omalizumab 300 mg monthly. The drug was well tolerated with no side-effects. Following the first dose of omalizumab the patient has been completely free of symptoms and a week after that he discontinued antihistamine therapy. To date, the patient has been on this therapy for 13 consecutive months. After the seventh month of treatment, we have been increasing the interval time between two consecutive doses by one week every two doses. At the moment, the patient receives 300 mg every seven weeks and he remains symptom free.

We also performed a skin biopsy on the 5th and 10th month of therapy (Fig. 1). Mast cells on the second biopsy (10^{th} month) were diminished compared to the first biopsy (5^{th} month), continuing the treatment with omalizumab (Fig. 2). The final infiltrate in the dermis appeared rather restricted using both hematoxylin-eosin and Giemsa staining. The latter (Fig. 3) distinguishes exclusively mast cells which on routine staining might resemble fibroblasts, pericytes or histiocytes. Using this staining, 70 mast cells/hpf (348 mast cells/mm^2) and 30 mast cells/hpf (147 mast cells/mm^2) were identified within the first and second skin biopsy specimens, respectively (microscope: Olympus BH-2, X40 field, diam. 0.5mm, surface 0.196mm^2). Serum IgE and tryptase levels measurements were repeated on the 5th and 10th month of treatment, changing from 280 KU/L to 341 KU/L and from 11 ng/mL to 8 ng/mL, respectively.

Discussion

Omalizumab conjugates with free serum IgE, reducing binding to the high affinity Fc RI on mast cells and ba-

Figure 1 - Cell infiltrate limited mostly to the upper half of the dermis before (A) and after (B) omalizumab. (x 25, Hematoxylin and Eosin (H-E) stain)

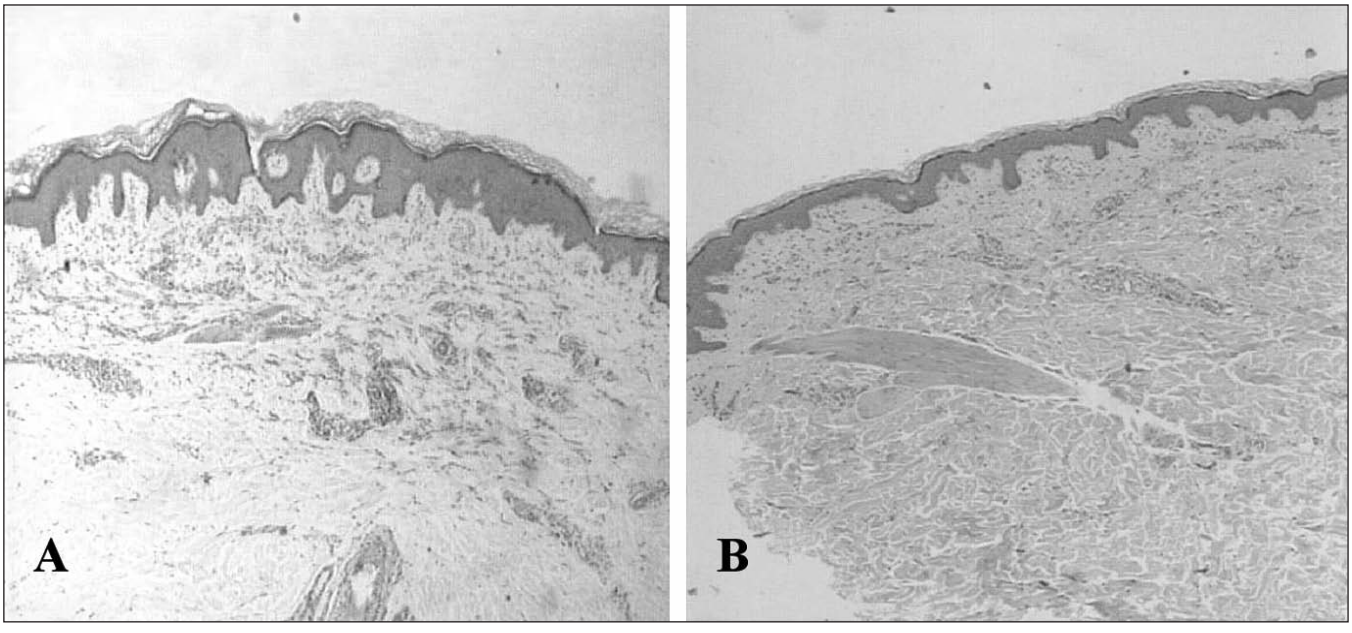


Figure 2 - Infiltrate of the dermis composed mostly of mast cells and few lymphocytes before (A) and after (B) omalizumab. The number of mast cells is diminished after treatment. (x 100, H-E stain)

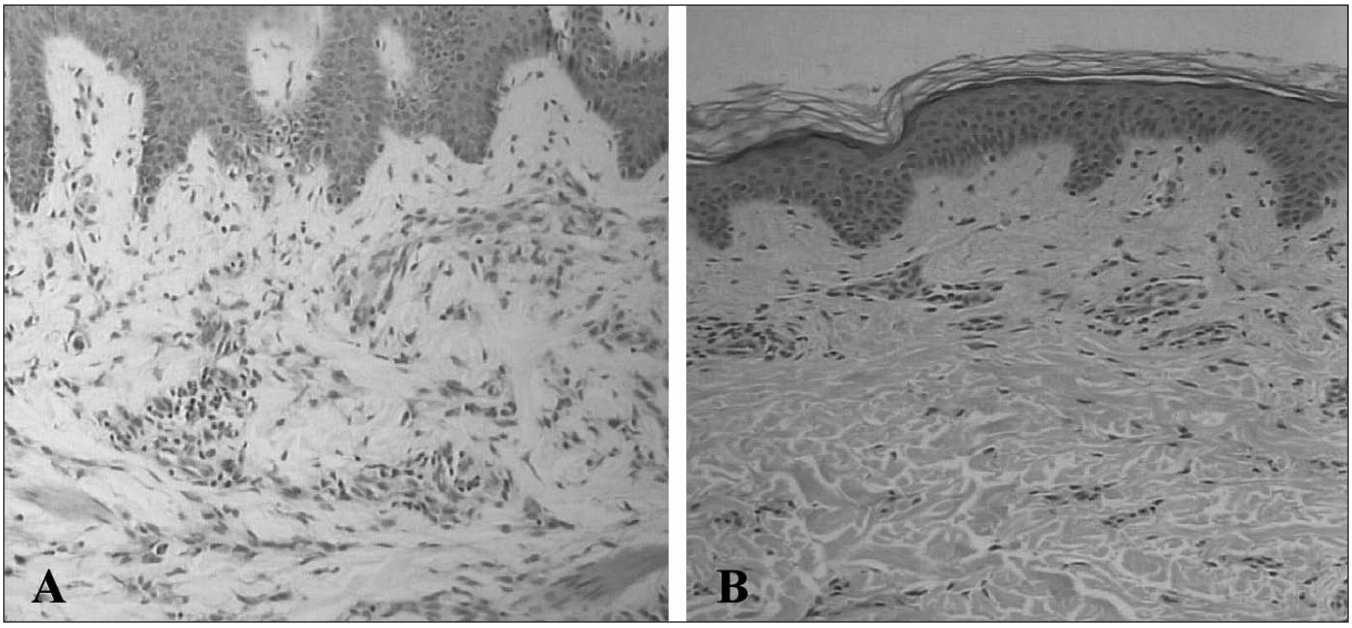
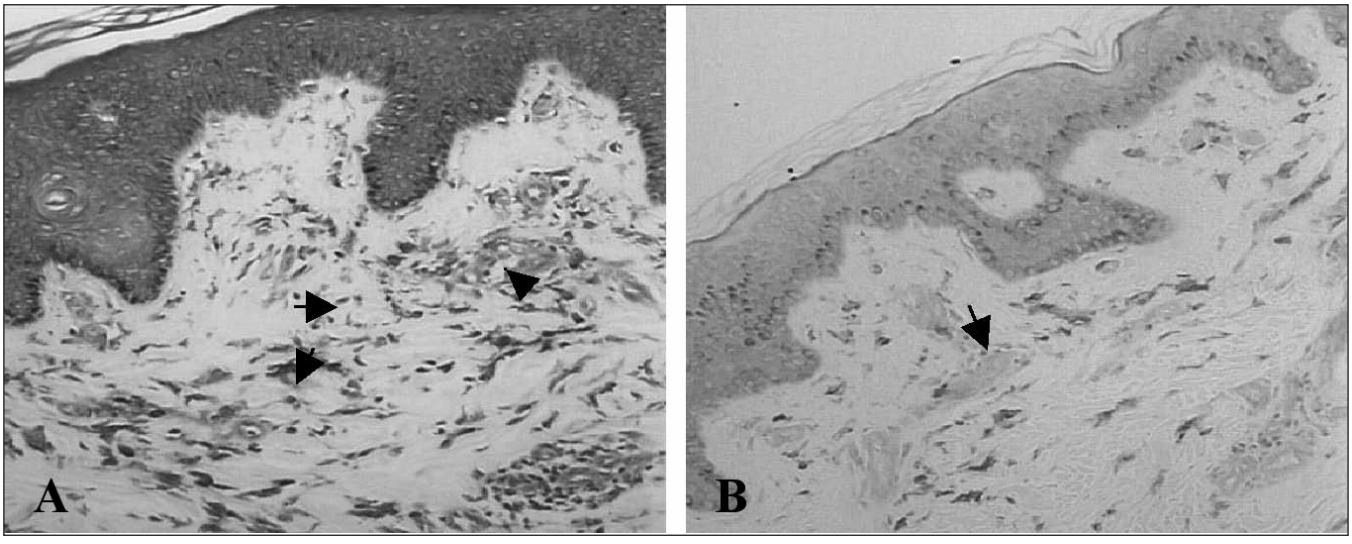


Figure 3 - Mast cells with their characteristics metachromatic granules before (A) and after (B) omalizumab. Most of the mast cells are spindle shaped and located around capillaries. An obvious reduction in their number after treatment is illustrated. (x 100, Giemsa stain)



sophils, thereby reducing the potential reactivity of these cells. Judging from our patient's clinical improvement with no kind of signs (papules were drastically diminished in size and number) or symptoms from the beginning of omalizumab, followed by an improved skin histology, this "stabilizing effect" on mast cells and at the same time the reduction of their infiltrate may be the major alleviating factors for our patient's clinical response. A hypothesis could be that the capture of free IgE could minimize the signal for further infiltration of the skin by mast cells in

the case of a mastocytic patient, but further immunohistologic research is anticipated on this field.

Indolent systemic mastocytosis is the most common type of mastocytosis in adult patients with generally good prognosis (3). Mast cell mediator release typically occurs through a non IgE– mediated mechanism at times triggered by physical stimuli, aspirin, stress, insects' bites and alcohol consumption. When clinical suspicion arises, serum tryptase is typically the appropriate first step in the diagnostic process. Of note, this clinical entity can still be diagnosed in the absence of elevated baseline tryptase levels in a small subset of patients (4). Our patient had clinical findings consistent with cutaneous mastocytosis and a positive skin biopsy, with typical infiltrates of mast cells, activated in many cases. Interestingly, regarding the activation and numbers of mast cells, there is no difference between the findings on a third skin biopsy (13th month of treatment) and the findings of the second biopsy (10th month of treatment). We assumed that, this was attributed to a plateau of the effect of omalizumab on mast cells, but as the patient was completely free of symptoms we decided not to increase the dose of omalizumab in order to study the effect on mast cells.

Taking under consideration the severity of the patient's anaphylactic symptoms, systemic antihistamines, corticosteroids and adrenaline treatment on acute episodes seemed a rather unsafe option in this case of mast cell disease. Based on recent publications that indicate an effective and protective role of omalizumab in mastocytosis (6, 7, 8, 9) we adopted this novel therapeutic approach for our patient. The role of omalizumab in mastocytosis treatment appears promising, as similar case reports in the medical literature advocate its therapeutic potential, but further research is needed on its mechanism of action.

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