



## SHORT COMMUNICATION

# Mastocytosis: A New Therapeutic Scenario with Omalizumab

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Mastocytosis includes multiple disorders characterized by proliferation and accumulation of clonal mast cells in many organs and tissues [1]. In pediatric population, it manifests with isolated skin mastocytoma, a red brown papule and nodule that may urticate (Darier's sign) or with multiple and diffuse similar lesions as observed in urticaria pigmentosa. Both condition usually remains localized to the skin and spontaneously regresses with age. In infants less than 3 year, it is also described a rare diffuse cutaneous mastocytosis with erythrodermia and bullous lesions; this skin disease is usually very scarring but still resolves spontaneously. Treatment is limited to high potency steroid creams, systemic antihistamine and in more severe cases PUVA [2].

In adults, mastocytosis can present with the so called "Telangiectasia eruptiva macularis perstans", with diffuse cutaneous red-brown macules and multiples telangiectasias. It is usually not associated to any systemic involvement

although affected subjects are considered at significant risk of development [3]. Systemic Mastocytosis (SM) is characterized by an indolent and persistent course with or without cutaneous involvement, usually urticaria pigmentosa, and overall mastocyte proliferation in multiple organs and tissues. Approximately 90% of adult patients with this form have a KIT D816V mutation on chromosome 4 q11-12, which is one of the criteria of WHO classification for making diagnosis of SM (Table 1), [4]. The mutation induces ligand-independent constitutive autophosphorylation of the KIT receptor, which leads to proliferation of mast cells and their accumulation in the body [5]. Some patients with mastocytosis can also present remarkable eosinophilia and they were found to carry interstitial deletion of chromosome 4q12 leading to juxtaposition of FIP1L1 and PDGFRA genes, a FIP1L1-PDGFRA rearrangement [6].

In SM, mastocyte infiltration is responsible of bone pain and osteoporosis, hepatosplenomegaly and lymphadenopathy. Leukemic forms are also possible as results of clonal expansion. However, in the majority of non-advanced cases, symptoms are due to degranulation

**Table 1:** Criteria of WHO for systemic mastocytosis [4]. Systemic mastocytosis can be diagnosed if one major and one minor or three minor criteria are met.

Major Criteria			
Multifocal, dense aggregates of mast cells (15 or more) in bone marrow sections and confirmed by tryptase immunohistochemistry or other special stains.			
Major Criteria			
1.	2.	3.	4.
More than 25% of the MC in the infiltrate in biopsy section have <i>atypical</i> morphology, or, of all the mast cells in the aspirate smear	Mast cells co-express CD117 with CD2 and/or CD25;	Detection of KIT D816V mutation in bone marrow, blood, or other extracutaneous organs	Serum total tryptase persistently > 20 ng/ml.

ulation and release of several mediators such as histamine, tryptase, chymase, carboxypeptidase A, heparin, prostaglandin D<sub>2</sub>, leukotrienes vascular endothelial growth factor, platelet-activating factor, multifunctional inflammatory cytokines and chemokines [7]. The most frequently reported symptoms are hence pruritus, flushing, diarrhoea, abdominal pain, musculoskeletal pain, vascular instability, headaches and neuropsychiatric symptoms. Other symptoms are related to mast cells specific IgE activation syndrome and include: Urticaria, angioedema, or more commonly nasal pruritus and congestion, wheezing, throat swelling. It is also well known that subjects with SM are at risk for severe, life-threatening reactions to Hymenoptera stings and also for reactions to venom immunotherapy [8]. As the clinical presentation of mastocytosis is heterogeneous, management is frequently shared by different specialists such as dermatologists, allergists, haematologists and paediatricians. Mastocytosis are treated by combination of H<sub>1</sub> and H<sub>2</sub> antihistamines, oral sodium cromoglycate and venom immunotherapy. In leukemic forms patients receive adequate treatment that can also include the C-Kit inhibitor imatinib. This medication is indicated in forms with wild type KIT and those with FIP1L1-PDGFR $\alpha$  rearrangement but not those with KIT D816V mutation [9].

Omalizumab is a recombinant humanized monoclonal IgG1 antibody, that targets circulating free IgE. By reducing their binding to the high-affinity IgE receptor (Fc $\epsilon$ RI) on mast cells and basophils, then stabilizing and diminishing the potential reactivity of these cells [10]. Recently, both the FDA and the EMA have approved omalizumab as add-on therapy for the treatment of Chronic Spontaneous Urticaria (CSU) in adults and adolescents (12 years of age and above) with inadequate response to H<sub>1</sub> antihistamine treatment [11]. There are some new interesting evidences that prove this medication to be effective in mastocytosis as an adjunctive treatment for both symptom improvement and reduction of anaphylactic episodes. Up to date, at least 11 studies relating to 15 patients with mastocytosis treated by omalizumab have been reported in medical literature [12-17] Almost all patients responded to 300 mg subcutaneously every 4 week, only one case was treated with a lower dose of 150 mg [18]. In all subjects remarkable reduction of gastrointestinal symptoms and anaphylactic episodes was reported. Furthermore, 3 patients with cutaneous mastocytosis responded well to the same 300 mg regime [19-21]. A very few side effects were noted in all cases. In one patient with SM who was treated to improve venom immunotherapy tolerability, debilitating fatigue and sleeping disturbances were observed. Length of treatment was variable from a few months up to 15 months [22].

Mastocytosis is in the group of non-IgE mediated disease responding to this new medication that include CSU and autoimmune urticaria, idiopathic angioede-

ma, nasal polyposis. Although the main mechanism of action is the interruption of the allergic cascade some other non IgE anti-inflammatory nonallergic effects are assumed. Reduction of free IgE levels downregulation of Fc $\epsilon$ RI expression on inflammatory cells and on dendritic cells, which may lead to a reduction in allergen presentation to T cells and attenuation in the Th<sub>2</sub>-mediated allergic pathway. In addition, omalizumab decreases mast-cell activation and sensitivity and reduces eosinophil infiltration and activation [23]. By depleting free IgE, receptor Fc $\epsilon$ RI on mast cells and basophils is downregulated to less than 5% within a few weeks to a few months. These cells are hence made insensitive to allergen stimulation and definitively they are stabilized and degranulation and release of inflammatory mediators is prevented [24]. All these effects can support the use of omalizumab and justify its clinical efficacy in other mastocyte sustained condition especially to prevent unexpected anaphylactic episodes. In summary, omalizumab is should be further investigated because of its efficacy in mastocytosis and large clinical trials on the long-term use and safety in this dermatologic condition are hence invited in the next future.

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