

Effective management of severe cutaneous mastocytosis in young children with omalizumab (Xolair[®])

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doi:10.1111/ced.13408

Summary

Omalizumab (Xolair[®]) is an anti-IgE monoclonal antibody, which may benefit adults with systemic mastocytosis. We report effective treatment with omalizumab in two toddlers with severe diffuse cutaneous mastocytosis. Our cases offer preliminary evidence to support the safe use of omalizumab in paediatric patients with cutaneous mastocytosis.

Mastocytosis is characterized by excessive accumulation of mast cells in tissues. Whereas cutaneous mastocytosis (CM) is limited to the skin, systemic mastocytosis (SM) involves extracutaneous organs.¹ Various triggers can lead to mast cell degranulation and give rise to problems such as urticaria, bullae formation, pruritus and/or gastrointestinal problems. Rarely, massive mediator release can cause life-threatening systemic presentations such as anaphylaxis.^{2,3} Despite the substantial morbidity associated with CM, little is known about the appropriate management of patients, particularly children. We describe two patients with paediatric-onset CM refractory to traditional therapies, who experienced substantial clinical improvement and steroid sparing with omalizumab.

Report

Patient 1 was a 2-year-old boy, who presented with a history of diffuse CM (Fig. 1a), which had been present since he was 3 months old. He experienced frequent

symptom flares associated with minimal trauma. Trypsin levels were elevated (45 µg/L; normal range 3.8–11.4 µg/L). Skin biopsy findings were consistent with CM, and a test for the KIT D816V mutation was negative. The patient was treated with topical sodium cromoglycate, hydroxyzine 10 mg daily, and ketotifen 1 mg twice daily, but continued to experience frequent flares triggered by respiratory infections/minor trauma, with blistering and secondary scarring requiring monthly oral steroids treatment.

Omalizumab (Xolair[®]; Genentech, San Francisco, CA, USA) 150 mg was administered subcutaneously monthly for 3 months. A modified weekly Mastocytosis Symptom Assessment Form¹ (MSAF) (Fig. 2a,b), completed prior to each injection revealed a decreased score with treatment. In addition, we assessed changes in the levels of two biomarkers related to mast cell activation: tryptase and CD63. Tryptase blood levels are considered to be a selective marker of mast cell activation,⁴ while tetraspanin (CD63) is a cell surface marker that is upregulated on degranulating basophils and mast cells, and can be measured by flow cytometry.^{5,6} There were no substantial changes in tryptase/CD63⁵ levels assessed at the same time (tryptase 40–35 µg/L and CD63 1.8–1.7%; normal range < 1.8%⁵). The patient was asymptomatic without disease flares within 1 month following treatment initiation.

Patient 2 was a 2-year-old boy, who presented with a history since birth of maculopapular polymorphic CM⁷

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Conflict of interest: the authors declare that they have no conflicts of interest.

Accepted for publication 3 August 2017



Figure 1 (a,b) Patient 1: (a) before and (b) after treatment with omalizumab. Patient 2: (a,b) before and (c) after treatment with omalizumab.

with frequent hives, often requiring systemic corticosteroids for symptom control (Fig. 1b). His tryptase levels ranged between 12 and 32 $\mu\text{g/L}$ (the latter during flares). Results of a bone marrow biopsy were normal and genetic testing was negative for KIT D816V mutation. Skin biopsy findings were consistent with the diagnosis of CM. Despite a high dose of antihistamines (hydroxysine 10 mg, desloratadine 5 mg and ketotifen 1 mg twice daily) and topical sodium cromolyn, the patient had frequent symptoms flares, which were treated with oral steroids and required weekly visits to the emergency department (ED).

One week after an initial dose of subcutaneous omalizumab 150 mg, the patient presented with a severe flare requiring an ED visit and oral steroid treatment. Two weeks later, he was started on 300 mg of omalizumab given subcutaneously every 2 weeks for a month. His MSAF score decreased (Fig. 2a,b), with relatively stable levels of tryptase and CD63 (range 12–4.6 $\mu\text{g/L}$ and 3.5–4.6%, respectively). Three months after beginning this treatment, the patient was symptom-free with no symptom flares, despite developing acute otitis media with perforation managed with amoxicillin.

(a)		7 Days Ago	6 Days Ago	5 Days Ago	4 Days Ago	3 Days Ago	2 Days Ago	1 Day Ago (Yesterday)	Comment
Symptoms: 0 (absent) to 10 (very severe)									
Itchy skin									
Dizziness									
Headache									
Fatigue (during the last week)									
Runny nose									
Shortness of breath									
Chest pain/palpitations									
Nausea/vomiting									
Diarrhea, stomach ache, cramps									
Bone pain/ muscle pain									
Concentration problems									
Depression, somberness									
Other, Describe:									
Attacks, with or without loss of consciousness.	Frequency per month:								
Flushing	Frequency per week:								
Rate with a number from 1 to 10 how much influence fatigue has had on:									
0 (no influence) to 10 (maximum influence)									
Activities (general)									
Mood/temper									
Mobility									
Chores									
Relationships									
Happiness									
Other, Describe:									

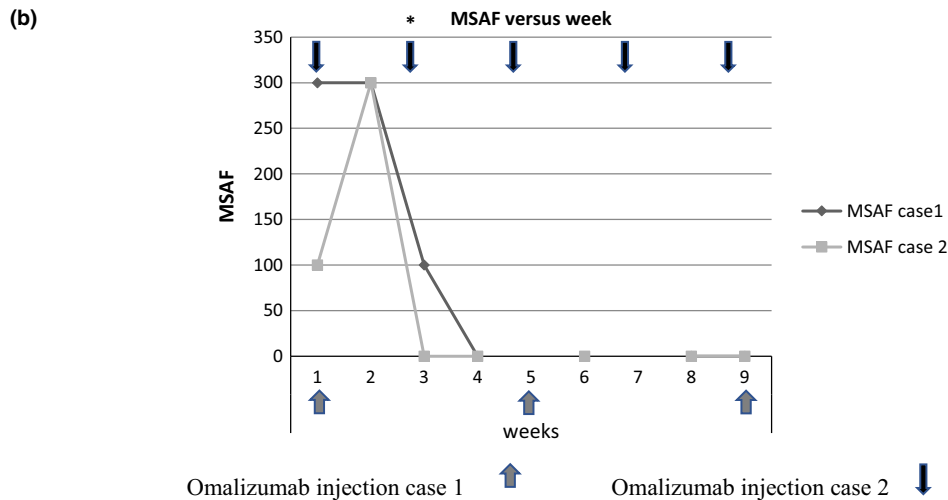


Figure 2 (a) Mastocytosis Symptom Assessment Form (MSAF). Each day is scored on a scale from 0 to 10, which provides a weekly range of 0–70 per symptom, with the total ranging from 0 to 1400. (b) MSAF scores for both patients; week 0 denotes the week prior to starting omalizumab. The first patient was given 150 mg/month, while the second was started on 150 mg but this was increased to 300 mg every 2 weeks. *Starting at week 3, all dosages were 300 mg every 2 weeks.

The treatment for paediatric CM is usually symptomatic, and consists mainly of administration of antihistamine and avoidance of precipitating factors. However, given that complete avoidance of triggers (e.g. respiratory infections and minor trauma) is challenging, especially in young children, and that more than a third of cases will have symptoms for at least 10 years,⁸ it is imperative to improve management by controlling symptoms.

Omalizumab is an IgG monoclonal antibody that inhibits IgE binding to high-affinity IgE receptors on mast cells and basophils. A few case reports have suggested the usefulness of omalizumab for adults with systemic mastocytosis,⁹ and for an adult¹⁰ and an adolescent¹¹ with CM, as well as a reduced risk of systemic reactions during venom immunotherapy in adults with CM.¹² However, no study has evaluated its use in paediatric cases of CM.

Our cases demonstrate the consistent and profound effect of omalizumab on CM flares in children and its important steroid-sparing effect. Given the stability of baseline tryptase and CD63 levels despite substantial improvement in flares and overall symptoms, we hypothesize that the major benefit of omalizumab relates to interference with mast cell mediator release, thereby improving symptom control. Our cases demonstrate that monitoring the clinical presentation is crucial in order to individualize effectively treatment with omalizumab. Large-scale randomized controlled trials are required to determine the optimal management protocol of omalizumab in these cases.

Learning points

- Cutaneous mastocytosis is a severe and challenging to manage disease in children.
- The MSAF is a useful clinical tool to follow control of symptoms in patients with cutaneous mastocytosis.
- Omalizumab may provide safe and effective management of severe cutaneous mastocytosis in children refractory to high-dose antihistamines, particularly in control of symptom flares.
- The dose of omalizumab should be individualized according to symptom control.

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