

## Omalizumab is effective in treating systemic mastocytosis in a nonatopic patient

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**Key words:** omalizumab; tryptase.

Systemic mastocytosis (SM), characterized by dysregulated accumulation of mast cells in extra-cutaneous tissues, can pose a serious clinical challenge.

Recurrent anaphylaxis and other symptoms including palpitations, flushing, urticaria, nausea and diarrhoea result from release of mast cell mediators

(1). Consensus classifications describe clinical variants ranging from indolent systemic mastocytosis to mast cell leukaemia (1). Mediator release may be because of intrinsic abnormalities of the

mast cells in mastocytosis rather than specific allergic sensitization.

We report a nonatopic patient with indolent SM, presenting with severe recurrent unprovoked anaphylaxis, who achieved an impressive clinical response to treatment with the humanized murine monoclonal anti-IgE biological, omalizumab. We also present data associating anti-IgE therapy with diminished basophil sensitivity suggesting that in this nonatopic patient the abnormal mast cell population is responsive to lowered IgE receptor stimulation.

A 54-year-old woman presented in September 2006 with severe anaphylaxis and cardiac arrest. Resuscitation was effective but she sustained hypoxic brain injury. There were no cutaneous stigmata of mastocytosis. Subsequent testing identified no allergic cause, and she was nonatopic. In September 2007, she had severe anaphylaxis while preparing a meal. Stress and occasional alcohol consumption were observed to trigger recurrent episodes of urticaria and anaphylaxis, suggesting SM.

In October 2007, baseline serum tryptase was elevated at 21.4 ng/ml (0–15 ng/ml), and her total IgE level was 9 kU/l (normal < 115). Bone marrow aspiration (BMA) demonstrated spindle-

shaped mast cells with co-expression of CD25 and CD2 and was positive by an allele-specific PCR assay for the *c-KIT* D816V mutation.

Recurrent episodes of anaphylaxis continued despite intensive anti-histamine therapy. In an effort to improve symptom control, cytoreductive treatment with cladribine was commenced in February 2008. Three cycles of chemotherapy were completed by June 2008. However, anaphylaxis with prolonged hypotension occurred in February, June and August 2008. Further treatment options were considered.

Two reports in the literature document omalizumab as an effective treatment for recurrent anaphylaxis in SM in three patients with allergic sensitizations (2, 3). Omalizumab complexes with free serum IgE, reducing binding to the high affinity FcεRI on mast cells and basophils, thereby reducing the potential reactivity of these cells. Down-regulation of FcεRI expression follows (4). Although nonatopic, the severity and frequency of unprovoked anaphylaxis in our patient prompted treatment with omalizumab.

From September 2008, she received omalizumab 150 mg subcutaneously fortnightly for the first month and then

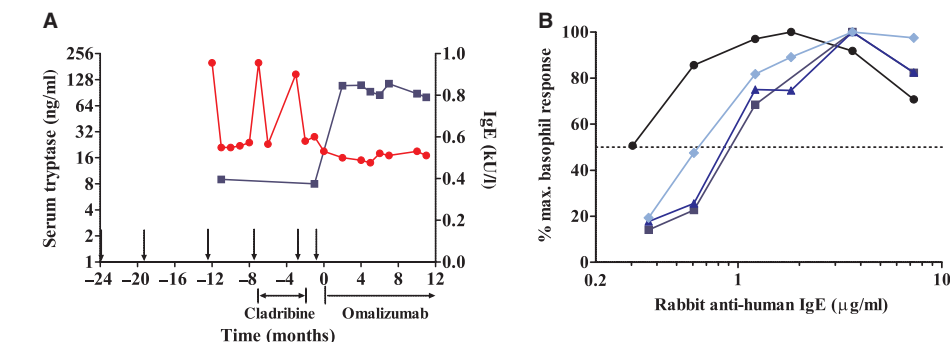


**Figure 1.** (A) Omalizumab is started at time 0. Total serum IgE (squares) increases and serum tryptase (circles) decreases following treatment with omalizumab. Episodes of anaphylaxis (arrows) have remitted since treatment with omalizumab. (B) Basophil activation test. To obtain 50% of maximal basophil response (shown by the dotted line) a marked increase in anti-IgE is required following omalizumab treatment. This indicates reduced basophil sensitivity. Results from before treatment (circles), after 6 weeks (triangles), 10 weeks (squares) and 10 months (diamonds) of treatment.

monthly. She has now received 14 months of therapy. Treatment has been well tolerated and life-changing. Her last episode of anaphylaxis was in August 2008, prior to omalizumab. Additionally, laboratory parameters confirm her response (see Fig. 1A) with random tryptase decreasing from 25.4 to 14 ng/ml.

We also assessed the activation status of this patient's basophils by flow cytometric measurement of surface expression of CD63 (5). In sequential basophil activation tests over the treatment period an increased concentration of anti-IgE was required to produce comparable basophil activation (see Fig. 1B) suggesting decreased sensitivity for activation (6). The cytofluorometric mean fluorescence intensity (MFI) fell from 120 before treatment to MFI 22 following omalizumab (data not shown) indicating a decreased IgE load on the basophils. We hypothesize that the favourable clinical response to omalizumab reflects decreased activation of mast cells (similar to the effect in basophils) because of decreased IgE binding to systemic mast cells, which has occurred in this nonatopic individual with an abnormal mast cell population.

A BMA performed 7 months after treatment commenced showed persistence of abnormal CD25 and CD2

positive mast cells, consistent with SM, despite the patient's dramatic clinical improvement.

Anaphylaxis associated with SM may have catastrophic consequences. We alert our colleagues to the efficacy of omalizumab for treatment of such patients whether atopic or nonatopic.

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