

Letter to the Editor

Successful treatment of cutaneous mastocytosis and Ménière disease with anti-IgE therapy

To the Editor:

The patient in this case was a female, 56-year-old former school teacher. Her history had begun at age 39 years with feelings of heat, red face, increased pulse, and sudden breathing difficulties. Pigmented maculae appeared first on the skin of the hands and spread in the subsequent years to the face, neck, upper body, thighs, and feet, along with wheal formation. She had reported episodes of difficulty breathing, tachycardia, and flushing at ages 42 to 43 years. At age 46 years, the patient had a slipped disk and an acute hearing loss in the right ear, which persisted long-term. During that year, she experienced occasional diarrhea, which spontaneously resolved. Because the skin pigmentation was continually increasing, the patient underwent 12 days of inpatient diagnostics and treatment at age 48 years. She acutely had further loss of hearing at age 52 years. The skin pigmentation continued to increase on her entire body, face, hands, and extremities, and wheal-and-flare-type skin reactions and/or angioedema lesions developed daily on the skin. By nearly age 54 years, the patient had constant tinnitus in the right ear, vertigo, and vomiting, which were severe enough to require a hospitalization. The state officially retired her on the basis of all these ongoing conditions, the slipped disk, a suspected Hashimoto, and a childhood history of bone tuberculosis. The patient had also had recurrent migraine headaches during much of the history. The vertigo attacks worsened and by age 56 years were occurring 2 to 3 times per week for 8 to 24 hours. She reported that her movements were too disordered (“like a complete drunkard”) to take part in public life, much less to drive a car.

A skin biopsy performed at age 42 years showed a subepidermal and perivascular mononuclear cell infiltrate, as well as some eosinophils and pigmented macrophages. Moreover, there was hyperpigmentation of the stratum basale. Giemsa staining revealed a mast cell infiltrate mainly located in the upper dermis. At age 48 years, routine laboratory tests, neurologic examinations, a colonoscopy, a lung function examination, and chest x-rays all found nothing unusual. Recent routine laboratory tests were unremarkable; IL-6 was 2.9 $\mu\text{g/L}$; unspecific IgE was 167 kU/L; tryptase was within the normal range at 10.4 $\mu\text{g/L}$.

The patient's skin exhibited reddish-brown maculae and papules disseminated over her entire body (predominantly on her trunk and extremities), which is characteristic of cutaneous mastocytosis (CM). She had a positive Darier sign, which supports the presence of increased mast cell numbers in the skin. The results of the earlier skin biopsy—showing mast cell infiltrates—had confirmed the diagnosis of cutaneous mastocytosis. At age 48 years, the history, clinical examination, and organ examinations (especially of the lungs and gastrointestinal tract) left

little reason to suspect there was systemic involvement. The patient's recent tryptase levels have been within the normal range, thus quite probably excluding recent systemic mastocytosis, even though this was never formally excluded by bone marrow analysis.¹⁻³ Thus, the diagnosis was maculopapular CM.

The patient also exhibited tinnitus, hearing loss, and vertigo/nausea. The patient records do not give any indication that these symptoms might have been a result of trauma, surgery, mumps infections, or syphilis, so they had been diagnosed as unilateral definite Ménière disease.^{4,5} To our awareness, there is no inherent relation between mastocytosis and Ménière disease. Their co-occurrence in this patient was a coincidence in our opinion, as was the chance to target them both with 1 therapy.

The hope for a root cure for CM remains distant in the future, but recent advances in basic research do provide the basis for a new treatment approach that is more than mere symptom suppression.⁶ It has been discovered that the binding of IgE to mast cells is not merely a passive sensitization step, as previously believed; instead, IgE actively plays an important role in promoting the survival of mast cells.⁷ On the basis of these recent scientific findings, it would have been reasonable to suspect that IgE was playing a role in maintaining an elevated level of mast cells in this patient and that neutralizing IgE would lead to a reduction of mast cell numbers, thus improving the mastocytosis closer to the cause than mere symptom alleviation.

Much less is known about the pathogenesis of Ménière disease, which remains controversial.^{4,8} It has long been thought though that Ménière disease might be immunomodulated, and successful treatment of patients' allergies has often led to resolution of their coexistent Ménière disease.⁸ Thus, although it was not clear whether an anti-IgE agent would be helpful for Ménière disease, it was not implausible.

Omalizumab is a recombinant humanized mAb against IgE. It acts by binding free IgE at the same site that IgE would bind to its high-affinity receptor (Fc ϵ RI) on mast cells, thereby reducing free IgE in the serum.⁹ Moreover, as a result of depleting free IgE, omalizumab strongly downregulates the expression of Fc ϵ RI on mast cells.¹⁰ Preliminary data demonstrate that omalizumab may have efficacy in preventing anaphylaxis in patients with systemic mastocytosis.¹¹ In the summer of 2006, at age 56 years, the patient began receiving 150-mg shots of omalizumab every 14 days for the first 4 shots. After that initial treatment of 4 shots, she has continued receiving similar shots as maintenance therapy once every 4 weeks to the present day.

Since completion of the initial 4 biweekly treatment shots, no further wheal formation or pruritus has occurred, and there have been no more attacks of vertigo or nausea (Fig 1). At the most recent follow-up (more than 6 months after completion of the initial therapy and after 6 further

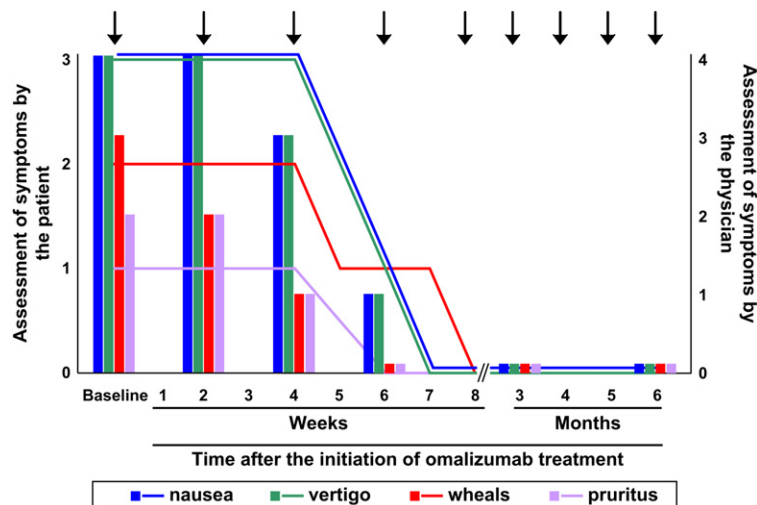


FIG 1. Omalizumab treatment results in the reduction of symptoms of mastocytosis and Ménière disease. Arrows indicate the time points of omalizumab shots. Bars represent the clinician's prospective scoring on a 5-point quantitative scale (0-4 + 's). Lines indicate the patient's retrospective scoring of symptoms on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe).

monthly maintenance shots), the patient's symptoms related to CM remain significantly improved (Fig 1). Although there is still pigmentation, she reports experiencing a 100% reduction of wheal formation after the treatment. The unilateral poor hearing and slight tinnitus remain, but she has been completely free of the debilitating vertigo and nausea of Ménière disease. Consistent with past studies,⁹ there have been no noteworthy side effects reported. The patient reports that since the third injection of omalizumab, she has been able to drive a car again and has a completely new feeling of life.

This case shows that both mastocytosis and Ménière disease can be rapidly and successfully treated with omalizumab without side effects. The rapid improvement supports the role of IgE in promoting mast cell stimulation, survival, and overaccumulation in mastocytosis. Researchers should explore how much benefit other patients with mastocytosis can benefit from anti-IgE agents, as well as whether other patients with Ménière syndrome can be similarly aided.

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