

produced by mites that had colonized the fabric but left that substrate before it was studied.

The finding of high allergen levels and the fact that mites can penetrate into these fabrics raise serious questions about the use of nonwoven fabrics for allergen avoidance.

Jeffrey D. Miller, MD^a

Lisa Naccara, BA^b

Shama Satinover, MS^b

Thomas A. E. Platts-Mills, MD, PhD^b

From ^aAllergy and Asthma Associates, Danbury, Conn, and ^bthe University of Virginia Health Sciences Center, Charlottesville, Va. E-mail: JeffreyMillerMD@comcast.net.

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Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab

To the Editor:

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody that is US Food and Drug Administration–approved for the treatment of moderate-to-severe persistent asthma.¹ Omalizumab also has demonstrable effects on inflammation in other conditions.²⁻⁵ We report 3 cases of refractory idiopathic angioedema that resolved on treatment with omalizumab.

Before instituting omalizumab, each patient had undergone aggressive medical management of idiopathic angioedema. Interventions included cessation of medications or foods associated with angioedema. Patients also had to demonstrate failure to respond to (patient 3) or tolerate tapering and cessation of (patients 1 and 2) systemic corticosteroids, despite pharmacologic interventions, including H1 and H2 blockade.⁶

Patient 1 is a 65-year-old white man with a history of moderate persistent asthma and sarcoidosis who had recurrent angioedema in 1999. He experienced swelling in his feet, scrotum, face, tongue, and larynx approximately twice weekly. These attacks required self-administered epinephrine and emergency department visits, hospitalizations, or both about twice monthly. The patient attributed his angioedema to certain foods, but dietary restriction of beef, peanuts, coffee, eggs, and chocolate was not beneficial. Angioedema recurred despite cessation of lisinopril, ibuprofen, aspirin, and allopurinol. Urticaria was absent. Physical examination was unremarkable. Laboratory findings included normal values for complete blood count (CBC) with differential, comprehensive metabolic panel, antinuclear antibody, and thyroid-stimulating hormone; C2 level of 2.1 mg/dL (1.6-4.0 mg/dL); C4 level of 30 mg/dL (16-47 mg/dL); C1 inhibitor level of 37 mg/dL (21-39 mg/dL); normal C1 inhibitor function; C1q level of 16.2 mg/dL (11.8-23.8 mg/dL); positive RAST result to coffee (class 0/1), egg white (class 2), and beef (class 3); and total IgE level of 244 kU/L (0-144 kU/L). In November 2005, 300 mg of subcutaneously administered omalizumab every 3 weeks was instituted for treatment of his asthma. Soon after omalizumab was initiated, the patient's angioedema regressed. He currently remains asymptomatic.

Patient 2 is a 63-year-old white man with a history of chronic obstructive pulmonary disease who had angioedema of his tongue and face in 2003. He denied any urticaria or pruritis with the angioedema. Angioedema remitted for 3 years; he then began having recurrent episodes of lip, tongue, and laryngeal edema, requiring 8 emergency department visits and a hospital admission. The patient required prolonged courses of oral steroids in addition to daily fexofenadine, cetirizine, and ranitidine. Angioedema episodes persisted, despite cessation of lisinopril and ibuprofen. The patient stated that his angioedema occasionally occurred after ingestion of shellfish, tuna, pineapple, chocolate, or coconut, but elimination of these foods did not alleviate the recurrent angioedema. Physical examination was unremarkable. Laboratory findings included the following: normal values for CBC with differential and comprehensive metabolic panel; negative results for anti-FcεRI; low thyroid-stimulating hormone value of 0.031 mIU/L (0.4-4.0 mIU/L) but normal free T4 and total T3 levels, no abnormal antithyroid peroxidase and antithyroglobulin antibody titers, and reduced thyroid radionuclide iodine uptake (4.2%), with slight diffuse gland enlargement; C2 level of 3.4 mg/dL (1.6-4.0 mg/dL); C4 level of 25 mg/dL (16-47 mg/dl); normal C1 inhibitor level and function; total

tryptase (includes precursor and mature forms) level of 7.7 ng/mL (<11.4 ng/mL); negative RAST results to blue mussel, crab, lobster, scallop, tuna, pineapple, cocoa, and coconut; serum protein electrophoresis with increased α_2 - and β -globulins but no monoclonal gammopathy on immunofixation electrophoresis; and total IgE level of 510 IU/mL (0-158 IU/mL). Because of the patient's angioedema, 375 mg of subcutaneously administered omalizumab every 2 weeks was begun as an off-label therapy on January 31, 2007, after obtaining written informed consent. His last episode of angioedema had been 1 week before initiation of therapy, and he has remained free of angioedema since omalizumab was begun more than 7 months ago. He recently has tolerated tapering and cessation of his oral steroids and continues to take fexofenadine and ranitidine.

Patient 3 is a 50-year-old black man with a history of severe persistent asthma who began experiencing recurrent angioedema of his lips, tongue, and larynx in 1997. Because of severe laryngeal edema, which occasionally occurred with bronchospasm, this patient required a total of 31 intubations, which resulted in a tracheostomy in May 2004. Urticaria was absent with these episodes. The angioedema was not associated with ingestion of any food, and he never received angiotensin-converting enzyme or angiotensin II inhibitors. Physical examination was remarkable only for tracheostomy. Laboratory findings included the following: normal values for CBC with differential and comprehensive metabolic panel; normal C1 inhibitor level and function; C2 level of 26.7 mg/dL (6-32.5 mg/dL); C4 level of 38 mg/dL (10-40 mg/dL); total (precursor and mature) tryptase level of 2.5 ng/mL (<11.4 ng/mL); total IgE level of 62.4 IU/mL (0-91 IU/mL); and negative immediate reaction to subcutaneous injection of autologous serum (negative anti-FC ϵ RI serum antibody). Because his asthma continued to be uncontrolled despite inhaled fluticasone/salmeterol and montelukast, 300 mg of subcutaneously administered omalizumab every 4 weeks was begun in October 2006. Since initiation of omalizumab, the patient has had only 1 minor episode of facial angioedema. His asthma has improved markedly as well.

Omalizumab is a humanized mAb currently used for moderate-to-severe persistent asthma by binding to the C3 domain of the heavy chain of IgE.^{1,2,7,8} This in turn down-regulates Fc ϵ RI on mast cells, basophils, and dendritic cells, thus decreasing the early- and late-phase responses to bronchial challenge.^{1,2} Additionally, omalizumab has been shown to produce immune-modulating effects beyond IgE and its receptors, including effects on peripheral eosinophil and T-lymphocyte function.^{2,9} We illustrate 3 cases of severe, recurrent, idiopathic angioedema that resolved soon after initiation of omalizumab administered at US Food and Drug Administration–approved doses for asthma management. The mechanism by which omalizumab might be working in these cases is not clear because they do not appear to be IgE-mediated events. This is further supported by the apparent rapid clinical improvement that occurred within several weeks (particularly in patient 2) because omalizumab's treatment

effects occur usually in 8 to 10 weeks in asthma and rhinitis concomitant with reduction of bound IgE and IgE receptors.² Because we report the cases of only 3 patients and this is not a randomized controlled study, the possibility exists that the observed clinical improvement might be attributed to either a placebo effect or spontaneous remission. However, these cases were selected, in part, because of the frequency and duration of severe angioedema episodes. Thus the likelihood that all 3 patients spontaneously improved by chance after institution of omalizumab is less likely, albeit still possible.

Assuming that the omalizumab was responsible for the improvement in these patients' angioedema, several possibilities exist. One possible explanation for these observations is that a subset of idiopathic angioedema is IgE mediated, despite our inability to identify an IgE-mediated trigger through standard clinical measures. This is possible, yet the clinical response appears to have occurred with anticipated reduction in free IgE levels but before reduction of bound IgE and IgE receptor levels. Alternatively, there might exist a subset of patients with angioedema whose disease mechanism or mechanisms are not directly IgE mediated but are modified by omalizumab through an unknown indirect pathway. This concept is supported by the work of Noga et al,⁹ in which omalizumab's anti-inflammatory activity was mediated, in part, by induction of eosinophil apoptosis and downregulation of the inflammatory cytokines IL-2 and IL-13.

In conclusion, these 3 cases illustrate that more investigation needs to be conducted to understand not only the pathogenesis of idiopathic angioedema but also the mechanism or mechanisms of therapeutic efficacy of omalizumab in this group of patients. The authors hope that this letter will accelerate the search for and identification of disease mechanisms, therapeutic mechanisms, or both responsible for these observations.

Mark F. Sands, MD^{a,b}

Jessica W. Blume, MD^a

Stanley A. Schwartz, MD, PhD^a

From ^athe Division of Allergy, Immunology, and Rheumatology, University at Buffalo, State University of New York, Buffalo, NY, and ^bthe VA Western New York Healthcare System, Buffalo, NY. E-mail: mfsands@buffalo.edu.

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