

although unique entities, are not specific diseases, and thus reflect heterogeneous underlying conditions, likely with distinct mechanisms. Therefore, it is possible that some cases of idiopathic angioedema may be truly allergic and mediated by IgE mechanisms, despite the fact that our current clinical and laboratory diagnostic tools cannot detect this. Conversely, some idiopathic urticaria patients may have non-IgE-mediated mechanisms. Omalizumab responsiveness suggests a mechanistic overlap between these 2 conditions. We hope that our case series will stimulate both discussion of and investigation into mechanisms of angioedema and the apparent therapeutic efficacy of omalizumab.

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Delayed allergic reactions to omalizumab: Are patients reporting all cases?

To the Editor:

We read with interest the article entitled "Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma" by Limb et al.¹ We write to describe a case of anaphylaxis to first administration of omalizumab that highlights the possibility of underreporting of reactions to this medication.

We treated a 44-year-old woman with severe persistent asthma with omalizumab. Asthma was diagnosed at 28 years of age and had remained poorly controlled in spite of optimal inhaled and oral therapies, including oral corticosteroids. Her serum IgE level was 190 kU/L, with a positive RAST result to house dust mite. *Aspergillus* species antibodies were negative, and her peripheral eosinophil count was $0.8 \times 10^9/L$ (range, $0.0-0.4 \times 10^9/L$). She was initiated on omalizumab therapy and observed in the hospital for 2 hours after administration, when she was reviewed by an attending respiratory physician and was well.

Two and a half hours after administration of omalizumab, while driving in her car, the patient experienced throat irritation, pruritus of her ears, and wheeze requiring use of inhaled salbutamol. Four hours after administration, she noticed lip and tongue swelling and periorbital edema. Reluctant to report her symptoms to the hospital in the knowledge that omalizumab therapy would be terminated, she contacted her family practitioner, who prescribed desloratadine. However, she did ask her family to take a digital photograph of her 5 hours after treatment (Fig 1). Her facial symptoms persisted until the following day, when she self-medicated with high-dose oral corticosteroids, resulting in symptom resolution over the following 24 hours. When the patient reconsidered and reported the reaction 3 days later, we asked her to take comparison photographs in the same clothing with the same background (Fig 1). The patient consented to medical publication of her images without blacking of her eyes, given the serious implications of this reaction for practitioners and patients.

This patient's presentation was typical of the series of patients reported by Limb et al.¹ In this group the mean age was 43 years, with a majority of female subjects, many of whom had delayed onset and protracted progression of symptoms. Our patient,



FIG 1. Patient 5 hours after first dose of omalizumab (left) and 3 days afterwards following treatment (right).

having experienced a prolonged period of poor asthma control, had “high hopes” for this new treatment for asthma. She was therefore reluctant to report this reaction because she anticipated that her omalizumab therapy might be terminated, despite specific counseling to report adverse symptoms. The patient might have dismissed her initial symptoms as typical fluctuating symptoms of poorly controlled asthma. However, her later symptoms could not have been explained in this way.

It is imperative to stress the importance of reporting anaphylactic and allergic reactions to patients, given their potential severity. Medical practitioners should be aware that in this vulnerable group of patients with poorly controlled symptoms who are anxious to be treated with novel medications that might improve their quality of life, anaphylactic or less severe allergic reactions might not be reported.

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Reply

To the Editor:

We thank Barry et al¹ for highlighting some of the difficulties in evaluating omalizumab-induced anaphylaxis. We suspect that omalizumab-induced anaphylaxis might go unrecognized and

underreported in the community for a variety of reasons, including atypical presentations, confounding atopic symptoms at baseline, and individual patient considerations, such as those described in their case report.

Such factors limit the accuracy of estimating event frequency on the basis of uncontrolled data. In our case series we relied primarily on postmarketing safety reports that are voluntarily submitted to the US Food and Drug Administration's Adverse Event Reporting System database. For other drug products and adverse events entered in this database, it is generally estimated that only 1% to 10% of all adverse events are ever reported.^{2,3} Whether the same adjustment is applicable to omalizumab-induced anaphylaxis remains unclear at this time. As Barry et al¹ point out, awareness on both the part of the physician and the part of the patient is necessary for expeditious management of these potentially severe reactions.

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The views expressed in this reply are those of the authors and do not necessarily reflect the views or policies of the US Food and Drug Administration.

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