

# Letters

## SEVERE STEROID-DEPENDENT IDIOPATHIC ANGIOEDEMA WITH RESPONSE TO RITUXIMAB

We describe a 19-year-old woman with recurrent episodes of severe angioedema involving airway compromise and multiple emergency department (ED) visits, culminating in a steroid-dependent, prolonged hospitalization and the failure of several typical, first-line, steroid-sparing agents. The patient gave consent for this publication.

Her first episode, which occurred in July 2009, involved her tongue, throat, lips, and face, with associated malaise, nausea, and vomiting. She was treated with oral antihistamines and her symptoms resolved. Subsequent episodes, however, were more severe and required aggressive management in the ED but always resolved quickly with epinephrine. Symptoms were always limited to tongue, lip, and throat swelling and hoarse voice (presumed laryngeal edema) but were severe, with a complete inability to swallow or breathe normally.

She had a history of asthma, which was well controlled with budesonide-formoterol and montelukast. Review of systems revealed photosensitivity but no malar rash. She had no human immunodeficiency virus, hepatitis B, or hepatitis C risk factors. There was no history of oral contraceptive use or any other medications, including nonsteroidal anti-inflammatory drugs.

She was assessed in the allergy/immunology clinic during an asymptomatic interval, with negative skin test results to a limited panel of environmental and food allergens (she had been told milk allergy was likely causal during one of her ED visits). Laboratory tests were ordered (Table 1), and prophylactic therapy was initiated with cetirizine, 20 mg twice daily, and ranitidine, 150 mg twice daily.

Despite this, she had repeated, severe episodes that required multiple and higher doses of epinephrine in the ED, one of which led to a 48-hour admission with intravenous corticosteroid treatment (methylprednisolone, 80 mg intravenously every 8 hours). After she was discharged, however, oral prednisone maintenance failed, leading to readmission 36 hours later. She required intramuscular epinephrine on presentation, was given methylprednisolone, 125 mg intravenously every 8 hours, and continued to take histamine<sub>1</sub>/histamine<sub>2</sub> blockers and montelukast. Direct laryngoscopy confirmed the absence of structural abnormalities; recurrent episodes of angioedema with associated voice hoarseness were witnessed by caregivers and both authors of this letter.

Episodes of angioedema always responded promptly to epinephrine and/or within hours of intravenous steroid administration. Because of ongoing epinephrine requirements (1-2 injections daily), her steroid interval was adjusted first to every 6 hours and then to every 4 hours; at this interval of intravenous steroid administration, her episodes were fully controlled with no epinephrine requirements. An empiric course of C1 esterase inhibitor was ineffective; C1 esterase inhibitor level and function were later determined to be

Table 1. Laboratory and Other Test Results

| Test                                                       | Result   |
|------------------------------------------------------------|----------|
| Immunologic                                                |          |
| Complement levels (c1q, C2, C3, C4, and CH <sub>50</sub> ) | Normal   |
| C1 esterase inhibitor (level and function)                 | Normal   |
| Histone antibody                                           | Negative |
| Tryptase level                                             | Normal   |
| Coombs' test                                               | Negative |
| Hematologic                                                |          |
| JAK-2 mutation                                             | Negative |
| BCR-ABL gene                                               | Negative |
| Serum/urine protein electrophoresis                        | Negative |
| Flow cytometry                                             | Normal   |
| Bone marrow aspiration and biopsy                          | Normal   |
| Infectious                                                 |          |
| HIV                                                        | Negative |
| Hepatitis B/C                                              | Negative |
| HTLV                                                       | Negative |
| Lyme serology                                              | Negative |
| Parvovirus B19, EBV, CMV                                   | Negative |
| Rheumatologic                                              |          |
| ANA                                                        | 1:640    |
| Anti-dsDNA                                                 | Negative |
| ANCA (P&C)                                                 | Negative |
| RF                                                         | Negative |
| Imaging                                                    |          |
| CT neck/chest/abdomen/pelvis                               | Normal   |

Abbreviations: ANA, antineutrophil antibody; ANCA, antineutrophil cytoplasmic antibodies; CH<sub>50</sub>, total hemolytic complement assay; CMV, cytomegalovirus; CT, computed tomography; dsDNA, double-stranded DNA; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; HTLV, human T-lymphotropic virus; RF, rheumatoid factor.

normal. Use of nonsteroidal anti-inflammatory drugs was restricted throughout admission.

Her antinuclear antibody test result was positive (titer = 1:640); accordingly, she was prescribed hydroxychloroquine, 200 mg twice daily. Two days later, an empiric course of intravenous immunoglobulin was given because of failed steroid-tapering attempts. During her second infusion, she experienced a generalized seizure with posterior reversible encephalopathy syndrome on magnetic resonance imaging of the head; hydroxychloroquine and intravenous immunoglobulin therapies were discontinued, presuming the seizure to be due to one or the other; the results of workup for other potential causes of seizure were negative.

After consultation with a rheumatologist, dapsone therapy was started after ruling out glucose-6-phosphate dehydrogenase deficiency. Unfortunately, she developed methemoglobinemia and hemolytic anemia from the dapsone, and its use was also discontinued.

Because episodes were recurring with any minimal tapering of corticosteroids and the patient had already developed complications from the corticosteroid therapy, including hyperglycemia, myopa-

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thy, and mood instability, an open tracheostomy tube was placed, at the patient's request and the medical team's agreement, to allow tapering with a secure airway. Episodes of angioedema recurred in the hour before and after the methylprednisolone dosing and were extremely uncomfortable for the patient but were tolerated, knowing that her airway was secure.

Because conventional options had failed due to adverse effects, permission was obtained from the Pharmacy and Therapeutics Committee for experimental use of rituximab (anti-CD20) at a dose of 375 mg/m<sup>2</sup> of body surface area (560 mg) intravenously weekly for 4 weeks. Written informed consent was obtained for this off-label, experimental use.

Her symptoms and signs improved significantly after the third and fourth infusions, with successful tapering of intravenous steroids and transfer to prednisone with ongoing taper. No recurrences followed the fourth infusion. The tracheostomy tube was removed, and she was transferred to a rehabilitation facility for physiotherapy. She was ultimately discharged with no steroids and remained in remission for 9 months of follow-up with maintenance cetirizine and ranitidine. At that point she once again experienced a flare of angioedema involving the tongue and throat that required admission to the hospital, but her symptoms were more easily controlled with a lower dose of methylprednisolone (80 mg intravenously every 6 hours), and she responded well to a repeat course of rituximab, given at the same dose as before. This episode only required 3 infusions of rituximab to produce complete resolution and full tapering of corticosteroids, however. She remains in remission, once again, for over 4 months as of the date this publication.

The term *idiopathic* is used for angioedema when 3 or more episodes of angioedema occur within a period of 6 months to 1 year without any cause identified after comprehensive evaluations.<sup>1</sup> Our patient's angioedema remained idiopathic, but the presence of a high-titer antinuclear antibody suggested an underlying autoimmune basis.

For idiopathic angioedema without urticaria, antihistamines remain first-line treatment.<sup>2</sup> There are reports of using dapsone, methotrexate, cyclosporin, sulfasalazine, and colchicine<sup>1</sup> in the treatment of angioedema and urticaria. Our patient was clearly resistant to

more conventional treatment modalities and unfortunately experienced adverse effects to others and remained steroid dependent before the trial of rituximab.

Rituximab is a B-cell-depleting, monoclonal, anti-CD20 antibody. Previous studies indicate a rapid decrease in the number of circulatory B cells even after a single dose of rituximab. Although B-cell recovery occurs almost 6 months later, there is a change in the phenotype of the recovered B cells, which become relatively deficient in CD27.<sup>3,4</sup> There have been successful reports of rituximab for various types of angioedema, mostly related to acquired C1 esterase inhibitor deficiency,<sup>5,6</sup> but to our knowledge there has not been a description of its successful use in idiopathic angioedema with normal complement levels. We hypothesized that given our patient's steroid responsiveness, her angioedema would respond well to a specific B-cell suppressive therapy. This case report highlights the potential benefit of rituximab in treating idiopathic and autoimmune angioedema, even in the absence of hypocomplementemia.

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