Severe Steroid-Dependent Idiopathic Angioedema: Response to Rituximab

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Abstract

Background: Angioedema is the result of swelling of cutaneous and/or mucosal tissue due to vascular leakage. The rate of idiopathic angioedema is reported to be up to 41% in previous clinical surveys. Most cases of idiopathic recurrent angioedema respond to a regimen of H1 and H2 receptor antagonists and/or corticosteroids and epinephrine.

Case Presentation: We report the case of a 19 year old female with recurrent idiopathic angioedema limited to tongue, throat swelling and hoarse voice (presumably laryngeal edema); never any wheeze or dyspnea nor decrease in SaO2 but rather swelling of throat and inability to breathe normally. She had no hives, loss of consciousness or GI manifestations (including GERD). Past history was significant for asthma. Her symptoms were escalating, requiring multiple and higher doses of epinephrine and corticosteroids to control recurrences, ultimately culminating in a protracted hospital admission. The patient was severely corticosteroid resistant, due to severe crropharyngeal angioedema. She was investigated extensively (see Table 1) with only the underlying etiology being a positive ANA (1:640), but anti-dsDNA was negative. A trial of hydroxychloroquine with immunomodulatory IVIG produced seizures and required discontinuation of both. Dapson was initiated and led to both methemoglobinemia and hemolytic anemia, despite a normal G6PD screen. An open tracheostomy was placed at the patient’s request to avoid corticosteroid tapering with a secure airway. Ultimately, Rituximab was initiated at a dose of 60 mg weekly for 4 weeks, and produced significant reduction of symptomatology after the 3rd and 4th infusion; this medication was used after having a written informed consent from the patient and approval from the hospital’s pharmacy and therapists committee.

Conclusion: We present a case of severe, steroid-dependent recurrent idiopathic/autoplastic angioedema intolerant of usual corticosteroid tapering agents that ultimately had an excellent response to Rituximab.

Background/Methods

Angioedema is self-limited, localized swelling of the skin or mucosal tissues, which results from extravasation of fluid into the interstitium due to a loss of vascular integrity.

The causes of angioedema can be subdivided into three groups: Most cell-mediated etiologies, Bradykinin-mediated etiologies and unknown causes (idiopathic). Idiopathic angioedema is the term applied to recurrent episodes of angioedema without urticaria, for which no explanation can be found after a thorough evaluation to exclude allergic disorders, drug reactions, and deficiencies in complement pathways. The rate of idiopathic angioedema is reported to be up to 41% in previous clinical surveys. Most cases of idiopathic recurrent angioedema respond to a regimen of H1 and H2 receptor antagonists and/or corticosteroids and epinephrine.

We describe the case of a 19 year old female who developed severe recurrent idiopathic angioedema, which was steroid-dependent and resistant to current conventional treatments requiring a 25% month hospitalization. It eventually responded well to treatment with Rituximab.

Case Presentation

A 19 year old nursing student was admitted to hospital after experiencing recurrent episodes of severe angioedema requiring ER treatment. It had been previously labelled case’s milk allergy, which was ruled out.

1st episode occurred in July 2009 while attending a camp in the Rocky Mountains. Swelling of her tongue, throat, lip, face, associated with malaise and N/V, treated with PO antihistamines, and resolved spontaneously.

Following episodes always required aggressive ER management but always resolved quickly with epinephrine, and some were managed by IPi pen at home.

She was assessed in the outpatient Allergy Clinic where skin testing was negative to environmental and common food allergens.

Symptoms were always limited to tongue, throat swelling and hoarse voice (presumably laryngeal edema), never any wheeze, acute shortness of breath or decrease in SaO2 but she was aware of throat closure and inability to breathe normally; no hives, loss of consciousness or GI manifestations.

Past Medical History included asthma, well controlled with Symbicort 200/60 and Singular 10mg Olol.

Review of Systems revealed photosensitivity described as “red prickly rash” in sun exposed areas, with no malar rash; otherwise no other connective tissue symptoms. No HIV or Hepatitis B risks factors aside from heterosexual consensual contacts.

Prophylactic therapy was begun with combined H1 and H2 receptor antagonists – i.e. cetirizine 10mg PO BID and ranitidine 150mg PO BID.

Despite this, she suffered repeated episodes of severe angioedema requiring multiple and/or higher doses of epinephrine in the ER, one of which lead to a 48hr admission for IV steroids.

After discharge, however, she failed oral prednisone maintenance (ranitidine and cetirizine had been continued as well) leading to readmission to hospital.

She was started on Solumedrol 125mg IV q8h, continued on H1/H2 LTRA, with epinephrine 0.3mg 0.5mg PRN.

Due to ongoing episodes requiring epinephrine (1-2 injections per day) her steroid regimen was adjusted first to q6h, then q4h (i.e. 125mg Solumedrol q6h).

An empiric course of C1 esterase inhibitor was ineffective; levels later determined to be normal.

After positive ANA result finding, Plaquenil was started at 200mg bid presumed autoimmune basis.

2 days later, an elevated CRP of 8mg was given due to failed steroid tapering attempts and breakthrough epinephrine requirements.

During her 2nd IVIG infusion she suffered a generalized seizure with posterior reversible encephalopathy syndrome (PRES) as an MRI finding; Plaquenil and IVIG were stopped.

Table 1: Categorized list of investigative studies performed

<table>
<thead>
<tr>
<th>Immunologic</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complement Levels (C1q, C2, C3, C4 &amp; CH50)</td>
<td>Normal</td>
</tr>
<tr>
<td>C1 Esterase Inhibitor (level &amp; function)</td>
<td>Normal</td>
</tr>
<tr>
<td>Anti-Histidine Antibodies</td>
<td>Negative</td>
</tr>
<tr>
<td>Trypsinial Levels</td>
<td>Negative</td>
</tr>
<tr>
<td>Coombs Test</td>
<td>Negative</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>1:640</td>
</tr>
<tr>
<td>Anti dsDNA</td>
<td>Negative</td>
</tr>
<tr>
<td>ANCA (P&amp;C)</td>
<td>Negative</td>
</tr>
<tr>
<td>RF</td>
<td>Negative</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
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<tr>
<td>Hepatitis B &amp; C</td>
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<tr>
<td>Lyme Serology</td>
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<tr>
<td>Parvovirus B15, B19, CMV</td>
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<tr>
<td>Imaging</td>
<td>Normal</td>
</tr>
<tr>
<td>C1 Chest/Abdomen/Pelvis</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Table 1. Categorized list of investigative studies performed

- work-up for other causes of seizure was entirely negative.
- With rheumatologic’s approval, she was started on Dapson 100mg bid as the next attempted steroid-sparing agent. Unfortunately she developed methemoglobinemia and hemolytic anemia (SGOT elevated) as a side-effect of Dapson, and it was stopped; patient was treated with methylene blue.
- An open tracheostomy was placed at the patient’s request to allow corticosteroid tapering with a secure airway, only slow tapering could be tolerated.

- Complications of steroid therapy developed, including diabetes mellitus, steroid-induced myopathy, and mood swings with hyperalgesia; these were managed with insulin and pregabalin.
- Permission was obtained from the hospital’s Pharmacy & Therapeutics Committee for experimental use of Rituximab (anti-CD20) (written informed consent obtained from patient; started at 100mg IV weekly x 4).
- Her symptoms improved dramatically after the 3rd and 4ths infusions, with successful tapering of the IV steroid dose, and transfer to oral prednisone with ongoing taper.
- Tracheostomy was removed, she was transferred to a rehab facility for inpatient physiotherapy.
- She was discharged home, some 3 weeks later off steroids entirely, and has remained in remission with maintenance cetirizine and ranitidine ever since.

Discussion

Rituximab is a B cell depleting mononal anti-CD20 antibody; it has been reported to have been used in cases of acquired C1-INH deficiency, and in other autoimmune conditions, but to our knowledge there has not been a report of successful use presumed autoimmune-mediated idiopathic angioedema.

We hypothesized that given her sensitivity to steroids yet resistance to corticosteroid taper that her angioedema would respond well to a more specific B-cell suppressive therapy and would allow for corticosteroid withdrawal. Our patient’s angioedema remained idiopathic, but the presence of ANA antibodies suggested an underlying autoimmune basis.

This case highlights the potential benefit of Rituximab in the treatment of autoimmune or idiopathic angioedema, even in the absence of hypocomplementemia.

References


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