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 aware of sensation of throat closure and inability to breath normally. She had no hives, loss of consciousness or GI manifestations (including GERD). Past history was significant for controlled asthma. Her symptoms were escalatory, requiring multiple and higher doses of epinephrine and corticosteroids to control recurrences, ultimately culminating in a protracted hospital admission as only parenteral corticosteroids could be administered due to severe oropharyngeal angioedema. She was investigated extensively (see Table 1) with the only clue to its 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. Dapsone 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 allow 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 therapeutics committee.

Conclusion: We present a case of severe, steroid-dependent recurrent idiopathic/autoimmune angioedema intolerant of usual corticosteroid sparing 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: Mast 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 defects 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-dependant and resistant to current conventional treatments requiring a 2½ 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 treatments; it had been previously labelled cow's milk allergy, which was ruled out.
- **1st episode** occurred in July 2009 while attending a camp in the Rocky Mountains involving her tongue, throat, lips and 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 Epi-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 200/6 BID and Singulair 10mg OD.
- **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 risk factors aside from heterosexual contacts.
- Prophylactic therapy was begun with combined H1 and H2 receptor antagonists – i.e. cetirizine 20mg 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 0.3-0.5 mg IM PRN.
- Due to **ongoing episodes** requiring epinephrine (1-2 injections per day) her steroid interval was adjusted first to q6h, then q4h (*i.e*. 125mg Solumedrol q4h).
- An empiric course of C1 esterase inhibitor was ineffective; levels later determine to be normal.
- After **positive ANA result** finding, **Plaquenil** was started at 200mg bid given presumed autoimmune basis.
- 2 days later, an empiric course of **IVIG** 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 investigational studies performed

Immunologic	
Complement Levels (c1q, C2, C3, C4 & CH50)	Normal
C1 Esterase Inhibitor (level & function)	Normal
Anti-Histone Antibodies	Negative
Tryptase Level	Negative
Coomb's Test	Negative
Rheumatologic	
ANA	**1:640**
Anti dsDNA	Negative
ANCA (P&C)	Negative
RF	Negative
Hematologic	
JAK-2 mutation	Negative
BCR-ABL gene	Negative
Serum/Urine Protein Electrophoresis	Negative
Flow-cytometery	Normal
Bone Marrow Aspiration & Biopsy	Normal
Infectious	
HIV	Negative
Hepatitis B & C	Negative
HTLV	Negative
Lyme Serology	Negative
Parvovirus B19, EBV, CMV	Negative
Imaging	
CT Chest/Abdomen/Pelvis	Normal

- Work up for other causes of seizure was entirely negative.
- With Rheumatology's approval, she was started on **Dapsone 100mg bid** as the next attempted steroid-sparing agent. Unfortunately she developed methemoglobinemia and hemolytic anemia (G6PD negative) as a side-effect of Dapsone, 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 **560mg IV weekly x 4**.
- Her **symptoms improved dramatically after the 3rd and 4th 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 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 monoclonal 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

1. Sanchez-Cano D *et al*. Successful use of rituximab in acquired C1 inhibitor deficiency secondary to Sjögren's syndrome, Lupus. 2008; 17(3):228-229.
2. Ziakas PD *et al*. Acquired angioedema: A new target for rituximab? Haematologica 2004; 89:ELT13.
3. Levi M, Hack CE, van Oers MH. Rituximab induced elimination of acquired angioedema due to C1-inhibitor deficiency. Am J Med 2006; 119:e3–e5.

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