

Angioedema in a child with a liver transplant, intussusception, and normal c4 levels

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ABSTRACT

Swelling is a common chief complaint among patients. Swelling and hives are not typical of hereditary angioedema. Organ transplantation drugs are associated with angioedema and may complicate diagnosis. Our objective was to manage a complex case of angioedema in a setting of rashes and liver transplantation. We present an illustrative case of angioedema, rashes, and intussusception in a setting of a liver transplant and tacrolimus use with a family history of autoimmune disease. Treatment with the kallikrein inhibitor, kalbitor, eliminated angioedema and intussusception, though not permanently. Serial C1 esterase inhibitor levels were only suppressed during severe attacks of angioedema. C1q autoantibody was elevated. Although 95% of cases of hereditary angioedema (HAE) have normal C4 levels, those with C1q immune complexes have autoantibodies leading to low-grade inflammation and eventual consumption of C1 esterase inhibitor levels with C4 unaffected. Rashes associated with angioedema are not urticarial. Physicians should learn to recognize the signs of attacks of HAE.

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Key words: Angioedema, autoantibody, C1q immune complex, c4, c1 esterase inhibitor, hereditary, intussusception, liver transplantation, tacrolimus

Question:

How do you diagnose and manage a teenager with a liver transplant on tacrolimus who complains of persistent swelling¹ of his jaw, hands, abdomen, and feet sometimes associated with a nonpruritic rash not relieved with 40 mg of prednisone and hydroxyzine daily for 2 years? (More than one may be correct.)

- A. Draw C4 level.
- B. Do not draw C4 level because he has a rash.
- C. Check chronic urticaria screen for FcεR1 IgE autoantibodies as well as antithyroid peroxidase antibodies and hepatitis titers.
- D. Treat empirically with higher-dose steroids and add zantac.
- E. Skin test for food allergy.²
- F. Biopsy lip and start danazol at pediatric dosages.
- G. Other testing not listed may be necessary.
- H. Foregoing tests are sufficient to exclude other diagnoses.

INTRODUCTION

Deficiency of C1 inhibitor alters bradykinin production due to uninhibited activated factor XII and plasma kallikrein. Localized swelling in hereditary angioedema from bradykinin production¹⁰ may disseminate. Activation along the endothelial cell surface involves cell membrane ligands of factor XII and high-molecular-weight kininogen, release of endothelial cell heat shock protein 90, activation of the high-molecular-weight kininogen–prekallikrein complex, and endothelial cell activation at the B2 receptor. Swelling episodes may be stopped by treatment with a kallikrein inhibitor or B2 receptor blockade. Replenishing C1 inhibitor can treat attacks of swelling and provide prophylaxis with i.v. administration.³

Chief Complaint

“Swelling of face, hands, and feet.”

History of Present Illness

A case of a 16-year-old boy with angioedema is presented. Once, his tongue swelled. Episodes of swelling started 1 year ago with swelling of the face, hands, and feet. He denies throat closure or wheezing. Symptoms are barely controlled with Allegra b.i.d., hydroxyzine, doxepin at a 30-mg dosage, and tagamet. His symptoms were attenuated minimally with 40 mg of prednisone. No one else swells in the family. Be-

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cause of abdominal pain and suspected intussusceptions, the pediatric gastroenterologist was interested in reducing swelling before any surgical intervention.

Medications

Prograf b.i.d.—can cause itchiness.
Allegra b.i.d.
Fiber choice (takes at 2 P.M.).
No asthma medications.

Drug Allergies

Penicillin and nafcillin caused hives when he was in septic shock.
Adverse reaction to vancomycin (given quickly) and cephalosporins.
Rash with EMLA cream(Astrazeneae).
Rash with Demerol and Versed.
Plasmapheresis—told only to get male blood donor.
Acyclovir caused a rash.
Reaction to additive in blood products.
Not allergic to latex.

Past Medical History

Pneumonia with cytomegalovirus was the last infection years ago.
“Rash” baby in Chicago.
Liver transplant ages 9, 20, and 24 months for biliary atresia.
Congenital absence of gallbladder.
Asthma, not on medicine.
Plicated diaphragm.
One hundred operations for biliary reconstruction and stent.
Avascular necrosis of hip secondary to steroids.
Sensorineural hearing loss at high frequencies from gentamicin.
Spinal spondylosis, cluster of veins around spine.
Fracture of vertebrae (missed most of the 9th grade).
Renal vein clotted.
Lactose intolerant.
Atopic dermatitis, eczema.
Ultrasound of liver negative last year.
Tacrolimus levels were reduced 2 years ago after an episode of chicken pox; swelling episodes began thereafter.

Surgical History

Cadaveric liver transplants three times.
Migraine headaches but not recently.
Tonsillectomy and adenoidectomy.
Epstein-Barr virus.

Social History

No tobacco use or alcohol use.

Exercises when weather is warm, plays basketball, and runs.
No pets.
Drinks a lot of coffee.

Family History

Mother with pressure-induced urticaria and penicillin allergy.
Brother healthy.

Adult Immunization Hx

Received flu and H1N1 vaccinations.

Review of Systems

Negative for fever, sweats, or chills.
Negative for fatigue or anorexia.
Negative for weight loss of >5 lb.
Positive for rashes around Christmas.
Positive for eye irritation; does not wear contact lenses.
Negative for change in vision.
Negative for earaches or seasonal allergies.
Negative for congested nose and green discharge.
Positive for heartburn and indigestion; no difficulty swallowing and no nausea or vomiting.
Positive for abdominal pain.
Negative for jaundice or hepatitis.
Negative for frequency or nocturia.
Negative for muscle aches or arthralgias or arthritis.
Negative for chest pain or palpitations or swelling of the ankles or paroxysmal nocturnal dyspnea.
Negative for dyspnea on exertion, no cough, sputum production, snoring, dry mouth, mouth ulcers, or sore throat.
Positive for swelling of eyebrow, lip, hands, feet, and arm.
Negative for history of anxiety disorder or depression or sleep disturbances.
Positive for headaches.
Negative for focal weakness, numbness, loss of consciousness, or dizziness.

Physical Examination

Blood pressure, 116/60; P 74; R 10; weight, 126.5 lb; height, 5 ft 5 in.; thin habitus.
Head, eyes, ears, nose, throat, tympanic membranes clear, no cerumen. Turbinates clear, capped teeth upper jaw.
Cardiac regular heart rate, no murmurs.
Respiratory lungs clear.
Gastrointestinal positive for bowel sounds.
Extremities no cyanosis, clubbing; positive edema; positive for xerosis of skin, dry. Skin creases over thenar eminence blunted, hands swollen, feet swollen but nonpitting jaw swollen.
Neuro alert, oriented ×3.

A 16-year-old boy with a third liver transplant on tacrolimus with atopy, eczema, and asthma, and now with angioedema/urticaria on antihistamines.

DIAGNOSIS

C4 analyses were repeatedly normal; C1 esterase inhibitor was 9 mg/dL (low) followed by 3 normal levels and then 18 mg/dL (low). He had positive C1q autoantibodies determined by a C1q immune complex index (5.9).⁴ Function of C1 esterase inhibitor was 96% and normal. The patient was taken off steroids and antihistamines during a pediatric hospital admission and had less swelling (jaw and hand and no rash) compared with more severe swelling during the initial visit (severe hand, jaw, and leg swelling associated with abdominal pain). His tacrolimus level was undetectable. Over the course of the following month, abdominal pain was severe and the patient lost 10 lb from lack of eating. A total parenteral nutrition line was placed. He underwent endoscopy which showed eosinophilic esophagitis and intussusception of a dynamic nature associated with severe intraluminal gastrointestinal swelling. Total parenteral nutrition was initiated. IgE panels to foods and aeroallergens were negative. He had normal tryptase, histamine, and chronic urticaria screen levels along with normal thyroid peroxidase antibody and thymoglobulin function. His hepatitis panels were negative. Autoantibodies to C1 esterase inhibitor were pending.⁵

The patient was treated with kallikrein inhibitor kalbitor.⁶ Facial, hand, leg, and abdominal swelling resolved over 1 hour and he began eating macaroni and cheese; 4 hours later he was able to eat at Outback Steakhouse for dinner. He was well for 4 days. The next day he was treated again with kalbitor to treat abdominal pain and swelling and facial/jaw, hand, and leg edema. This time he abated for 24 hours. A week later i.v. IgG was infused over 24 hours at a dose of 400 mg/kg. He did not have adverse side effects. Kalbitor was started at the end of intravenous immunoglobulin infusion. This time his symptoms abated for <24 hours. The CT scan of the abdomen was normal 24 hours after kalbitor when the patient began recurrent vomiting of undigested food. There was no intussusception. At home he had rashes not seen while admitted to the hospital. His complete blood count was noted to be within normal range with 4.5% eosinophilia. His tacrolimus level was increased to achieve a level of 7.4 ng/mL from 0. His spontaneous eosinophilia abated. A week later, the latest c1 esterase inhibitor level was returned as low (18). The tacrolimus is being reduced to achieve a level closer to 5.

MANAGEMENT

Cinryze⁷ has been ordered t.i.d. and when he goes for dental work berinert human-derived c1 esterase⁸ is to be available in the operating room.

Answer to the Question

This case illustrates the complexity of managing angioedema in a setting of immunosuppression for liver transplant.

- A. Draw C4 level. YES—REPEATEDLY IN THIS CASE, A SETTING OF C1q AUTOANTIBODY BUT NOT C1 ESTERASE DEFICIENCY.
- B. Do not draw C4 level because he has a rash. NO.
- C. Check chronic urticaria screen for FceR1 IgE autoantibodies as well as antithyroid peroxidase antibodies and hepatitis titers. YES, ALTHOUGH THEY WERE NORMAL.
- D. Treat empirically with higher dose of steroids and add zantac. NO, BECAUSE HE WAS BETTER OFF NOT TAKING THESE MEDICINES (SWELLING WENT AWAY OFF MEDS).
- E. Skin test for food allergy. IN THIS CASE, HIS IgE WAS UNDETECTABLE TO FOOD AND SKIN TESTS WERE NEGATIVE.
- F. Biopsy lip and start danazol at pediatric dosages. NO, SPONTANEOUS ATTACKS RESOLVED WITHOUT SCARRING AND SIGNIFICANT IMPAIRMENT IN LIVER FUNCTION IS A CONTRA-INDICATION.
- G. Other testing not listed may be necessary. YES, C1Q AUTOANTIBODY (C1Q IMMUNE COMPLEX).
- H. Aforementioned tests are sufficient to exclude other diagnoses. NO.

Pearls

- Although 95% of hereditary angioedema is associated with depressed c4 levels even between attacks,⁹ this case illustrates the rare subset with normal c4 levels. The reason is that his underlying problem appears to be an autoantibody versus c1q. This leads to low-grade inflammation and activation of the complement cascade.¹¹
- At times, when his swelling was the most pronounced, the c1 esterase inhibitor level was severely depressed. However, with his baseline swelling of the hands, jaw, and abdomen, levels of c1 INH were normal. The erythema associated with his angioedema during severe attacks was not urticaria (not raised hives).

Pitfalls

- The complicating aspect of this case is the rash-like urticarial vasculitis, which has been described in c1q

immune complex settings. He did not have this rash for prolonged periods of swelling, but at other times, it manifested persistently.

- In this case, angioedema of the gut mimicked intussusception and did warrant the use of narcotics for pain control. The resolution on CT after kalbitor points to an angioedema origin.
- Decreasing efficacy of kalbitor, which suggests a counterregulatory pathway or the development of autoantibodies. It is, however, approved for acute attacks and the half-life is 2 hours. In this patient the initial persistent benefit of 4 days is unlikely related to spontaneous attacks. A definitive test is an IgG4 versus c1q. This is not widely available or approved by the Food and Drug Administration.

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