

C1-esterase inhibitor autoantibodies in a patient with acute tongue swelling

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ABSTRACT

Angioedema occurs when there is fluid leakage into the deep dermis of the skin and underlying subcutaneous tissues. Affected individuals usually present with swelling of the face or extremities. Acquired angioedema is an uncommon but potentially life-threatening disease in the older adult population. After the individual is cleared of the initial danger period, a thorough workup for an underlying etiology must be done. We report a 62-year-old male presenting with significant tongue swelling who was diagnosed with acquired angioedema. He had autoantibodies to C1 esterase inhibitor and was subsequently diagnosed with a lymphoma. Angioedema should be recognized by clinicians as a potential presentation of a more ominous malignancy.

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Key words: Acquired angioedema, angioedema, C1-esterase inhibitor autoantibody

CASE PRESENTATION

History of Present Illness

A 62-year-old Caucasian man presented to the Allergy and Immunology Clinic with a history of sudden-onset, isolated tongue swelling. This was the first swelling episode he had ever experienced. There were no stressful preceding events or recent changes in medications. He was rushed to the emergency room because of impending airway obstruction and received a dose of intramuscular epinephrine. He received no other supportive medications. The tongue swelling gradually abated over the next few hours and he was discharged without further medical interventions. The patient presented to our clinic 1 month later for evaluation; he had not experienced any further swelling episodes aside from this isolated incident. Review of systems was unremarkable. For several years, the patient has been taking niacin for elevated serum cholesterol as well as aspirin, and he has had no adverse reactions to either medication. There is no family history of angioedema (AE).

Physical Examination

The patient was afebrile with stable vital signs. His physical examination was unremarkable with no evidence of tongue swelling or skin abnormalities.

Laboratory and Other Diagnostic Findings

No laboratory studies, including complement testing, were done during the tongue swelling episode. Laboratory studies, although asymptomatic, showed a normal complete blood count with no eosinophilia. Sedimentation rate was elevated at 64 mm/hour (normal range, 0–10 mm/hour). Complement studies showed a C4 of <10 mg/dL (normal range, 12–34 mg/dL) and CH50 was <60 complement activity enzyme (CAE) units (normal range, above 60 CAE units). C1 esterase inhibitor (C1-INH) quantity was <4 mg/dL (normal, 11–25 mg/dL), and C1-INH function was 3% (normal, ≥68%). C1q was normal at 6.6 mg/dL. Antinuclear antibody, rheumatoid factor, and thyroid autoantibodies were negative. Urinalysis was unremarkable. Serum immune protein electrophoresis showed faint monoclonal IgM κ -protein.

Bone marrow biopsy showed atypical lymphoid aggregates but no monoclonality or evidence of lymphoma. Follow-up serum and urine immunofixation showed increased presence of monoclonal IgM κ -protein. CT scan of the chest, abdomen, and pelvis showed slightly enlarged retroperitoneal lymph nodes, and he was given a preliminary diagnosis of a very low-grade lymphoproliferative disease.

Clinical Course

The patient was diagnosed with acquired AE (AAE) and was started on danazol with close follow-up. There were no further AE attacks. His complement studies, including C1-INH quantity and function as well as C4 levels, normalized after 8 months of ther-

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apy. The patient continued on danazol without complications. Approximately 18 months after the tongue swelling incident, the patient was diagnosed with a lymphoma.

QUESTIONS

What Is the Differential Diagnosis?

In order of least likely to most likely, the differential diagnosis includes:

1. Gleich syndrome
2. Allergic AE secondary to food or medications
3. Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)-associated AE
4. Physical AE: pressure AE or vibratory AE
5. AE secondary to infection: bacterial, fungal, viral, or helminthic
6. Systemic illness: collagen vascular disease or malignancy
7. Chronic idiopathic AE
8. Hereditary AE (HAE)
9. AAE

What Additional Laboratory Data or Investigations Would Be Helpful in Arriving at a Diagnosis in This Patient?

Additional laboratory data regarding autoantibody to C1-INH would be helpful in diagnosing this patient.

DISCUSSION

AE develops secondary to fluid leakage into the deep dermis and subcutaneous tissues. It was first described in 1876 by John Laws Milton as "giant urticaria."¹ Urticaria also is caused by fluid leakage but only into the superficial dermis. AE most commonly affects the extremities, lips, tongue, eyelids, and the genitalia; lesions are nonpitting. Approximately 10% of Americans develop isolated AE with no associated urticaria.

Gleich syndrome (episodic AE with eosinophils)² is a rare but benign condition involving recurrent AE associated with peripheral blood and/or tissue eosinophilia. Attacks vary in length and frequency and occasionally may be associated with urticaria and fever.

IgE-mediated allergic reactions to foods and drugs is the most common cause of acute urticaria and/or AE. However, our patient's clinical and laboratory histories did not suggest these possible causes of AE.

AE also can develop during ACE inhibitor therapy, even occurring months after initiating medication. Symptoms likely occur secondary to increased bradykinin and its metabolites, which are normally metabolized by ACE. Increased bradykinin leads to vasodilation and fluid extravasation into the interstitial space. There have been scattered cases of AE associated with ARB use³; the exact mechanism is unknown. Neverthe-

less, most patients who develop AE with ACE inhibitors have safely switched to ARBs with no further attacks.⁴

Patients with physical AE develop symptoms after an environmental trigger. Pressure-induced AE can develop 4–6 hours after a pressure stimulus to the affected area. Vibratory AE can be inherited in an autosomal dominant pattern⁵ and symptoms occur within minutes after a vibratory stimulus. Infections including hepatitis and helminths also have been associated with AE. Our patient had no clinical history or laboratory studies suggesting a physical trigger or infection.

AE also can be an associated symptom of an underlying systemic illness such as collagen vascular disease or malignancy. Chronic idiopathic AE is diagnosed after an individual has had >6 weeks of recurrent symptoms and all other possible diagnoses have been ruled out.

Our patient's history and abnormal complement studies were more consistent with HAE or AAE. HAE is an autosomal dominant disease caused by a defective C1 esterase inhibitor enzyme (C1-INH). The prevalence of the disease is ~1 in 50,000 with no ethnic or gender predominance.⁶ Affected patients usually present with AE in childhood. The frequency of AE bouts in HAE patients can be variable throughout an individual's life and does not correlate with laboratory findings. C1-INH controls activation of the complement system by limiting the autoactivation of the C1 component. The enzyme also controls contact phase activation by inhibiting kallikrein, the protease involved in bradykinin release. Approximately 85% of HAE patients have low levels of C1-INH and are considered to have type I HAE.⁷ Although there is one functional gene, plasma levels of C1-INH are usually 5–30% of normal, likely because of increased catabolism of the enzyme.⁸ The remaining 15% have the type II variant and have normal to high C1-INH levels, but the enzyme is dysfunctional. Patients with HAE I and II have uncontrolled complement system activation; laboratory studies show low C4, low C2, and decreased C1-INH levels and/or activity. Recently, another presentation of HAE not associated with the C1-INH mutation has been described and is believed to be estrogen dependent. These patients had normal C4 as well as normal C1-INH levels and function.^{9,10} All cases have been in female patients with a dominant mode of inheritance. Our patient did not appear to have HAE because he had no family history of AE and his initial presentation occurred in adulthood.

Approximately 4.4% of patients with nonallergic AE are diagnosed with AAE.¹¹ Patients with AAE are clinically similar to patients with HAE, but there is no family history of AE. Initial presentation usually occurs during the fourth decade of life or later, as in our

patient. AE results from excessive catabolism of C1-INH and subsequent hyperactivation of the classic complement pathway. Therefore, patients are classically described as having not only low C1-INH and C4 levels but also decreased C1q levels. AAE often is classified into two types; type I is associated with B-cell lymphoproliferative disease and type II is rarely associated with an autoimmune disorder. Lymphoproliferative diseases include multiple myeloma,¹² Waldenstrom macroglobulinemia,¹³ gastric carcinoma,¹⁴ and B-cell lymphoma.¹⁵ Neoplastic lymphatic tissues consume C1-INH¹⁶ and/or classic pathway components,¹⁷ leading to enzyme deficiency and more bradykinin release. Autoimmune processes include Churg-Strauss vasculitis¹⁸ and systemic lupus erythematosus.¹⁹ These patients produce autoantibodies to C1-INH,²⁰ enhancing immune-mediated cleavage of the enzyme and thereby inactivating it. The differentiation between the two AAE types may not be so clear, however; patients with lymphoproliferative disease and AAE also can develop C1-INH autoantibodies. Final diagnoses ranged from monoclonal gammopathy of unknown significance to B-cell lymphoma.²¹

Our patient's free C1-INH IgG autoantibody level was elevated at 70.8 (normal range, <14.3). However, his C1q was in the normal range. Cicardi *et al.* reported that 5 of 23 AAE patients who developed lymphoproliferative disease had normal C1q levels.²² Hence, some patients with AAE associated with lymphoproliferative disease also have normal C1q.

Initial laboratory workup for AE includes a C1-INH level and function as well as a C4 level. If low, then C1q should be ordered to distinguish between hereditary or acquired C1-INH deficiency. However, C1q levels are not always depressed in AAE, so history and physical examination should help determine the final diagnosis. If autoimmune disease is suspected, then an ANA, rheumatoid factor, and sedimentation rate should be ordered. If AAE is suspected, then workup for an underlying malignancy should be pursued. This includes immunophenotyping of peripheral blood lymphocytes for circulating malignant B cells; serum protein electrophoresis and immunoelectrophoresis for underlying dysproteinemia; and CT of the chest, abdomen, and pelvis. Bone marrow biopsy is also helpful.

Treatment for acute AE of the larynx, pharynx, and tongue should be approached as life-threatening emergencies. If airway obstruction is suspected, then emergency procedures include epinephrine and intubation. However, commonly used agents for airway edema such as epinephrine as well as glucocorticoids and antihistamines have not been effective in treating C1-INH-deficient patients because the underlying pathogenesis is not histamine-mediated. More effectively, C1-INH concentrate can treat acute HAE and AAE attacks. C1-INH preparations are currently unavailable

in the United States, but preliminary studies investigating its effectiveness are promising. Sixty-nine percent of attacks abated within 30 minutes of infusion, and 95% of attacks were relieved within 4 hours.¹¹ In AAE, higher doses of C1-INH may be required because of the rapid catabolism of C1-INH that characterizes AAE.

Fresh frozen plasma (FFP) is widely used in the United States for treatment of acute AE attacks and as short-term prophylaxis before surgery because it contains complement components.^{23–25} However, there is concern that administration of additional complement proteins in FFP can also exacerbate AE attacks.²⁶ There is also a risk of urticaria, anaphylactic shock, hemolysis, and infectious agent transmission during an FFP infusion. For abdominal pain during attacks, spasmolytics such as butylscopolamine may be used.¹¹

Long-term prophylaxis is indicated for patients who have more than one disabling attack a month.¹¹ These agents include attenuated androgens and antifibrinolytics. Danazol and stanozolol are attenuated androgens that increase hepatic synthesis of C1-INH. Long-term administration may be associated with weight gain, virilization in women, hemorrhagic cystitis, hepatotoxicity, hepatic adenocarcinomas, and liver cell carcinomas. Hepatic studies should be followed while patients are on attenuated androgens; liver ultrasounds may be more sensitive than changes in aminotransaminase levels for early diagnosis of liver tumors.

Patients with AAE may benefit more from long-term treatment with antifibrinolytic agents, such as tranexamic acid, which act by inhibiting plasminogen activation. The production of plasmin also can facilitate the release of bradykinin. Side effects of antifibrinolytics include abdominal discomfort, diarrhea, and nausea. ϵ -aminocaproic acid is also used but adverse effects including postural hypotension and weakness could be more severe. There is a theoretical risk of increased thrombosis in patients taking antifibrinolytics.

Other options are being investigated for treatment of acute AAE attacks.¹¹ The kallikrein inhibitor DX-88 has a high affinity for kallikrein and therefore blocks the release of bradykinin from high molecular weight kininogen. Icatibant, a bradykinin antagonist, is a synthetic bradykinin-like peptide with the same affinity for bradykinin receptors. Finally, recombinant C1-INH has been developed from the milk of transgenic rabbits.

In autoantibody-mediated AAE, the underlying syndrome needs to be identified and treated for successful control of symptoms. Immunosuppressive therapy such as cyclophosphamide²⁷ and rituximab,²⁸ a chimeric monoclonal antibody that causes rapid and specific B-cell depletion in the peripheral blood,²⁹ have led to complete and partial remissions. Nevertheless, the

therapeutic or palliative effects of these options are still unclear.

Final Diagnosis

The final diagnosis was AAE secondary to autoantibodies to C1-INH associated with lymphoproliferative disease.

SUMMARY

AAE is an uncommon but potentially life-threatening disease in the older adult population. After the individual is cleared of the initial danger period, a thorough workup for an underlying etiology must be done. C1-INH autoantibody-producing lymphoproliferative disease is a rare cause of AAE.

REFERENCES

1. Milton JL. On giant urticaria. *Edinburgh Med J* 22:513–514, 1876.
2. Gleich GJ, Schroeter AL, Marcoux JP, et al. Episodic angioedema associated with eosinophilia. *N Engl J Med* 310:1621–1626, 1984.
3. Irons BK, and Kumar A. Valsartan-induced angioedema. *Ann Pharmacother* 7–8:1024–1027, 2003.
4. Cicardi M, Zingale LC, Bergamaschini L, et al. Angioedema associated with angiotensin-converting enzyme inhibitor use: Outcome after switching to a different treatment. *Arch Intern Med* 164:910–913, 2004.
5. Patterson R, Mellies CJ, Blankenship ML, et al. Vibratory angioedema: A hereditary type of physical hypersensitivity. *J Allergy Clin Immunol* 50:174–182, 1972.
6. Tosi M. Molecular GENETICS of C-inhibitor. *Immunobiology* 199:358–365, 1998.
7. Frank MM. Hereditary angioedema: A half century of progress. *J Allergy Clin Immunol* 114:626–628, 2004.
8. Prada AE, Zahedi K, and Davis AE. Regulation of C1-inhibitor synthesis. *Immunobiology* 199:377–388, 1998.
9. Binkley KE, and Davis A. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 106:546–550, 2000.
10. Abdi R, Dong VM, Lee CJ, et al. Angiotensin II receptor blocker-associated angioedema: On the heels of ACE inhibitor angioedema. *Pharmacotherapy* 22:1173–1175, 2002.
11. Agostini A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol* 114(suppl 3):S51–S131, 2004.
12. Gordon EH, Beall GN, and Klaustermeyer WB. Angioedema and multiple myeloma. I. *Ann Allergy* 51:349–350, 1983.
13. Delmer A, Garban F, Le Tourneau A, et al. Waldenstrom's macroglobulinemia with prominent splenomegaly and multiple immune disorders. *Haematologica* 78:408–410, 1993.
14. Wasserfallen JB, Spaeth P, Guillou L, et al. Acquired deficiency in C1-inhibitor associated with signet ring cell gastric adenocarcinoma: A probably connection of antitumor-associated antibodies, hemolytic anemia, and complement turnover. *J Allergy Clin Immunol* 95:124–131, 1995.
15. Mathur R, Toghiani PJ, and Johnston ID. Acquired C1 inhibitor deficiency with lymphoma causing recurrent angioedema. *Postgrad Med* 69:646–648, 1993.
16. Schreiber AD, Zweiman B, Atkins P, et al. Acquired angioedema with lymphoproliferative disorder: Association of C1 inhibitor deficiency with cellular abnormality. *Blood* 48:567–580, 1976.
17. Hauptmann G, Petitjean F, Lang JM, et al. Acquired C1 inhibitor deficiency in a case of lymphosarcoma of the spleen: Reversal of complement abnormalities after splenectomy. *Clin Exp Immunol* 37:523–531, 1979.
18. Pasquali JL, Christmann D, Modert F, et al. First case of acquired functional C1(-)INH deficiency: Association with angioedema during Churg and Strauss vasculitis. *Int Arch Allergy Appl Immunol* 74:284–285, 1984.
19. Massa MC, and Connolly SM. An association between C1 esterase inhibitor deficiency and lupus erythematosus: Report of two cases and review of the literature. *J Am Acad Dermatol* 7:255–264, 1982.
20. Jackson J, Sim RB, Whelan A, et al. An IgG autoantibody which inactivates C1-inhibitor. *Nature* 323:722–724, 1986.
21. Fremeaux-Bacchi V, Dragon-Durey MA, Blouin J, et al. Prevalence of monoclonal gammopathy in patients presenting with acquired angioedema type 2. *Am J Med* 113:194–199, 2002.
22. Cicardi M, Zingale LC, Pappalardo E, et al. Autoantibodies and lymphoproliferative disease in acquired C1 inhibitor deficiencies. *Medicine* 82:274–281, 2003.
23. Galan HL, Reedy MB, Starr J, et al. Fresh frozen plasma prophylaxis for hereditary angioedema during pregnancy: A case report. *J Reprod Med* 41:541–544, 1996.
24. Warrior MR, Copilevitz CA, Dykewicz MS, et al. Fresh frozen plasma in the treatment of resistant angiotensin-converting enzyme inhibitor angioedema. *Ann Allergy Asthma Immunol* 92:573–575, 2004.
25. Hill BJ, Thomas SH, and McCabe C. Fresh frozen plasma for acute exacerbations of hereditary angioedema. *Am J Emerg Med* 22:633, 2004.
26. Zuraw BL. Diagnosis and management of hereditary angioedema: An American approach. *Transfus Apher Sci* 29:239–245, 2003.
27. Heymann WR. Acquired angioedema. *J Am Acad Dermatol* 36:611–615, 1997.
28. Ziakas PD, Giannouli S, Psimenou E, et al. Acquired angioedema: A new target for rituximab? *Haematologica* 89:ELT 13, 2004.
29. Rastetter W, Molina A, and White CA. Rituximab: Expanding role in therapy for lymphomas and autoimmune diseases. *Annu Rev Med* 55:477–503, 2004. □