

Acquired angioedema: Autoantibody associations and C1q utility as a diagnostic tool

Seth Ilias Breitbart, M.D.,¹ and Leonard Bielory, M.D.²

ABSTRACT

Acquired Angioedema (AAE) is a rare condition classified into two subtypes: Type I, which is associated with lymphoproliferative disorders, and Type II, which is linked with autoantibodies against C1-esterase inhibitor (C1-INH). Unlike Type I AAE, Type II has no correlation with lymphoproliferative disorders. We report the evaluation of angioedema that was associated with an underlying lymphoproliferative disorder for the purpose of discussing the relationship between C1q and a diagnosis of AAE. A literature review was completed for the purpose of assessing the diagnostic value of C1q when used in the workup of AAE. A PubMed/Web of Science search (1976–2010) produced 78 references (yielding 167 individual cases of AAE) using terminology “AAE.” The case described a patient with a depressed C1q (<3.5 mg/dL), decreased C4 (<3 mg/dL), decreased C1-inhibitor (1 mg/dL), decreased functional C1-INH (12%), and decreased total complement (<10 U/mL). Autoantibodies against C1-INH (free and bound respectively) were normal (12.4% and 10.1% of the standard of deviation). Using the above figures and data collected from the literature search, we tabulated 168 individual cases of AAE. Of the 168 cases, C1q was drawn in 104 cases, and 64 cases have no information regarding C1q. There are 10 cases where the C1q was documented as normal. With these values, a correlation between C1q and a diagnosis of AAE was assessed: A decreased C1q correlated with a diagnosis of AAE approximately 56%–94% of the time. C1q is a useful tool when working up a case of AAE.

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CASE PRESENTATION

Chief Complaint

A 75-year-old man is referred for evaluation of recurrent angioedema.

History of Present Illness

A 75-year-old man with a medical/surgical history significant for diabetes mellitus type II, hypertension, osteoarthritis, and benign prostatic hyperplasia was referred for recurrent angioedema that began 4 years ago. He denied exposure to toxic inhalants, chemicals, or radiation. Although he denied any allergic reaction to foods/insects, he admitted using lisinopril in the past, which had been discontinued by a physician because of suspicion that it may have caused angioedema. He denied any reactions to other medications.

There was no family history of angioedema. His parents both died from cancer. A brother has coronary artery disease, and his son and daughter were reportedly healthy.

Medications taken at home included the following: tamsulosin hydrochloride, meloxicam, simvastatin/niacin extended release, losartan, potassium-hydrochlorothiazide, oxybutynin, glimepiride, metformin, folic acid, multivitamins, omega-3 fatty acid, and aspirin.

The initial episode of angioedema occurred approximately 4 years ago, described by a swelling of his foot that progressed over 1 day, which later advanced to involve the tongue and throat. The patient went to the emergency department, was admitted for observation, and was treated with i.v. corticosteroids and diphenhydramine. He had been taking lisinopril, which was discontinued on the hospital admission.

QUESTION 1

Looking at the aforementioned medication list, are there any other medications that you would discontinue, given the patient's symptoms of angioedema?

Answer

See Review Questions section for answers. Since his discharge, he continued to have recurrent episodes of

From the ¹Mount Sinai School of Medicine Program, Englewood Hospital and Medical Center, Englewood, New Jersey, and ²STARx Allergy and Asthma Center, LLC, Medicine, Pediatrics, Ophthalmology, and Visual Sciences, Center for Environment Prediction, Rutgers University, New Brunswick, New Jersey

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Address correspondence and reprint requests to Seth Breitbart, M.D., Englewood Hospital and Medical Center, 350 Engle Street, Englewood, NJ 07631

E-mail address: sethibreitbart@hotmail.com

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angioedema, occurring every 4 months, which involved his extremities and oropharynx. He also mentioned multiple bouts of abdominal pain that typically last for 1 day and resolve spontaneously, although they have never occurred concurrently with airway/extremity swelling. He denied hospitalizations for small bowel obstruction.

When the symptoms appear, he often proceeds to obtain emergency room care and is usually treated with i.v. corticosteroids and diphenhydramine. He was uncertain if these treatments are contributing to his symptomatic improvement, because he had noticed angioedema episodes that have resolved spontaneously in the absence of intervention. The patient stated that these episodes will completely resolve after 2 days regardless of intervention, and many times improvement will occur within several hours. His last episode occurred 1 month before his first visit in our office, while in recovery after a cardiac catheterization. This episode followed a similar course as the prior events.

The patient had been referred to hematology/oncology and allergy/immunology offices for an extensive diagnostic workup 4 months before coming to our office.

QUESTION 2

How would you begin the diagnostic workup? What laboratory tests would you order to facilitate making a diagnosis?

Answer

See Laboratory and Other Diagnostic Data and Clinical Course sections. Also, see angioedema algorithm (Fig. 1) and angioedema subtypes review (Table 1).

Physical Examination

Vital signs obtained in our office showed the following: temperature of 98.8°F, pulse rate of 110 beats/minute, blood pressure of 162/90 mmHg, and oxygen saturation of 94% on room air. He was a healthy-appearing elderly man and measured 175 cm tall. The remainder of the exam was unremarkable. An inspection of the skin and oral mucous membranes revealed no signs of angioedema. There was a scar over chest wall/sternum from previous open heart surgery.

Laboratory and Other Diagnostic Data

Laboratory data before the referral to our office had revealed the presence of hypogammaglobulinemia: total IgG count of 446 (lower limit of normal is 650). A repeat total IgG of 382 confirmed the diagnosis. Liver function tests and complete blood counts had been unremarkable. Previous comprehensive metabolic profiles had also shown values within normal limits. A lymphoma/leukemia panel was drawn, showing an

elevated percentage of CD19 (26%) and CD20 (29%). This documented elevation of B-cell markers was suspicious for chronic B-cell leukemia among other malignancies, prompting further investigation.

Serum protein electrophoresis with immunofixation additionally showed a faint IgM- κ monoclonal spike as well as faint bands in IgG and - λ against a dense polyclonal background. Peripheral blood flow cytometry/lymphoma panel conveyed a small monoclonal B-cell population that was consistent with atypical B-cell chronic lymphocytic leukemia or non-Hodgkin's lymphoma.

The aforementioned laboratory data were collected from 2 years ago until 4 months before the patient's initial visit in our office.

Clinical Course

The patient had been appropriately referred to a hematologist/oncologist for a bone marrow biopsy 4 months before our first office encounter, which recently returned negative for malignancy. He was subsequently seen in our office. Flow cytometry was repeated, yielding similar findings as those documented 2 years ago, regarding the likelihood of chronic B-cell leukemia. Serum electrophoresis was additionally repeated, showing a κ -spike.

QUESTION 3

What is the possible significance of the κ -spike that is shown in the serum protein electrophoresis?

Answer

In monoclonal gammopathy of undetermined significance or in multiple myeloma, plasma cells typically produce more light chains than are required to create a whole immunoglobulin. The excess light chains enter the blood stream as free light chains (unattached to the heavy chains). Normal levels of free light chains in serum have recently been reported, along with the normal ratio of κ -free light chains to λ -free light chains. A high κ -light chain in conjunction with a normal λ -light chain supports the diagnosis of a monoclonal gammopathy and thus requires a bone marrow biopsy. The fact that the levels of the κ - and λ -light chains are high and normal, respectively, suggests that if a monoclonal gammopathy does indeed exist, there is no bone marrow suppression. If either the λ - or κ -levels had been low, then that would suggest possible bone marrow suppression.

Laboratory data attained by our office recently revealed a low C1q at <3.5 mg/dL (reference, 5.0–8.6 mg/dL), a decreased C4 at <3 mg/dL (reference, 16–47 mg/dL), a decreased C1-esterase inhibitor level (C1-INH) at 1 mg/dL (reference, 11–26 mg/dL), decreased functional C1-INH at 12% (reference, $\geq 68\%$),

Table 1 Acquired Angioedema Subtypes Review

Subtype	Overview	Symptoms	Complement System Assessment	Treatment
AAE type I ^{13,50}	Illustrated by the presence of a C1 inhibitor deficiency and a strong association with lymphoproliferative diseases, usually affecting the B-cell line, or other malignant diseases	Largely similar to HAE type I, fatal laryngeal edema can also occur in AAE; symptoms most commonly begin after 40 years; no family history is noted	Decreased C4 level Decreased C1q level Decreased or normal C1-INH level Anti-C1-INH antibody is absent	Treatment of the underlying lymphoproliferative disease will often remedy the angioedema Antifibrinolytics such as tranexamic acid and ϵ -aminocaproic acid for possible prevention Androgens, such as danazol or stanozolol, may be useful in AAE type I; prostate cancer and pregnancy preclude the use of androgens
AAE type II ¹⁴	Defined by the presence of autoantibodies against C1-INH, and thereby leading to the unopposed activation of the complement cascade, without a correlation with lymphoproliferative diseases	Same symptoms as in AAE type I	Decreased C4 level Decreased C1q level Decreased or normal C1-INH level Anti-C1-INH antibody is present	As in HAE, C1-INH concentrates or, if unavailable, fresh-frozen plasma may be used Androgens have not shown to be beneficial in AAE-II Antifibrinolytics, such as those mentioned above in the AAE type I section, have been found to be effective for long-term prophylaxis in those with AAE

AAE = acquired angioedema; C1-INH = C1-esterase inhibitor; HAE = hereditary angioedema.

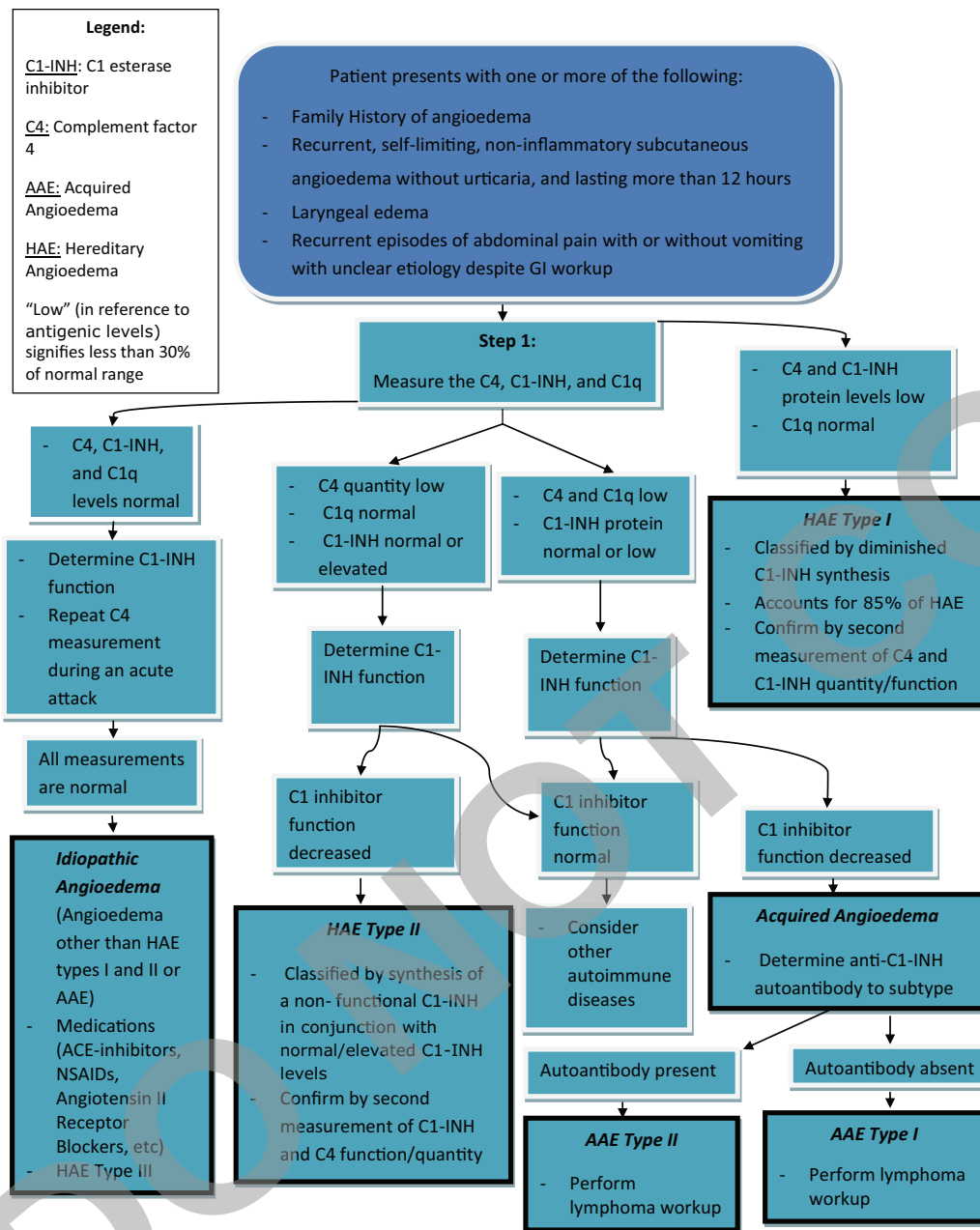


Figure 1. Angioedema Algorithm: Diagnosis of angioedema (Source: Refs. 6, 49, and with permission from the authors of Ref. 48).

and a decreased total complement at <10 U/mL (reference, 31–66 U/mL). C1-INH autoantibody levels were obtained 6 months after the patient's initial office visit: the free IgG autoantibody was within the normal range at 12.4% of the SD (reference, 0.89–36.1%), and the bound IgG autoantibody was also within the normal range at 10.1% of the SD (reference, 0.3–46.3%).

REVIEW QUESTIONS

1. What is the Differential Diagnosis?

The differential diagnosis includes acquired angioedema (AAE) type I, AAE type II, hereditary angioedema (type I, II, or III), medication-induced angioedema, pressure or vibratory angioedema, episodic

angioedema with eosinophilia (a.k.a. Gleich's syndrome), or idiopathic angioedema.

AAE type I should be ranked the highest on the differential diagnosis, given the laboratory suggestion of a lymphoproliferative disorder. Medication-induced angioedema still remains a possibility, despite the discontinuation of the lisinopril. Gleich's syndrome should be ranked low on a differential, because there was no eosinophilia seen on a complete blood count. AAE type II was ruled out, given the normal levels of autoantibody against C1-INH. Hereditary angioedema was ruled out given the lack of a family history of angioedema and low C1q. (For the diagnostic criteria of hereditary angioedema and AAE types I and II, please see Fig. 1.)

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

No additional tests are required to determine the diagnosis (see angioedema algorithm for review of laboratory testing). Medications commonly known for causing angioedema should be discontinued immediately. The angiotensin-converting enzyme inhibitor was stopped, but the patient was taking nonsteroidal anti-inflammatory drugs, specifically meloxicam, and an angiotensin receptor blocker (ARB), specifically losartan. Nonsteroidal anti-inflammatory drugs are well known for causing angioedema¹ and should be ceased entirely to thoroughly exclude medication-induced angioedema from the differential diagnosis. Although ARBs cause angioedema less commonly than angiotensin-converting enzyme inhibitors,² the possibility still exists that the ARB may be the cause of the patient's angioedema, and thus it should be stopped as well.

DISCUSSION

AAE is a rare condition characterized by the recurrent bouts of nonpitting mucocutaneous edema involving subcutaneous tissues, the larynx,³ or the gastrointestinal tract^{4,5} in patients who have no family history of similar occurrences. Episodes of the angioedema most commonly will present after 50 years.⁶ When the subcutaneous tissues are involved, the swelling is classically nonpruritic and painless. This swelling, especially when affecting the larynx and tongue, can be fatal without proper intervention.⁷ It is important to distinguish this condition from the hereditary form, which is much more common in comparison.⁸ There are two known forms of AAE, denoted as type I and type II.

AAE type I illustrates a C1 inhibitor deficiency and a strong association with lymphoproliferative diseases⁹ (mainly affecting B cells) or other malignant diseases, such as multiple myeloma, chronic lymphocytic leukemia, myelofibrosis, Waldenström macroglobulinemia, or non-Hodgkin's lymphoma.¹⁰ In fact, non-Hodgkin's lymphoma is found in 20% of these patients and monoclonal gammopathy is observed in 35%.¹¹ This relationship between AAE type I is so strong that some researchers have advised a full workup for acquired angioedema, including C1q, in anyone with presumed B-cell lymphoma. In addition, often, the presenting clinical sign of a lymphoproliferative disorder of B lymphocytes may be angioedema.^{12,13}

Although a thorough diagnostic workup for AAE is indicated in all patients diagnosed with B-cell lymphoma, the converse is also true, and anyone diagnosed with AAE should have a full hematologic workup for lymphoma, because the association between the two is so clear. AAE's coexistence with a

true B-cell malignancy, nonmalignant B-cell proliferation, or pathogenic autoimmune responses suggests that a large percentage of AAE patients are affected by altered B-cell proliferation control, although clinical outcomes may vary.¹³ Our patient was appropriately referred to a hematology/oncology office for a comprehensive diagnostic workup.

The prognosis for AAE is variable and often depends on controlling the underlying disorder (usually a lymphoproliferative disorder/malignancy in AAE type I). AAE type II is linked to the presence of autoantibodies against C1-INH, thereby leading to the unopposed activation of the complement cascade.¹⁴ Contrary to AAE type I, AAE type II typically does not have a correlation with lymphoproliferative diseases. However, the presence of coexisting AAE types I and II¹⁵⁻¹⁸ indicates that the discrimination of the two forms of AAE may be ill defined.

AAE is an extremely rare disease, with >140 cases worldwide.^{11,19} The association of AAE type II disease occurring simultaneously with AAE type I is even more extraordinary, with only eight reported cases.¹⁵⁻¹⁸

An attempt has been made to assess the correlation of C1q and a diagnosis AAE. A Pubmed literature search using the keywords "acquired angioedema" (looking at all case reports, clinical trials, and review articles with full text) yielded 167 individual cases of AAE. If we add our aforementioned case to the literature, there is a total yield of 168 AAE cases. Of those 168 cases, C1q has been drawn 104 times. The remaining 64 cases have no information regarding C1q, and the diagnosis of AAE in those cases is made by a lack of family history of angioedema in conjunction with a low C4 and/or low C1-INH or low C1-INH function. Further review of the 168 cases of AAE shows that the C1q value is reportedly normal in 10 cases^{6,15,18,20} and diminished in 94 cases.^{6,10,17,18,21-47} Thus, we can determine the correlation of C1q and a diagnosis of AAE in a range: a decreased C1q correlates with a diagnosis of AAE ~56-94% of the time. (This range of percentages has been calculated by looking at the two extremes: the first extreme assumes that the 64 cases with no information regarding C1q have a normal C1q value, and the second extreme assumes that all 64 cases with no information about C1q have a diminished C1q value.)

With the use of C1q in conjunction with a diagnosis of AAE established previously, we believe that C1q remains a valuable tool in the workup of angioedema. (For information regarding the diagnosis and treatment of angioedema, see Fig. 1.)

FINAL DIAGNOSIS

The final diagnosis was AAE type I.

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