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A unique case of delayed diagnosis of early onset acquired angioedema

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Abstract

Acquired angioedema (AAE) is a very rare condition caused by an acquired deficiency in C1 esterase inhibitor (C1 INH). Pathogenesis of AAE can entail abnormal B cell lymphoproliferation ranging from benign monoclonal gammopathy of undetermined significance (MGUS) to malignant forms of lymphoma. Symptoms related to MGUS or malignancy are often salient and age is often used as a diagnostic tool in considering in making this diagnosis. These bradykinin-mediated angioedema episodes commonly involve face, gastrointestinal system, and pharynx with associated potential for fatality and lack associated urticaria. Hence early diagnosis is vital. This case is unique, in that it describes a very early age of presentation of AAE related to MGUS. Given young age and lack of symptoms associated with MGUS, diagnosis was delayed and significant patient morbidity and healthcare expenses occurred which could have been avoided. A 41 year-old male presented to the allergy/immunology clinic with facial, lip, and tongue swelling following tooth extraction. His history began 5 years prior, after suffering complications from a motor vehicle accident including anterograde amnesia, multiple broken ribs, and a splenic hemorrhage requiring splenectomy. Six months after the accident he developed acute onset bilateral facial swelling, lip swelling, and difficulty breathing. He had no family history of angioedema, was not taking any medications, and his serum tryptase level checked during the episode was normal. He was diagnosed with presumed food-induced allergic angioedema. The patient suffered four additional episodes of varying degree over the next five years and developed clinical depression. Immunological evaluation showed low C1-INH, low C1-INH functional percentage, C4, C2, and C1q, consistent with AAE. Further workup to determine the etiology of AAE included serum protein electrophoresis demonstrating an M-spike in the gamma region with immunofixation showing a monoclonal protein band and a serum IgM level of 1.3 g/dl. The patient was diagnosed with AAE related to MGUS.

Keywords: Acquired angioedema, monoclonal gammopathy of undetermined significance, C1 esterase inhibitor

Background

Acquired angioedema (AAE) is a very rare condition associated with episodic mucosal swelling commonly involving the face, gastrointestinal system, and pharynx caused by an acquired deficiency in C1 esterase inhibitor (C1 INH). Pathogenesis of AAE can involve abnormal B cell lymphoproliferation ranging from benign monoclonal gammopathy of undetermined significance (MGUS) to malignant forms of lymphoma. This case describes a very early age of presentation of AAE related to MGUS.

Case presentation

We present the case of a 41 year-old male who presented to the allergy/immunology clinic after having an episode of facial, lip, and tongue swelling following tooth extraction. His history began five years prior, when he presented to an emergency room after being in a near-fatal motorcycle accident. He had suffered extensive injuries including brain contusions resulting in the development of anterograde amnesia and multiple fractured ribs, as well as splenic hemorrhage requiring splenectomy. Six months later, the patient had an episode of bilateral facial swelling, lip swelling, and difficulty breathing. He was evaluated in the local emergency room, and was given epinephrine, diphenhydramine, and methylprednisolone. Because of the patient's anterograde amnesia and inability to recall specific food consumed, evaluating physicians assumed he was having a food-related allergic reaction. Tryptase level was checked during the attack and it was found to be 2.8 µg/L (reference range 2.1–13.1). The patient did not have a history of allergies or family history of angioedema. The patient was not taking any medications at that time. The patient was observed in the hospital observation unit for 48 hours and discharged with an epinephrine pen. He subsequently had approximately 4-5 similar episodes of varying degree per year over the next 5 years. He required intubation on one occasion for airway protection. He developed significant depression and required placement in a nursing home.

Given the clinical presentation of recurrent isolated angioedema without urticaria, bradykinin-mediated angioedema was high on the differential. Patient had low C1-INH 12 mg/dL (21-39), C1-INH functional percentage 1% (<47% abnormal), C4 1.67 mg/dL (16-38), C2 .2 mg/dL (1-4), and C1q <2 mg/dL (7-48). Low levels of C1-INH, C1-INH functional percentage,

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and C4 can also be seen in patients with type 1 HAE (often also with family history of angioedema), however the low C1q level indicated the diagnosis of AAE (reduced in 70% of patients with AAE) [2]. Workup for AAE included evaluation for both lymphoproliferative and autoimmune disease. Diagnostic testing included complete blood cell count with differential, serum protein electrophoresis, antinuclear antibodies, chest radiograph, and abdominal ultrasound to assess lymphoid tissue. Testing was unrevealing except for serum protein electrophoresis which demonstrated an M-spike in the gamma region, with immunofixation demonstrating a IgM-monoclonal protein band with serum IgM level of 1.3 g/dL. Subsequent bone marrow biopsy and FISH did not show any clonal abnormalities or evidence of malignancy. Hence, etiology of AAE was determined to be IgM-monoclonal gammopathy of undetermined significance (MGUS). Patient was subsequently started on long term AAE prophylaxis with 600 mg danazol daily, and patient has not had an episode of angioedema in 6 months.

Discussion

This is a unique case describing early onset AAE related to MGUS with significantly delayed diagnosis. His early age of onset of MGUS as a cause of AAE, physical impairment of amnesia, and misdiagnosis of food allergy were critical in delay of diagnosis. This case highlights the importance of continued understanding and awareness of the different causes of angioedema and early diagnosis.

Acquired angioedema (AAE) is a syndrome characterized by acquired deficiency of C1 esterase inhibitor (C1-INH), leading to excessive activation of the complement system and subsequent bradykinin-mediated angioedema. As in hereditary angioedema (HAE), which is also bradykinin-mediated, AAE also presents with episodic mucosal swelling involving the oropharynx, larynx, face, genitals, and gastrointestinal tract. Symptoms of face, lip, and tongue swelling as well as life-threatening pharyngeal involvement are typical [1]. AAE diagnosis is often difficult to make because of the lack of family history (present in HAE) and trigger that can be obtained via clinical history. Delay in diagnosis leads to an impedance in receiving appropriate treatment. Untreated, recurrent episodes of angioedema lead to significant impairment in quality of life, increased risk of morbidity and death, as well as increased healthcare costs.

AAE is characterized by recurrent angioedema without urticaria, and an acquired deficiency of C1-INH leading to hyperactivation of the complement system. AAE is extremely rare with roughly 100 reported cases in literature [3]. HAE prevalence has been estimated between 1:10,000 and 1:50,000 [4]. AAE is more uncommon with rough estimate prevalence for AAE of 1:100,000 and 1:500,000. AAE is traditionally related to a B cell disorder ranging from production of anti-C1 INH auto-antibodies to monoclonal gammopathy of undetermined significance and non-Hodgkin lymphoma causing C1 INH consumption. This deficiency of C1 INH leads to activation of the classic complement pathway, and depletion of C1, C2, and C4. The contact system is activated, kallikrein is generated that cleaves high molecular weight kinninogen producing bradykinin (primary mediator in AAE) which increases vascular permeability causing mucosal edema [5]. AAE has also rarely been reported in patients with systemic lupus erythematosus (SLE) and other infections. HAE is an autosomal dominant hereditary disease caused by a C1-INH deficiency due to mutations in C1-INH gene (SERPING1 gene) on chromosome 11 [4]. Clinically symptoms are similar to AAE, but age of onset is earlier. Generally, in HAE initial symptoms manifest in 90% of the patients during the second decade of life, while in AAE patients are usually over 40 years of age [7]. This case is also unique in that it seems to be one of the youngest patients (36) with AAE that has been reported. Standard treatment for an AAE episode is replacement therapy with plasma-derived C1-INH concentrate (pd C1-INH), however some patients become progressively less responsive to pd C1-INH over time. Case studies have shown efficacy in AAE treatment with Icatibant (a selective bradykinin B_2 receptor antagonist), Ecallantide (a kallikrein inhibitor), and Rituximab (CD20 monoclonal ab) [3-5].

The explanation for delay in diagnosis is multifactorial. The patient being an unreliable historian (anterograde amnesia), lack of knowledge and understanding of AAE in the medical community, and the low prevalence of AAE all contributed to delayed diagnosis. Additionally, a lack of symptoms associated with MGUS, the underlying cause of AAE in this patient, made it more difficult to diagnose. Ability to differentiate other causes of angioedema based on clinical history, triggers, family history, and time of symptom onset can help expedite identification of the etiology. (**Table 1**) outlines the factors that can be helpful in differential diagnosis. Healthcare costs and psychological studies on the burden of AAE have not been done, but in HAE recurring attacks have been shown to cause significant evidence of depression, decreased work productivity, and overall activity impairment. Additionally, HAE attacks lead to approximately 15,000 to 30,000 emergency department visits each year, with significant associated hospital costs [10]. With new successful advances in HAE (and also AAE since therapy is similar), such psychological impairment and healthcare expenses can be curtailed with early diagnosis.

In summary, we present a unique case of delayed diagnosis of early onset AAE. When evaluating patients with recurrent angioedema without urticaria, clinicians must consider all causes of C1-INH deficiency including AAE. Symptoms related to a cause of AAE like MGUS may be missing but diagnosis should be considered even if of younger age. Delay in diagnosis may lead to unnecessary psychological stress and excessive healthcare expenses.

Competing interests

The authors declare that they have no competing interests.

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Table 1. General characteristics of different causes of angioedema.

Type of Angioedema	Age of Onset	Location of Edema	Associated Urticaria	Trigger	Diagnosis	Treatment Principle
Histamine-induced	Variable	Variable	YES	Type 1 IgE-mediated hypersensitivity to food, drugs, or insect venom	Clinical history, allergy testing	Identification of allergy and avoidance, or desensitization in certain drugs or venom
Angiotensin-converting enzyme (ACE)-induced	2/3 of episodes occur within first 3 months of therapy [8]	Lips, tongue, face are common. Pharyngeal/ laryngeal reported, GI tract least likely [8]	NO	ACE-inhibitor or aldosterone receptor blocker (ARB) medications	Clinical history, use of ACE-inhibitors	Discontinuation of medication
HAE	40% before age 5, 75% by age 15 [8], 90% within 2nd decade [7]	80% GI tract involvement; laryngeal/pharyngeal, cutaneous involvement frequently limbs [7]	NO	Mild trauma, dental work, surgery, stress, cold-exposure, estrogen-derivatives, ACE-Inhibitors [4]	Type I: Low C1 INH, C1 INH function, C4, normal C1q Type II: Low C1 INH function, C4, normal C1 INH, C1q Type III: All normal complement levels	Airway protection, C1-INH replacement, Bradykinin B2 receptor antagonist (Icatibant), Kallikrein inhibitor (Ecallantide)
AAE	Over 40*	30-50% GI tract; laryngeal/pharyngeal, cutaneous recurrence face>limbs [7]	No	Similar to HAE	Low C1 INH, C1 INH function, C4, C1q	Treatment of underlying cause (ie lymphoma), otherwise similar to HAE

*This case describes a patient who presented at age of 36 which is very uncommon.

Authors' contributions

Authors' contributions	NGP	JY	WK
Research concept and design	✓	--	--
Collection and/or assembly of data	✓	--	--
Data analysis and interpretation	✓	--	--
Writing the article	✓	--	--
Critical revision of the article	✓	--	--
Final approval of article	✓	✓	✓
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