Case Report

Systemic Lupus Erythematous Presenting as Acquired Angioedema: A Case Report and Review of the Literature

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Received: July 26, 2017; Accepted: August 06, 2017; Published: August 13, 2017

Abstract

This case reports a previously healthy 30-year-old woman who developed angioedema with acquired C1 inhibitor deficiency as a rare presentation of systemic lupus erythematos. The patient had no previous family history, did not use any known inciting drugs, and had a negative work-up for lymphoproliferative disease. Her symptoms were managed with glucocorticoids and anti-histamines without significant improvement. The angioedema slowly resolved over the next several days. The subsequent episodes resolved with icatibant and she is currently receiving C1 esterase inhibitor prophylaxis. The relevant literature on acquired angioedema and systemic lupus erythematos is also reviewed.

Keywords: angioedema, systemic lupus erythematos

Introduction

Angioedema is a painless, non-pruritic, non-erythematos, subcutaneous swelling that often involves the face, hands, feet, gastrointestinal tract and airway. Angioedema can be classified as histaminergic or non-histaminergic, hereditary or acquired. Histamine release from cutaneous mast cell degranulation or from the blood basophil causes arteriolar vasodilation and increases endothelial permeability, leading to fluid extravasation and swelling. Angioedema related to histamine release suggest a possible atopic etiology and identifying the underlying cause is the starting point of evaluation. Histaminergic angioedema is the most common form of angioedema, is often associated with urticaria and responds to treatment with anti-histamines and corticosteroids. The absence of urticaria and lack of response to initial therapy suggests a non-histaminergic etiology, such as hereditary angioedema or kinin-mediated acquired angioedema [1].

Hereditary angioedema (HAE) is distinguished from acquired angioedema (AAE) by early age of onset, a positive family history and lack of medical comorbidities. The first episode of HAE typically begins in childhood or...
adolescence and worsens throughout the patient’s lifetime. The prevalence of HAE is estimated at 1 in 50,000 in the United States [2]. Compared to HAE, the acquired form is considered to be much rarer, with an estimated prevalence ranging from 1 in 100,000 up to 1 in 500,000. A literature review from 2010 identified a total of 168 probable cases of AAE [3,4].

Hereditary angioedema is an autosomal dominant disease caused by a defect in the gene that controls the inhibition of C1 component of complement (C1-INH). C1 esterase inhibitor plays a critical role in regulating the activation of both the complement system and kinin system. A quantitative (type I HAE) or qualitative (type II) defect in C1-INH results in unregulated activation of both complement and kallikrein, which increases vascular permeability and fluid extravasation, and leads to subcutaneous and mucosal swelling [5]. The first-line therapy for kinin-mediated angioedema includes the use of C1 inhibitor concentrate derived from human plasma or a synthetic bradykinin B2-receptor antagonist [6,7].

The first case of acquired angioedema documented in the literature was reported by Caldwell et al. in 1972, which occurred in the setting of lymphoma [8]. Since the initial report, similar AAE cases have strengthen the paraneoplastic association with lymphoproliferative disorders and is now known as type I AAE. Type II AAE was subsequently described by Jackson et al. in 1986, when a patient was found to have an autoreactive immunoglobulin G against C1-INH in the absence of a lymphoproliferative disorder [9]. The decrease in C1-INH due to destruction by autoantibodies displays similar AAE symptomatology as those with a hereditary quantitative defect of C1-INH. Although the types of AAE have a distinct pathogenesis, they are not mutually exclusive. It has been reported that these two conditions can coexist in patients [10].

A new category of AAE has emerged in the literature in the recent years and appears to be associated with systemic lupus erythematosus (SLE) [11-14]. This paper reports a case of a young woman who presented with symptoms of angioedema that subsequently led to the diagnosis of systemic lupus erythematosus.

**Report of Case**

A 30-year-old Hispanic woman presented to the emergency department complaining of lip swelling that started suddenly twelve hours prior to admission. Patient has no history of similar symptoms in herself or family members and does not take any medications regularly. Patient has no known drug allergies. Physical exam was remarkable for upper and lower lip swelling, and right cheek swelling without erythema, fluctuance, tenderness or warmth. There was no urticaria present. While in the ED, she was treated with famotidine, diphenhydramine, and methylprednisolone without significant improvement. The otolaryngology service performed a bedside laryngoscopy, which showed no evidence of laryngeal edema. Patient was admitted to the ICU for observation and her symptoms resolved slowly over several days despite high dose cetirizine, famotidine, and dexamethasone. The patient tested positive for antinuclear antibody (ANA) >1:1280, anti-Ro/SSA and anti-La/SSB antibodies. C1 Esterase inhibitor panel showed a low C1-INH level of 7 mg/dL (normal 21-39), with 40% functional (normal >68%). Complement component 1Q (C1q) level was low at <50 µg/mL (normal 109-242), C1q IgG was high at 35 (normal 0.0-3.9 ugE/mL), complement component 3 was low at 44 mg/dL (normal 86-184), and complement component 4 was also low at <2 mg/dL (normal 10-40). The patient had a negative workup for malignancy and monoclonal gammopathy, which included a chest CT, abdomen and pelvis CT with and without contrast, along with serum and urine protein electrophoresis.

Based on the absence of family history, age of onset, lack of known AAE inciting drugs, lack of response to treatment with anti-histamines and steroids, negative malignancy workup, and laboratory findings of low complement levels C3 and C4, low C1 esterase inhibitor and function, low c1q level and high ANA, anti-Ro/SSA and...
anti-La/SSB, the patient was diagnosed with acquired C1 esterase inhibitor deficiency related to autoimmunity, most likely systemic lupus erythematosus. Further history reveals that patient had painful ulcers on her palate 4-5 years ago, which she attributed to drinking grapefruit juice, but denies any oral lesions since that time. She complains of occasional knee pain after prolonged standing, but denies other joint pain, swelling or erythema. She denies photosensitivity and a history of a malar rash.

Two months after the initial episode, patient presented to the ED for a one-day history of abdominal pain with five episodes of vomiting. She reports previous episodes of similar pain 3-4 times in the past 6 months. CT Abdomen/pelvis showed marked small bowel wall edema consistent with intestinal angioedema. Symptoms improved with supportive therapy and patient was discharged to follow up in clinic. Since the last hospital admission, patient had subsequent episodes of lip swelling and abdominal pain that were responsive to icatibant and has now been started on prophylactic treatment with replacement C1 esterase inhibitor.

Discussion

Systemic lupus erythematosus is a chronic inflammatory disease related to autoimmunity. The epidemiology of SLE is similar to AAE. There is a female predisposition and the age of onset is classically seen during childbearing age [15].

SLE can affect virtually every organ, and the clinical course is highly variable among patients. The range of diagnostic findings for SLE includes cutaneous disease, oral ulcers, nonerosive arthritis, serositis, renal disease, neurologic and hematologic disorders. Additional immunologic criteria include the presence of anti-nuclear antibodies, anti-double-stranded DNA antibody, antibody to Smith nuclear antigen, and low complement C3, C4 [16].

SLE disease activity is generally categorized into three patterns, including quiescent, relapsing and remitting to chronically active disease [17]. Disease monitoring is required given the heterogeneity of presentation and clinical course. Clinicians must interpret the findings in the context of clinical history and physical exam, since there is no single marker of SLE disease activity. The five-year survival rate for patients with SLE is over 90%, which is partly attributed to increased detection, more sensitive diagnostic tests, and the prompt treatment of disease and complications [15,18]. Factors associated with a poor prognosis include male sex, low socioeconomic status, paediatric age or over 50 years at time of SLE onset, African-American race, presence of antiphospholipid antibodies, hypertension, renal disease, and high overall disease activity [15,19,20].

Many reported cases of acquired angioedema associated with SLE are symptomatic at the time of presentation [12,13]. This case is unusual in that the patient had no identifiable signs or symptoms of SLE at the time of admission. The patient presented with findings of low C3 and C4, low C1-INH, low C1q and high titer IgG anti-C1q antibody. This pattern suggested complement consumption mediated by the classical pathway due to a combination of low C1 inhibitor activity from auto-destruction, and the presence of an autoantibody presumably initiating the activation of C1q. The low level of C1q is an important distinguishing lab value between HAE and AAE. This value is normal in HAE since the defect is intrinsic to C1 esterase inhibitor.

The underlying pathophysiology of acquired angioedema and lupus has not been delineated. An early case report proposed that in the setting of SLE, the catabolism of C1-INH may be accelerated unrelated to an autoantibody against C1-INH [21]. Siegert et al. later published a study reporting that thirty to fifty percent of all patients with SLE contained IgG autoantibodies reactive to C1q in the sera. It was noted that these IgG autoantibodies recognize collagen-like region C1q. In addition, positive correlations were found between C1q IgG titers with nephritis, dermatitis, hypocomplementemia and dsDNA antibodies [22].
Conclusion

AAE is a kinin-mediated angioedema due to a deficiency in C1 inhibitor not related to heredity. The association between AAE and SLE is rarely reported in the literature. This is one of the few cases of AAE that presented in the absence of SLE symptoms. New onset AAE should not only prompt the search for underlying lymphoproliferative disorders, it should also include investigations to look for systemic autoimmunity.

References