Angioedema in the Absence of C1 Esterase Inhibitor Deficiency in a Young Patient With Anti-dsDNA Negative Lupus Nephritis

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Abstract

Hereditary angioedema (HAE) is an autosomal dominant condition marked by a lack of functioning C1 esterase inhibitor (C1-INH). In contrast, acquired angioedema (AAE) due to a deficiency of C1 esterase inhibitor (AEE-C1-INH) may be the manifestation of an underlying lymphoproliferative, neoplastic, or autoimmune condition. Both are potentially fatal. The C1q protein is normal in HAE but low in AAE. A third mechanism has been reported to cause angioedema, especially in systemic lupus erythematosus (SLE) patients. AAE, which happens in association with SLE, may respond well to steroids. Here we present a case of AAE in a young female with SLE that led to upper airway compromise, requiring endotracheal intubation. Early detection and treatment of such cases can lead to an outstanding prognosis by preventing airway compromise and anoxic brain injury. Even though it is a condition of either very young or middle-aged patients, practitioners must be aware of this uncommon disease linked with SLE in adolescents and young adults.

Introduction

Angioedema (AE) is a localized edema of the skin or mucosal surfaces which happens due to a localized inflammatory reaction leading to the extravasation of fluid into the interstitial compartment due to a loss of vascular integrity. An acquired uncommon condition of recurring angioedema episodes without urticaria that may or may not be associated with deficiency of C1 esterase inhibitor (C1-INH) is referred to as acquired angioedema (AAE) [1]. It constitutes 6-10% of all angioedema cases [2]. Swelling events both in AAE and hereditary angioedema (HAE) can be classified as either dermal, digestive, or upper airways. Patients with hereditary angioedema (HAE) are fairly healthy, whereas those with AAE-C1-INH may have a lymphoproliferative, malignant, or autoimmune disorder such as systemic lupus erythematosus (SLE) [3]. Laryngeal edema is a life-threatening condition that affects roughly half of AAE patients [4]. The exact pathogenesis is unknown, but it is thought to be caused by bradykinin, autoantibodies against the C1-INH protein, or activation of classical complement pathways [5]. The management strategy focuses on patient education about potential triggers as well as the treatment of the underlying condition [6].

Case Presentation

A 22-year-old female with a known history of hepatitis B e-antigen (HBeAg) negative chronic hepatitis B virus (HBV) infection presented with increasing bilateral lower extremity swelling, dark urine, and weight gain. Medical history was negative for associated fever, night sweats, skin rash, joint pain or swelling, hair loss, oral ulcers, photosensitivity, chest pain, shortness of breath, or abdominal pain. She denied tobacco, ethanol, or illicit drug use. The family history was negative for angioedema. She was not taking any over-the-counter or prescription medications. Her vital signs showed her afebrile with a blood pressure of 110/75 mm Hg, a heart rate of 91 beats per minute, and oxygen saturation of 96% on room air. Her physical exam was unremarkable except for bilateral lower extremities pitting edema up to the knees. Initial labs revealed a hemoglobin of 10.9 with a mean corpuscular volume (MCV) of 83 and a creatinine level of 2.1 mg/dL (n = 0.3-1.3 mg/dL), a C reactive protein (CRP) of 337 mg/L (n < 5 mg/L) and an albumin level of 2.8 g/dL (n = 3.3-4.4 g/dL). The rest of the labs consisting of platelets, white cell counts, electrolytes, and liver function tests, were normal. She was admitted for further workup of renal dysfunction. A renal ultrasound showed bilateral edematous kidneys with renal parenchymal hyperechogenicity and loss of normal corticomedullary differentiation without hydropnephrosis. Advanced diagnostic workup revealed positive antinuclear antibodies-ANA (IFA titer of 1:360, speckled pattern) with a negative anti-double-stranded DNA (anti-dsDNA), anti-smith antibodies, cryoglobulins level, anti-neutrophilic cytoplasmic autoantibody (c and p-ANCA), and extractable nuclear antigen (ENA) panel. Complement studies showed hypocomplementemia with a C3 level of 37 mg/dL (n = 83-193 mg/dL) and a C4 level of 10.8 mg/dL (n = 15.0 - 57.0 mg/dL). Further

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lab work was also negative for cardiolipin immunoglobulin (Ig)G & IgM antibody, lupus inhibitor, beta-2 glycoprotein IgG & IgM, and dilute Russell viper venom time. Viral serology was negative for hepatitis C and HIV with positive hepatitis B surface antigen, hepatitis B core IgG, and positive hepatitis B e-antibodies. She underwent a renal biopsy that revealed exotoxin-associated membranous glomerulopathy and diffuse proliferative glomerulonephritis, an immune complex type specific for SLE nephritis.

She was started on mycophenolate mofetil, tacrolimus, oral steroids, and loop diuretics. On day-3 of admission, she reported throat swelling without associated lips swelling, pruritis, or hives. Vital signs showed signs of mild distress but no hypotension. CT neck revealed hypopharyngeal and retropharyngeal edema (Figure 1) and laryngeal edema at the level of true vocal cords (Figure 2).

FIGURE 1: CT scan of the neck (axial section)
The white arrow shows hypopharyngeal edema.
FIGURE 2: CT scan of the neck (axial section)

White arrows show laryngeal edema at the level of true vocal cords.

Subsequently, she underwent a bedside flexible laryngoscopy assessment positive for significant epiglottis and arytenoid edema, followed by endotracheal intubation for airway protection. Further evaluation for angioedema showed normal C1 esterase inhibitors quantitative and functional assays with low C1q levels. She was started on high-dose intravenous steroids and continued immunosuppressive medications. Upon discharge, she continued immune suppressants with no further episodes of laryngeal edema on outpatient follow-up. A repeat C1q level after three months has normalized, and her renal function has been stable.

Discussion

AE can broadly be classified into three types based on etiology and pathologic mechanism: mast cell-mediated, kinin-mediated, and unclassified. The first category is caused by mast cell degranulation and is usually associated with urticaria, wheezing, and hypotension. A trigger can usually be identified, typically an allergen causing a type-1 hypersensitivity reaction, radiocontrast media causing direct mast-cell degranulation, or a non-steroidal anti-inflammatory drug causing excessive leukotriene production through inhibition of cyclooxygenase. It can further be divided into idiopathic histaminergic (IH-AE) (responsive to antihistamine treatment) and idiopathic non-histaminergic (InH-AE) (non-responsive to antihistamines).

On the other hand, kinin-mediated angioedema is characterized by angioedema in the absence of an identifiable trigger and without urticaria or other features of mast cell degranulation, as described above. Some examples of unclassified angioedema include angioedema related to drugs such as angiotensin-converting enzyme (ACE)-inhibitors (ACE-I-AAE) and fibrinolytic agents and urticarial vasculitis [7,8].

Kinin-mediated angioedema is caused by qualitative or quantitative deficiency of C1 esterase inhibitors which could be either hereditary or acquired. HEA is the most well-described form and is divided into type 1
seems less likely based on negative family history, no OCP/HRT use, and excellent response to steroids factor 12 or plasminogen that could categorize it in type 3 HAE or estrogen-dependent AE. But this entity major complement activation and transient rise in bradykinin levels. She responded well to steroids hinting whereas the typical onset of AAE is in the 4th decade of life nephritis and had negative anti-dsDNA and anti-smith antibodies. She presented at a relatively young age, Our patient presents a unique case from multiple aspects. She has no other SLE findings other than lupus indicating the interplay of mast cells and kinin pathways in this subset of angioedema patients related to underlying autoimmunity. Antihistamines have also been used in these cases successfully, highlighting the primary pathologic driving force as the massive complement pathway activation likely like its pathophysiology, is complex and not clear. Steroids have shown efficacy in multiple reports frequency and severity of attacks as well as remission in some cases a few case reports of monoclonal antibodies, such as rituximab use in this category, showing the reduction in InH-AE has the least supported treatment evidence available in the literature, and there are a few case reports of milder attacks using ecallantide and icatibant with variable success. This also reflects onto heterogeneity and complex pathophysiology of this particular type of AE [10]. ACE-I-AAE therapy involves avoiding the trigger, i.e., ACE-I permanently. Bradykinin-targeted drugs such as ecacillantide and icatibant have shown a quick resolution of symptoms and early discharge from the hospitals [17]. In addition, angiotensin receptor blockers (ARBs) in these patients are not shown to increase the frequency or severity of recurrent attacks. Treatment of C1-INH AAE involves using bradykinin-targeted agents like HAE in addition to treating underlying diseases such as immunoproliferative disorders. There are a few case reports of monoclonal antibodies, such as rituximab use in this category, showing the reduction in frequency and severity of attacks as well as remission in some cases [10]. Treatment for AE in lupus patients, like its pathophysiology, is complex and not clear. Steroids have shown efficacy in multiple reports highlighting the primary pathologic driving force as the massive complement pathway activation likely related to underlying autoimmunity. Antihistamines have also been used in these cases successfully, indicating the interplay of mast cells and kinin pathways in this subset of angioedema patients [13,14].

Our patient presents a unique case from multiple aspects. She has no other SLE findings other than lupus nephritis and had negative anti-dsDNA and anti-smith antibodies. She presented at a relatively young age, whereas the typical onset of AAE is in the 4th decade of life [15]. She had normal C1-INH level and function with low C3 level, indicating a complex pathophysiology independent of C1-INH, likely a combination of major complement activation and transient rise in bradykinin levels. She responded well to steroids hinting at the mast-cell pathway's potential role. The limitation, in this case, is that no genetic testing was done for factor 12 or plasminogen that could categorize it in type 3 HAE or estrogen-dependent AE. But this entity seems less likely based on negative family history, no OCP/HRT use, and excellent response to steroids [10].
Conclusions

AAE may happen in adolescents and young adults. It could be an early manifestation of SLE. The level and function of C1-INH may be normal in SLE patients who develop AE. The potential mechanism behind this type of angioedema is a complex interplay of both bradykinin and mast cell pathways and is likely related to massive complement activation and a transient rise in bradykinin levels.

Additional Information

Disclosures

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