CLINICAL VIGNETTE

Acquired C1 Esterase Deficiency in a Patient with Monoclonal Gammopathy of Uncertain Significance

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A 49-year-old man with a history of traumatic brain injury from a motorcycle injury twenty years prior was admitted with respiratory failure after being intubated in the field by paramedics. The patient's family noted over the prior few years he had sudden episodes of bilateral facial swelling which cleared spontaneously. On this occasion he had been in his usual state of health when he noted onset of facial swelling in the morning but was associated with difficulty breathing and chest tightness. There was no specific chest pain, facial flushing, hives, pruritis, lightheadedness, slurred speech, or abdominal pain. He did not have fevers or chills. They reported that he had an intermittent dry cough with the with the shortness of breath but no skin rash or hives. He had a prior allergy to pork products which caused a rash and oral tingling sensation. He avoided eating these products. He was also listed allergies to: pistachio nuts (rash and scratchy throat), Novocaine (rash), and lamotrigine (rash). He was a former 25 pack years of smoker but quit seven years prior. He did not drink alcohol and his family history was negative for any allergic or autoimmune disease. Specifically, no family members experienced symptoms suggestive of angioedema. The patient's medications were: hydrochlorothiazide 12.5 milligrams daily and atenolol 50 milligrams daily. He had never taken angiotensin converting enzyme inhibitors for hypertension. He had not taken any aspirin or non-steroidal anti-inflammatory drugs.

His prior medical history included traumatic brain injury (TBI) after a motorcycle accident two decades earlier associated with a subdural hematoma that required prolonged hospitalization. He also underwent splenectomy for a ruptured spleen associated with the accident. He was given seizure medication lamotrigine after his accident, but was no longer on medication and had seizure activity for over fifteen years.

On physical exam the patient was, awake, and alert, with blood pressure 118/70 mmHg, regular heart rate was 84 bpm, respiratory rate 12/min with oxygen saturation 99% on 2 liters nasal cannula post extubation in the emergency department (ED). Conjunctiva were clear without discharge, non-boggy without enlarged turbinates. Oropharynx was clear but his tongue was mildly edematous. Neck was without lymphadenopathy, and chest was clear to auscultation with mild bilateral stridor intermittently on exhalation. Cardiac apex non-displaced, normal heart sounds without murmurs, rubs, or gallop. Abdominal exam revealed an old LUQ splenectomy scar, no hepatomegaly. Soft and non-tender abdomen with normal bowel sounds. Skin revealed no rashes, urticaria, or induced dermatographism.

Labs included hemoglobin of 13.1 g/dL, hematocrit 39.1%, white blood count of 13.8, a neutrophil fraction 11,000 per mm^3, platelets were 177per mm^3. Potassium 4.5 mmol/l, sodium 134 mmol/l, glucose 121 mg/dL, blood urea nitrogen of 29 mg/dL, creatinine 0.49 mg/dL and a CO2 of 28.8 mmol/l. Chest x-ray was unremarkable, and his twelve-lead ECG had shown normal heart rate and rhythm without significant ST or T wave changes. His peripheral smear revealed no atypical lymphocytes. In the emergency department (ED) the patient was given antihistamines and subcutaneous epinephrine but did not respond immediately and methylprednisolone and fresh frozen plasma were given with some improvement.

Our patient's presentation was consistent with acute laryngeal edema secondary to acquired angioedema due to deficiency of C1 esterase inhibitor (acquired angioedema or C1INH-AAE). This was based on having new onset angioedema, no associated urticaria, being in his fourth decade of life or older, and having no prior personal or family history of angioedema. The Allergy/Immunology service consulted and agreed there was a high clinical probability of the proposed diagnosis, as clinical criteria were all satisfied. However, food and drug allergy needed to be ruled out and they recommended obtaining a serum complement factor three (C3) level, four (C4) level and a C1 inhibitor antigenic protein level. As well as a C1 inhibitor functional level to confirm the diagnosis of C1INH-AAE. They recommended giving him human C1 inhibitor replacement protein (Berinert) 2000 units infusion as well as starting Danazol 200mg every eight hours. The initial lab results returned with a C1 esterase inhibitor level of 58 mg/dL (reference range = 21-39mg/dL), his esterase function was 3% (low), his C1Q concentration <2 (low), C3 level was 23 mg/dL (reference range = 92-190) his C4 level was 1.67 mg/dL (reference range = 11.8-24.4) Also, serum Ig E level was 175 and he had 2.4% eosinophils on his differential. Ultimately both his food and aeroallergen panels were negative, and his pork and pistachio Ig E levels were normal at <0.35 ku/l.

Further evaluation for newly diagnosed C1INH-AAE should always include an evaluation for and B-Cell neoplasia due to a strong clinical association. Our patient's immunoglobulin studies were checked to investigate the possibility of acquired angioedema secondary to a B-cell neoplasm (70% of patients).

Serum electrophoresis indicated a monoclonal band in the gamma region with normal amounts of immunoglobulin, but antibodies were not detected. Based on the findings of monoclonal gammopathy of uncertain significance (MGUS), the presumptive diagnosis of C1INH-AAE due to monoclonal gammopathy was eventually made.

Discussion

Acquired angioedema due to C1 esterase inhibitor deficiency (AAE-C1-INH) is a comparatively rare syndrome characterized by recurrent episodes of angioedema, without pruritis or urticaria. It is often (67%) associated with a B-cell lymphoproliferative disorders[1] such as lymphatic malignancies or monoclonal gammopathies as in our case. Fortunately, the rate of progression of MGUS to overt multiple myeloma is low.[2] Sudden swelling or angioedema typically affects the skin or mucosal tissues of the proximal airway or bowel. The inflammation is usually transient lasting 4-5 days. In some cases, as in our patient, laryngeal swelling can be so severe as to require tracheal intubation. This syndrome can present in a clinically identical way to hereditary angioedema (HAE). Differentiation factors include: AAE-C1-INH develops in patients over forty and is often associated with underlying disease, whereas HAE tends to manifest in seemingly healthier younger patients.[3] AAE-C1-INH develops as an uncontrolled clonal proliferation of B-lymphocytes, but how this triggers a drop in C1-INH levels via neutralizing autoantibodies and angioedema has not been fully elucidated.[4] Bradykinin production appears to play a major role in the pathogeneses due to tissue injury and triggering a pro-inflammatory cascade. Most patients will have measurable autoantibodies against the C1-INH protein. Once the bradykinin pathway kicks in most patients with AAE-C1-INH have massive depletion in complement including C1q which differs from the presentation of HAE. The two syndromes differ in pathogenesis and AAE-C1-INH is so closely linked to lymphoproliferative states, suggesting an autoimmune or paraneoplastic process has been suggested for the latter.[5]

Confirming the diagnosis relies on a high clinical suspicion and a classical abnormal complement profile on lab testing as seen in our patient. The triad of angioedema, age over 40 and no prior family history of angioedema coupled with a low C4, a low C1q (<50%) and a low or normal C1 antigen or quantitative protein level will clinch the diagnosis. If a patient fits this classic pattern further testing for an underlying B-cell disorder is essential.

Treatment begins with patient education. Triggers and early recognition of onset of angioedema attacks is key. Asphyxiation from upper airway angioedema is a potential life-threatening consequence. If stridor or signs of respiratory arrest are present intubation should be provided immediately. Emergency cricothyroidotomy may be needed in rare cases with difficult intubations. Prescribing appropriate "on-demand" pharmacotherapies for attacks of angioedema and ensuring that the patient can self-administer or quickly get to an ED is strongly advised. Four drugs are the mainstay of treatment: C1INH concentrate, derived from human plasma (pdC1-INH), recombinant human C1-INH (rhC1-INH, conestat alfa), Icatibant, a synthetic bradykinin B_2-receptor antagonist and Ecallantide, a recombinant plasma kallikrein inhibitor. Unfortunately, no high-quality controlled studies have been published on the best treatment regimen for AAE-C1-INH, and no therapies are currently approved for this condition. The guidelines are based on expert opinion in the field. The most widely used therapy for acute laryngeal edema is pdC1-INH, which is available as Cinryze or Berinert. Observational studies indicate that pdC1-INH is effective in reducing the average attack duration by 60 percent.[6] Icatibant is helpful in treating a small number of patients not responsive to C1-INH concentrate[7] because it does not depend on the patients C1-INH catabolic rate. In the absence of these drugs, plasma, which contains an abundance of complement components, including C1-INH, can be used for angioedema and severe abdominal attacks, though overall efficacy has not been studied in detail. Finally, Ecallantide can be used to treat severe angioedema based on its anti-kallikrein effects. Patients should be advised to use prophylaxis if they are undergoing surgical procedures or dental work. Either plasma-derived (pdC1-INH) or recombinant human C1-INH (rhC1-INH) concentrates are effective for these situations[8].

Anabolic androgens, such as danazol can also be used as in, our patient. These drugs can control symptoms in approximately one-half of patients. Those who respond well to this therapy sometimes achieve control of symptoms with very low doses and remain on this agent for years. However, in the remaining patients, androgens either do not work from the outset or become ineffective after a period of time.[9] Only time and close follow up will determine if our patient has a durable therapeutic response.

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