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The Gravid Patient Presenting with Laryngeal Angioedema

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Abstract

Laryngeal swelling can be life threatening with etiologies including angioedema and cellulitis. While both involve swelling of subcutaneous tissues angioedema involves extravasation of fluid into interstitium while cellulitis is caused by direct extension of a spreading infection. The cause of angioedema involves multiple etiologies with response to treatment varying with underlying pathophysiology. While some exposures are extrinsic, and thus able to be avoided, estrogen or estrogenic excess has been shown to be intimately involved in certain patients presenting with acute angioedema. We present a gravid patient with new onset neck swelling and airway compromise requiring airway protection and emergent cesarean section delivery. The patient provides insight into the multiple risk factors and difficulties in discerning a single inciting event while emphasizing the importance of obstetric physician awareness to angioedema, etiologies, and management.

Keywords

Angioedema, Pregnancy, Airway, Gravid, Estrogen, Hereditary, Idiopathic, Cellulitis

Introduction

Angioedema can affect any organ and cause life threatening airway compromise. The multiple etiologies provide a diagnostic challenge especially in an acute patient. This case presents such a patient with multiple risk factors including pregnancy itself. Though a relationship between attacks and increased estrogen has been observed in individuals with traditional hereditary subtypes, it is now recognized that there are estrogen dependent etiologies that present without the typical pattern of complement consumption. The obstetrician should be able to navigate both immediate care and diagnosis.

Case

A 21-year-old G2 P0-0-1-0 African American female presented to obstetric triage at 36 weeks gestation with new onset severe right neck swelling and airway compromise. The patient had a known history of drug allergies to trimethoprim sulfamethoxazole and amoxicillin, untreated hypertension, previous methicillin resistant *Staphylococcus aureus* (MRSA), and systemic lupus erythematous (SLE) treated with hydroxychloroquine. Upon initial exam the patient had a weak voice without stridor and was only able to provide a limited history. She denied new foods, environmental exposures, tooth pain, or medication beyond hydroxychloroquine. Vital signs revealed a fever up to 101 Fahrenheit and tachypnea at 30-40 breaths per minute with oxygen saturation of 100% on supplemental oxygen. Physical exam demonstrated fairly severe pain and tenderness surrounding a markedly swollen lower facial area and neck without any erythema. Active SLE was ruled out. Hydroxychloroquine was discontinued and vancomycin 1g intravenous q 12 was started for suspected infection and history of MRSA. The patient was subsequently intubated due to worsening respiratory distress and inability to protect her edematous airway. The operating room (OR) was prepped for emergency cesarean section delivery and intravenous dexamethasone was administered. The patient was taken to the OR the night of hospital day zero and remained intubated during primary low transverse cesarean section. The cesarean section was without complications and the patient gave birth to a viable male with Apgars 6 and 7 at 1 and 5 minutes respectively with the newborn requiring ventilation treatment.

The patient was moved to the ICU and remained intubated postoperatively. Postoperative computed tomography (CT) with contrast of the neck and soft tissues was performed on postoperative day (POD) zero for suspected abscess formation. Findings were consistent with edema, right slightly greater than left, of the subcutaneous soft tissues, suggesting angioedema (Figure 1).

On POD zero, hospital day one, the patient remained intubated and was afebrile at 98.6 Fahrenheit. Gram stain of blood, drawn previously, showed gram-positive cocci later confirmed as group B streptococcus susceptible to, but not limited to, vancomycin and clindamycin. Given the initial fever and marked tenderness upon presentation, with cultures isolating an organism known to cause cellulitis, an underlying infectious etiology was included in the differential diagnosis. Intravenous meropenem 500mg q6 and clindamycin 900mg q8 were then added for broad-spectrum coverage.

The patients swelling and edema did not resolve despite continued treatment with antibiotics and high dose corticosteroids and required prolonged intubation. On POD two labs were drawn to assess complement levels. C3 level was slightly low at 76.3 (<83mg/uL); while C4 (32.8mg/DL), C1 esterase inhibitor quantitative (34mg/dl), and C1 esterase inhibitor functional (120%) tests were all well within normal limits. Repeat CT on hospital day four showed continued edema of soft tissues in the neck with findings similar to the prior

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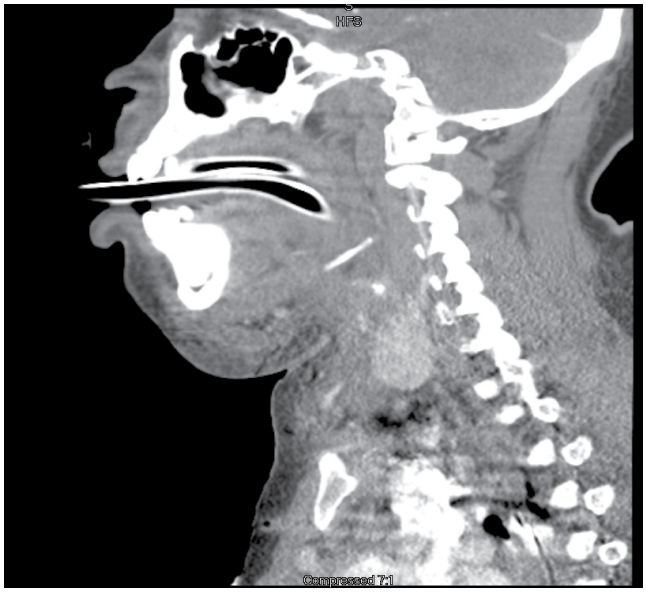

Figure 1: Computed tomography of neck and soft tissues with contrast showing edema of the subcutaneous soft tissues with fullness of the submandibular and parotid glands without discrete abnormality. Findings suggest angioedema.

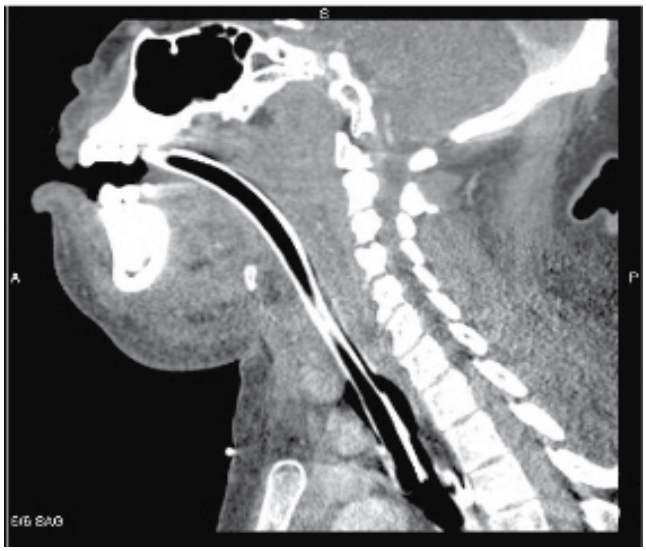

Figure 2: Computed tomography of neck and soft tissues with contrast showing continued edema in both soft tissues of the neck and fullness of salivary glands

study (Figure 2). The patient continued high dose corticosteroid and antibiotic therapy and remained afebrile for the duration of her care.

The patient remained intubated until hospital day 14 when airway swelling was minimal and extubation tolerated successfully. At this time further questioning was performed. There was no history of prior episodes of angioedema in the patient or any family history of events. On POD day 18 the patient was discharged after she met all postpartum milestones and her airway was stable. Final differential diagnosis included idiopathic, or possible hereditary angioedema, and streptococcal bacteremia. The patient was discharged to home with a prednisone taper and instructions for routine outpatient postnatal care, as well as follow up with rheumatology for additional management, but was subsequently lost to follow-up without repeat C1-INH levels or additional immunologic testing.

Discussion

Angioedema has been described with many etiologies, which all result in increased capillary permeability with fluid extravasation into subcutaneous or submucosal tissue manifesting as localized non pitting swelling. This can be disfiguring or even life threatening as multiple body systems can be involved [1]. The causes are multiple and include allergic responses to ingested or environmental exposures, temperature changes, drug induced, idiopathic, acquired angioedema, and two classical hereditary subtypes involving genetic deficiencies of the C1 inhibitor (C1-INH)[1]. Recent literature has demonstrated a third type with normal C1-INH quantity and function while additional reports emphasize a role of estrogen or suggest an estrogen-dependent type [2].

Hereditary angioedema (HAE) is a rare condition afflicting up to 1 in 10000 individuals and has been historically described as two types with both involving the serine protease inhibitor C1-INH. Both are transmitted as an autosomal dominant trait and are indistinguishable from each other clinically with attacks typically subsiding spontaneously after 2-5 days. Type 1 is the more common variant being responsible for up to 85% of the cases of HAE and is caused by decreased production of C1-INH which manifests as decreased antigenic levels in both blood and tissue. Type 2 presents as normal or elevated antigenic levels of a functionally impaired C1-INH. Patients with HAE suffer from lifelong episodic subcutaneous and sub mucosal angioedema that can be brought on by minor trauma or stress [1].

A third type of hereditary angioedema has been reported mostly in women with individuals having normal concentration and function of C1-INH [2,3]. This type appears to be inherited in an x-linked dominant [2] or autosomal dominant estrogen-dependent [3] mode and has been referred to as hereditary angioedema type 3. In addition to having normal levels and function of C1-INH, patients suspected of having HAE type 3 also had normal C4 concentration as opposed to decreased values seen in individuals with HAE types 1 and 2 [2].

The role of estrogen and its causal effect on recurrent angioedema, whether or not unique to this HAE type 3, has also been suggested. Though estrogen may worsen angioedema in patients with HAE types 1 or 2, support that HAE type 3 is uniquely influenced by estrogen is shown by a decrease in attack frequency in late pregnancy with increased frequency at menopause in HAE types 1 and 2: which are periods when estrogen levels are typically low. This relationship is reversed in patients with HAE type 3 [3,4]. With suspected HAE type 3, Bork et al. [2] reported swelling and gastrointestinal symptoms coinciding with the onset of oral contraceptive use and relapsing skin swelling and abdominal pain attacks only during pregnancy. In 2000 Binkley et al. [4] presents a family, without history of consanguinity, with history through three generations with typical symptoms of HAE. Individuals' incidence of angioedema was restricted to conditions of high estrogen including pregnancy, use or oral contraceptives, or estrogen replacement therapy. Baseline (not pregnant or receiving exogenous estrogen) measurements of C1-INH quantity, C1-INH function, and C4 levels were within normal limits [4].

Treatment for hereditary angioedema with normal C1-INH can be difficult. As with HAE types 1 and 2, antihistamines and corticosteroids are not effective. All three HAE subtypes may show response to treatment with a bradykinin-B2 receptor antagonist (icatibant), fibrinolytics (tranexamic acid), attenuated androgens (danazol), or C1-INH concentrate, with C1-INH concentrate being a first choice in acute episodes [5-7]. Due to the severity of attacks and possibility of recurrence, prophylactic therapy can be considered for any patient with a history of organ involvement secondary to HAE. In addition to C1-INH concentrate prophylaxis, use of attenuated androgens or fibrinolytics has been shown to prevent symptomatic attacks and increase C1-INH levels. Attenuated androgens are noted as being more effective than fibrinolytics with fibrinolytic agents being reserved for children and women secondary to contraindications to attenuated androgens including pregnancy, lactation, prostate cancer, and childhood [1,7].

Though reports have varied as to when during pregnancy attack rates of HAE occur, becoming pregnant appears to increase

attacks and inherently involves risk factors associated with increased exacerbations and incidence. Despite the increased rates of attacks during pregnancy, risks of spontaneous abortion, preterm labor, or need for cesarean section have not been shown to be increased in patients with HAE versus the general population. If a diagnosis of HAE needs to be determined it can be made by evaluation of blood complement levels or genetic analysis of DNA obtained from cells. Blood evaluations should however be repeated postpartum due to plasma C1-INH levels decreasing during normal pregnancy relative to the increase in plasma volume. Normalization of levels after pregnancy has been reported in both women with and without HAE. C1-INH is the treatment of choice for acute or long-term management of patients during pregnancy and while routine prophylaxis before uncomplicated natural deliveries is not recommended, prophylaxis with C1-INH concentrate is recommended before cesarean section, and can also to be given prophylactically to patients before any invasive procedure. Epidural anesthesia is preferred over endotracheal intubation during cesarean delivery to avoid aggravation of the airway. In addition to its role in treatment during pregnancy C1-INH concentrate is also appears to be safe and effective for short term or long-term treatment during lactation [6,7].

Angioedema can present similarly to cellulitis with both involving swelling of subcutaneous tissues. Cellulitis has been defined as a spreading infection involving the dermis and subcutaneous tissues and presents almost invariably with pain, redness, warmth, and tenderness. Cellulitis most commonly affects the lower extremities but can involve the upper extremities, head, and neck. Depending on the severity, systemic symptoms can be mild or absent. The most common causative organisms have classically been *Staphylococcus aureus* and *β-hemolytic streptococci* with MRSA becoming more common. In mild or uncomplicated cases of cellulitis treatment is usually provided empirically. In patients who are admitted to the hospital, obtaining blood cultures is routine practice although yield is notably low with needle aspiration and needle biopsies being reserved for those who are immunocompromised. Hospitalized patients, by definition, have complicated cellulitis and are often provided empiric treatment with vancomycin or other agents covering for MRSA. For non-purulent cellulitis β–lactam therapy remains an acceptable option although empiric coverage for β-hemolytic streptococci is considered unnecessary. Although the average length of hospitalization for a patient with cellulitis is less than five days, antimicrobial treatment is often continued for up to ten days or until 3 days after the acute inflammation has disappeared [8].

In conclusion, while the complex nature may preclude the ability to discern a precise etiology, the severity of angioedema versus cellulitis requires that the physician be aware of risk factors, including estrogenic excess, and management. Our patient, who presented in acute distress, had multiple risk factors for multiple etiologies. After supportive measures are taken, which in this case included both maintenance of airway and emergent delivery, further investigations increased suspicion for an idiopathic or hereditary angioedema. The care and clinical course presented in this case are demonstrative of how awareness of current diagnostic and treatment options will optimize the efficacy of management as this patient required prolonged care secondary to her failure to improve with corticosteroids. As was stated, HAE is often resistant to treatment with corticosteroids and if a physician suspects this process C1-INH concentrate is the first line therapy. For prevention of future attacks, prophylaxis with plasma derived C1-INH concentrate would be a first choice as it has been shown to be both safe and effective and can be continued during pregnancy and, if needed, delivery.

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