Case Report

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Acute Throat Swelling in Pregnancy: Review of the Literature and Management

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Scenario

A middle aged black female arrives in the emergency department of a large metropolitan hospital where she usually goes for prenatal care. She is a multiparous patient presently 19 weeks pregnant with a so far uncomplicated prenatal course. She complains of about an hour of increasing difficulty inhaling, stridor and dyspnea. She has no history of allergies including food allergies and reported an evening meal of baked pork chops and rice about 3 hours before the onset of dyspnea. Her past history includes HIV infection for about 10 years which has been well controlled with a HAART regimen with the most recent viral count being zero and multiple previous c sections for failure to progress. She has no other medical or surgical history. On first arrival her vital signs are normal except for a heart rate of 120. Physical exam appears normal including lung auscultation. She is found to have external neck swelling under the jaw and on exam oral swelling of the uvula and posterior pharynx. She is given subcutaneous epinephrine with immediate improvement but recurrence of symptoms within half an hour. She is given a repeated epinephrine dosage this time using inhaled racemic epinephrine then an inhaled terbutaline treatment, intravenous diphenhydramine and dexamethasone. She improves over several hours and is transferred to the adult ICU where she does well, requires no other treatments and is discharged to home in 48 hours.

Question

What is her diagnosis? A differential might include food allergy, infectious epiglottitis, anaphylaxis from: Hymenoptera, drug reaction, an allergic reaction to an unknown source, or angioneurotic edema.

Differential Diagnosis

History is important in this patient. Has this swelling occurred before? Is there a history of drug or other allergic reactions? Is there a family history of this condition? Without a specific history of an inciting allergen we cannot be certain as to the cause of this pharyngeal edema. The most common cause is probably a food allergen. A specific history of Hymenoptera sting or envenomation from any source would grant you a presumed inciting origin of swelling. Epiglottitis is another cause of this rare condition. Finally, angioneurotic edema is another rare but important cause of acute upper airway swelling in adults.

Allergic Reaction

Allergic reaction is probably the most common cause of acute upper airway swelling in adults and also in pregnancy. There is usually a history of allergic reaction and hopefully a known exposure to the allergen. A common example today is peanut allergy which can be from eating or inhaling allergens of the peanut. All of the allergic reactions whether inhaled, eaten or injected have the same mechanism of pathophysiology and the same treatment regimen. It is especially catastrophic for this to occur in labor or delivery when to most common inciting agents are latex and B-lactam antibiotics [1]. The reaction is caused by an allergen reaching a significant number of mast cells and basophils which have on their surface receptors for immunoglobulin E antibodies [2]. The immunoglobulin E antibodies interact with the allergen which then activate the receptors which then activate multiple tyrosine kinases leading to calcium ion influx into the mast cells and basophils and extracellular release of stored intracellular granules [3]. Although mast cells were thought to be tissue located basophils these are actually different cells. They both express receptors for immunoglobulin E. Basophils are mostly circulating in the bloodstream and lymph. They are involved in determining when an antigen's antibody switches from immunoglobulin M to E through production of large amounts of interleukin-4 which mast cells barely produce [4]. Mast cells are mostly located near large blood vessels and epithelial surfaces. Mast cells release histamine. Basophils release histamine releasing factor. Both also release many other

effectors some of which are described and understood some of which are neither.

Eosinophils are a type of cells involved in allergic reactions. They are a type of granulocyte that of course produces granules that stain intensely with Eosin. They have surface receptors for immunoglobulin G and A. They reside in tissue especially the gastrointestinal tract which includes the mouth and pharynx. Eosinophils release thromboxane, platelet-activating factor and multiple cytokines and enhance inflammatory responses [5].

An allergic reaction thus requires someone to have had a prior exposure to the inciting antigen or a closely similar antigen that can interact with immunoglobulins and elicit the "allergic response" which can and often does include swelling in the pharynx, throat or airways. The prior exposure is frequently not known and is sometimes not determinable, but there has to be immunoglobins, from prior exposure to the antigen, of various classes associated with Ig E, A and G receptors on the surface of mast cells, basophils, and eosinophils capable of interacting with an offending allergen. The reaction then depends on the amount of allergen, the length of time since the last exposure, the innate responsiveness of an individual and the route of exposure. Whether allergic reactions are worse the same or less in pregnancy are not known [6]. Especially in the third trimester because of production of many substances by the placenta, mothers seem predisposed to increased swelling from any inciting agent in any part of the body.

Infectious Epiglotitis

Acute epiglottitis is a rare but life-threatening disorder in adults. It is thought to have an incidence of 1 to 4 per 100,000 [7]. There are reports that that epiglottitis is increasing in adults perhaps because childhood vaccination for *Hemophilus* wanes in adulthood. It may also be increasing because of the very low rate of tonsillectomy in childhood now [8]. The main other syndromes of the differential diagnosis of epiglottitis in one article are croup and a foreign body in the airway. Additional observations of drooling and dysphagia with the absence of a cough in epiglottitis are related. The usual cause in children is *Hemophilus influenza* type b, it is found in only 17% of adult cases. There is usually a one to several day history of worsening throat soreness and stridor and dysphagia [9]. It can however present with 24 hours or less of symptoms [10]. In a large retrospective series of cases the most frequent symptom was odynophagia (100%), inability to swallow secretions, (83%), sore throat (67%), dyspnea (58%), and hoarseness (50%) [11]. There is a high mortality associated with it in adults, described as between 7 and up to 20%. It can also present as a fulminant rapidly worsening bacterial infection [12]. As opposed to the aggressive treatment and airway protection in children conservative management is still the usual care in adults [13].

Hereditary Angioedema

Hereditary Angioedema, HAE, is a very rare inherited condition occurring in 1 in 10,000 to 1 in 50,000 adults. It was recently thought that there was an inherited defect in C1 inhibitor that led to excess bradykinin which cause the symptom complex [14]. Now there are reports of at least three different types of HAE all with different inherited genetic defects in different pathways leading to the various described clinical types of HAE [15]. This is a rare inherited condition in which Complement 1 Inhibitor is either produced at very low levels or is defective as to its enzymatic function which is involved in reducing bradykinin production. Patients with HAE produce too much bradykinin in reaction to an allergenic or non-allergic stimulus such as hot or cold water, heat excess or stress. This leads to the identical response caused by a reaction to an allergen. A family history of HAE or recurrent angioedema without urticaria or even a single episode of unexplained laryngeal edema should lead to ordering a C4 level which is diminished in the majority of HAE patients. This reaction is to bradykinin so will not improve with antihistamines but will respond in a limited fashion to epinephrine and to corticosteroids. There is also HAE that develops as a result of angiotensin converting enzyme inhibition, ACE. This is because ACE also catabolizes bradykinin so inhibiting this enzyme increases the serum and tissues levels of bradykinin [16]. Since ACE inhibitors are commonly used this may become the most common pathway of developing HAE. It is excess bradykinin that causes the persistent cough some patients have in association with ACE inhibition [17].

The incidence of anaphylaxis, epiglottitis and of angioneurotic edema is unknown in pregnancy and it is unknown if the incidence is higher, lower or unchanged compared to the non-pregnant state. It is also unknown if the reaction or outcome is more likely to be worse or better during pregnancy.

Return to Case Scenario

Although there is no evidence either way maternal fetal medicine specialists would rather await delivery before getting allergen testing performed. This particular patient however gives a history of urticaria following a very hot or cold shower. Although not diagnostic this certainly points to a diagnosis of hereditary or acquired angioneurotic edema, HAE. In addition, allergic reactions should occur with urticaria and will respond to antihistamines since the reaction starts with histamine release which was not seen in this case. HAE has also been described as being more common in AIDS although not in a controlled HIV infection [18]. This patient also presents with no history of fever and no other symptoms. Examination of the oropharynx by careful tongue depression led to the tentative diagnosis of epiglottitis.

Acute Treatment

Although the specific cause of throat swelling in this patient is not known the immediate starting treatment is the same. The emergency department physicians and ENT specialists should be the primary managers of this condition. Although as an obstetrician you will probably not be called to advise on the differential diagnosis you may well be called about the safety of various drugs used in this situation during pregnancy, specifically: Epinephrine, asthma treatments, antihistamine and corticosteroids and antibiotics. You will also be called on to monitor a fetus that is at

viability or beyond. In this setting continuous FHR monitoring is reasonable and give additional insight into maternal oxygenation and vascular health. If medications are not rapidly effective then intubation by ENT and anesthesiology in the operating room, with equipment for tracheotomy if needed, is ideal. This decision is best left to those specialists.

Epinephrine is a class X drug in pregnancy. It causes a temporary reduction in maternal uterine blood flow and probably fetal placental blood flow. In this instance it can be lifesaving to the mother and thus also to the fetus. Racemic epinephrine will have the same effect on the maternal and fetal circulation as parenteral epinephrine injections. Epinephrine is of course broken down before oral absorption. Any drug, even category X, can be used in a situation to save the life of the mother as pregnancy prolongation is obviously impossible with maternal death.

Antihistamines including benadryl are category B and safely used. Beta mimetics by inhalation or subcutaneous are category B or C but are commonly used in asthma throughout pregnancy as rescue treatments for worsening asthma. Terbutaline although classified for many years as category B was reclassified by the FDA as category C in 2011 after a petition by citizens in 2008 [19]. This was in response to usage of terbutaline over more than 48 hours for prolongation of labor which the FDA specifically says it has b approve usage in acute situations where there might be benefits to a patient from using it.

Corticosteroids are considered possibly teratogenic in the first trimester but again in the instance of a life-saving situation are used in pregnancy and they are used commonly in the early third trimester in humans to accelerate fetal lung maturation. Prednisone has not been classified for pregnancy use by the FDA [20]. However prednisolone, it's active metabolite, has been classified as category C [21]. All corticosteroids work in the same manner on the same receptors and so differ only in relative strength and elimination half-life. They probably all cross the placenta to the same degree although this has not been definitively studied in humans. Dexamethasone is probably the corticosteroid most used in pregnancy because it is commonly used to enhance fetal lung maturity in most hospitals in the United States. It is pregnancy category C also [22].

The antibiotics commonly used for infectious epiglottitis; penicillins, cephalosporins are all safe in any trimester in pregnancy. This is assuming that the patient is not allergic to them. Macrolides have had purported links to an increase in cerebral palsy, congenital heart disease and pyloric stenosis. A recent exhausting survey found them to have no statistical association with any of these birth defects [23].

Return to the Clinical Scenario

The patient's symptoms subsided in the ED after her examination and treatment with injected epinephrine, nebulized racemic epinephrine, nebulized terbutaline, parenteral diphenhydramine and parenteral dexamethasone. She was evaluated by ENT who felt she did not need immediate intubation. She was watched and then transferred to the adult ICU. She had throat cultures, repeat CBC s and parenteral cephalosporins. She never developed an elevated temperature or an elevated white blood cell count. She was fed clear liquids 12 hours after admission and never required any other treatment. She was discharged to home 3 days after admission on no medications but after education on it's use with an Epi-pen. She was seen in the Maternal Fetal Medicine clinic for 20 more weeks then underwent an uneventful repeat cesarean section at 39 weeks gestation under neuraxial anesthesia. She has never reported another airway symptom.

To reemphasize; after the initial evaluation and monitoring of vitals, close observation for lack of improvement or airway worsening should prompt a consultation from ENT both for diagnosis and for possible surgical airway intervention. After the initial emergency department evaluation and treatment, which will probably occur before you are consulted, comes the longer term management, which you as an obstetrician might be involved in. This will involve actually establishing a working diagnosis and longer term management.

Treatment after discharge any patient with a life-threatening anaphylaxis or laryngeal edema should include discharge to home with an epi-pen. This is a portable easily usable epinephrine injector. They are available in three doses and several different needles. The epinephrine must be given intramuscularly since a subcutaneous injection will lead to slow absorption from the localized vasoconstriction of the epinephrine. The needle should be of a length sufficient to ensure reaching a muscle in the thigh. Thus people with a higher body-mass index need a longer needle. The patient and potentially the family should be taught how to use the epi-injector prior to the patient's discharge from the hospital, as occurred in this case.

The purpose of this article is not to make an expert of airway management of an Obstetrician or a Maternal Fetal Medicine specialist but to familiarize someone with the basic working diagnosis and management of acute upper airway problems and some recent literature on this rare subject. Always get help early in this situation.

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