CLINICAL VIGNETTE

Airway Compromise in ACE Inhibitor Induced Angioedema

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Case Report

A 64-year-old male presented to the emergency department with five hours of tongue swelling with difficulty breathing and swallowing. He reported vague history of prior tongue swelling and could not give specific details. History was limited by the patient's inability to articulate due to significant tongue swelling. He was unable to speak in full sentences due to tongue swelling.

On physical exam, the patient appeared anxious and was in moderate distress. Initial vital signs were HR 98, BP 147/94, RR 22, SpO2 98%. Oropharynx exam demonstrated severe macroglossia with a raised and edematous submental space that forced the patient's tongue toward the roof of his mouth with dramatic resting elevation that obscured further view of his entire mouth (Figure 1). The patient was sitting in a tripod position with his neck in extension. A non-rebreather mask was placed over his nose and mouth immediately upon arrival. His past medical history includes diabetes, hyperlipidemia, abdominal aortic aneurysm, and hypertension on lisinopril.

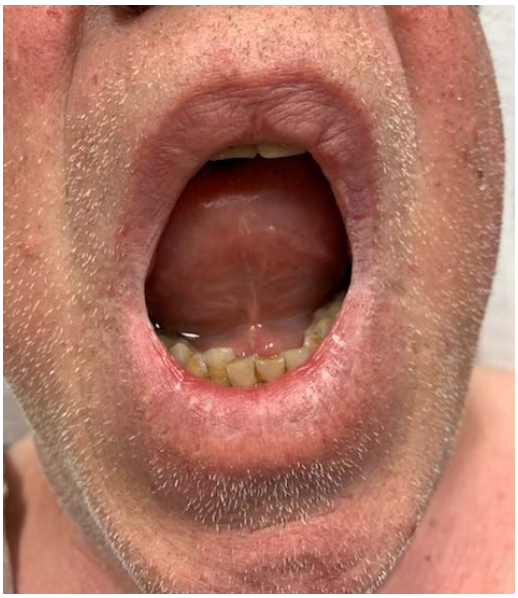

Figure 1: Macroglossia causing elevation of tongue.

The patient was emergently transferred to an open room and otolaryngology immediately consulted for assistance with an anticipated difficult airway. A cricothyroidotomy kit was placed at bedside with landmarks of the anterior neck assessed and not easily identified due to perceived anterior neck swelling. The patient was given intramuscular (IM) epinephrine in addition to intravenous (IV) solumedrol, diphenhydramine and famotidine. He was also given IV icatibant given possible remote history of tongue swelling in the past and the severity of his presentation.

In preparation for awake intubation, the patient was given topical lidocaine, and nebulized 4% lidocaine. Nasal fiberoptic laryngoscopy performed by Otolaryngology revealed thick pooling of secretions in the vallecula and swelling of the glottis (Figure 2). During attempted awake nasotracheal intubation, the patient was unable to tolerate repeat passage of the fiberoptic scope with the endotracheal tube and became acutely agitated despite significant topical anesthesia. He was given a low dose of midazolam for anxiolysis, but he remained very sensitive to any further attempts at fiberoptic laryngoscopy and he became physically aggressive when the scope was near him. Although awake intubation was the preferred approach for maintenance of airway control, the patient was not able to tolerate the procedure safely, and his airway needed to be secured emergently. Therefore, the decision was made to slowly administer ketamine, with repeat aliquots until the patient was dissociated enough to tolerate successful nasotracheal intubation with a 6mm endotracheal tube.

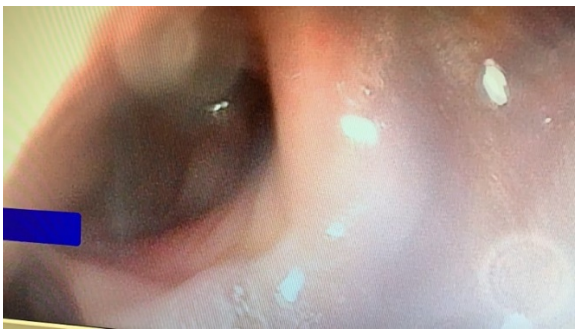

Figure 2: Edematous airway with obscuration of landmarks

The maximal depth of endotracheal tube placement terminated just above the level of the vocal cords, a complication thought due to distorted anatomy from swelling. However, a longer tube was not immediately available. Fortunately, the patient was able to be oxygenated and ventilated with the endotracheal tube positioned just above the vocal cords until it was later replaced by a longer endotracheal tube in the Intensive Care Unit. Additionally, there was concern for possible Ludwig's Angina given the severity of sublingual edema and anterior neck swelling.

The patient was taken for computerized tomography (CT) scan, which revealed only submandibular edema without evidence of infection. He was then transferred to the ICU for close airway monitoring and ventilation management. His hospital course was uneventful with resolution of swelling after 72 hours followed by extubation.

Discussion

Angioedema is a rapid-onset of swelling beneath the skin or mucosal tissue that can affect various parts of the body. The incidence of Angiotensin-converting enzyme inhibitor (ACE-I) associated angioedema varies from 0.1% to 0.7%.[1] Despite this relatively low incidence, ACE-inhibitors are associated with approximately one-third of all emergency department visits for angioedema because of their common use.[2] ACE-I angioedema can be a life-threatening complication of ACE-I usage that requires prompt diagnosis and treatment. Fortunately, overall mortality appears to be low. Mortality is approximately 2000 deaths from 1979-2010 with only 18 of those documented as being due to ACE-I,[3] although ACE-I associated deaths may be underreported.

The pathophysiology of ACE-I angioedema involves elevated levels of bradykinin and substance P, which lead to vasodilatation of blood vessels and plasma extravasation into surrounding tissues.[4] As an anti-hypertensive medication, ACE inhibitors competitively inhibit angiotension-converting enzyme (ACE), which then blocks angiotensin II and results in systemic arterial and venous vasodilation and a reduction in both preload and afterload. ACE also inhibits the degradation of bradykinin, which leads to elevated levels that cause vasodilatation, hypotension and plasma extravasation leading to angioedema.[4,5]

The diagnosis of ACE-I induced angioedema is made clinically and definitive treatment is cessation of the ACE-I. No specific laboratory tests are needed to confirm the diagnosis, however, it may be helpful to send specific studies to rule out C1 esterase deficiency-associated angioedema (hereditary or acquired) due to recurrent episodes of angioedema without urticaria. Some patients diagnosed with ACE-I angioedema may have recurrent angioedema even after discontinuation of the ACE-I.[6] One retrospective study, reported 46% with further recurrences with the overwhelming majority of relapses occurring within the first month of ACE-I cessation. However, some may have recurrences of angioedema even years after ACE-I discontinuation, suggesting that while use of an ACE-I may have triggered angioedema, another etiology including C1 esterase deficiency or idiopathic, may predisposes some to recurrent angioedema.[6]

Treatment

Acute management of ACE-I angioedema includes airway monitoring and discontinuation of the offending medication. If significant airway compromise is imminent, acute intubation is required. ACE-I induced angioedema typically resolves within 24-72 hours.[7]

While the treatment for ACE-I induced angioedema remains supportive and without a consensus on the most effective pharmacologic therapies, many physicians administer treatments used for allergic angioedema such as H1 and H2 blockers, glucocorticoids, and epinephrine with limited efficacy.[7] In addition, therapies such as C1 inhibitor concentrate, fresh frozen plasma, ecallantide, and icatibant can be used, however, their role is limited in ACE-I induced angioedema and more appropriate for hereditary induced angioedema. Despite limited evidence, there are reports of clinical improvement with off-label use of these therapies in ACE-I induced angioedema, with improved time to resolution.[8-10]

ACE-I angioedema is thought to be mediated by bradykinin activation of vascular B2 receptors, therefore, there is a theoretical role for treatment with icatibant, which is a bradykinin B2 receptor antagonist. There is some evidence from case series supporting the effectiveness of icatibant for treating ACE-I angioedema, however, the results of controlled trials have been mixed.[11-16] Icatibant remains an off-label therapy for ACE-I induced angioedema and is primarily used for the treatment of hereditary angioedema. Our patient received 30mg of subcutaneous icatibant, which did not result in immediate efficacy and had uncertain impact on the resolution of angioedema, which approached the expected upper limit of spontaneous resolution following ACE-I discontinuation.

Furthermore, while not used in the treatment of our patient, there may be a role for tranexamic acid (TXA) in the treatment of ACE-I angioedema. This inhibits the conversion of plasminogen into plasmin, which down regulates amplification of other proteins needed to create bradykinin, thereby theoretically inhibiting bradykinin-mediated angioedema. TXA has long been used in the treatment of hereditary angioedema,[17] including as maintenance therapy, which has shown a reduction in angioedema episodes.[18] Additionally, a retrospective study showed improvement in patients with ACE-I angioedema administered TXA as first line treatment.[19]

Summary

This case illustrates the rare but emergent complication of upper airway obstruction from ACE-I angioedema. It also highlights some challenges associated with such a presentation such as the difficulty of an awake intubation with distorted anatomy. If nasotracheal intubation is planned, preparation with an elongated endotracheal tube such as a nasal right angle endotracheal (RAE) tube is ideal. Management of the airway is the priority of treatment. There is no consensus on best pharmacologic therapies, but medications directed at histamine-mediated angioedema and C1 esterase-deficiency angioedema have all been used with variable success. Therapies directed at an allergic etiology should be given if there is uncertainty of whether the angioedema is histamine-mediated. There may be an increasing role for tranexamic acid as an effective therapy, especially given its relative accessibility and cost efficiency relative to other agents.

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