Postoperative Angioedema: A Rarely Encountered Postoperative Emergency

AUTHORS:
Michelle E. Wakeley, MD; Catherine M. Dickinson, MD; Annmarie Duncan MD, FACS; Daithi S. Heffernan MD, FACS, AFRCIS

CORRESPONDENCE AUTHOR:
Daithi S. Heffernan MD  FACS  AFRCSI
Dept of Surgery
VA Medical Center Providence
830 Chalkstone Ave
Providence, RI 02908
Phone: 273-7100
Email: daithi_heffernan@brown.edu

Background
Angioedema is a potentially life threatening condition characterized by acute local edema frequently involving the face and lips. Etiologies for angioedema are broad and mainly medical, including hereditary mutation, allergy, and angiotensin converting enzyme inhibitors (ACEi) or other drugs. Drug-induced angioedema represents the most common cause. Typically, drug-induced angioedema presents shortly after initiation of a drug, however more remote presentations months to years later have been reported.

Summary
This case describes a rare presentation of delayed drug-induced life threatening angioedema occurring following an elective surgical procedure. The severity of this patient’s reaction required airway protection and a prolonged ICU stay. We review the complex etiologies of angioedema along with their management strategies and characteristics of high risk populations to prepare surgeons to care for their own patients who may present similarly.

Conclusion
Our case highlights the need for surgeons to rapidly recognize early warning signs of airway loss and willing to undertake prompt delivery of care in rare conditions that may present as life threatening emergencies in the peri-operative period. Patients with severe angioedema will often require ventilator support and may benefit from use of specialized treatments targeting kallirenin or bradykinin receptors in addition to classic allergic interventions.

Keywords
Angioedema; elective surgery; airway

DISCLOSURE STATEMENT:
The authors have no conflicts of interest to disclose.

MEETING PRESENTATION:
Residents and Fellows Case Reviews Membership Meeting
Rhode Island Chapter of the American College of Surgeons
Providence, Rhode Island
September, 2018.

Case Description

Angioedema is a condition of focal edematous changes to the face, lips, tongue, pharynx, genital and gastrointestinal tissues which typically presents acutely and can progress to cause airway compromise and respiratory distress.\(^1,2\) Angioedema results from a broad range of etiologies including drugs such as angiotensin converting enzyme inhibitors (ACEi), histamine-mediated allergies, and hereditary mutations. While angioedema does not often affect surgical patients, when it does occur it is can be immediately life threatening. Here we describe an unusual presentation of life-threatening angioedema induced by a long-standing home medication, Lisinopril, which required prolonged mechanical ventilation and ICU stay immediately following an elective hernia repair.

An 83-year-old man presented to clinic with a large, chronic, and painful left inguinal hernia. The patient had a surgical history notable for prostatectomy and coronary stenting, and a past medical history significant for hypertension, coronary artery disease, severe COPD, chronic kidney disease and diabetes. His medications were appropriate for his comorbidities, including metformin, omeprazole, albuterol, aspirin, lisinopril and hydrochlorothiazide. He reported no known drug allergies. He was taken to the operating room for an uneventful elective hernia repair under monitored anesthesia care (MAC). The patient took both of his home medications, Lisinopril, which required prolonged home medication, Lisinopril, which required prolonged evaluation showed no defects and the patient was transitioned to a diet. The allergy list was updated to include hydralazine and ACEi class medications. The patient was discharged to a subacute nursing facility for rehabilitation on post-operative day 8. On follow up he was noted to have no airway or hernia complaints.

Shortly thereafter the patient began reporting lingual swelling and dyspnea. On exam significant edema of his lips and tongue were noted with a respiratory rate below 20 and an oxygen saturation greater than 95%. He was placed on a non-rebreather mask and IV Benadryl and hydrocortisone were administered. Over the subsequent thirty minutes his lingual edema worsened, his respirations became sonorous with marked tachypnea, and the decision was made to intubate the patient. Intubation was accomplished on the first attempt by an attending anesthesiologist using a fiberoptic Glidescope who noted an edematous posterior oropharynx.

In the ICU he was easily ventilated with volume control ventilation, and he continued to receive IV antihistamine, corticosteroids, and famotidine. The otorhinolaryngology and medical critical care teams were involved in the patients care to assist with management. Surgical and anesthesia providers involved with the case reviewed the operative record in conjunction with records from the patient’s prior prostatectomy, noting that no new medications were administered in this case. Upon review, the patient had previously received oral and IV hydralazine without issue, however he began Lisinopril therapy 3 months prior and had been suffering from a dry cough at home since initiation. The patient demonstrated no noticeable response to antihistamine and steroid treatment for the first 48 hours, however, at 72 hours the patient demonstrated improvement in his lingual edema, had a positive cuff leak and minimal posterior oropharyngeal edema on nasopharyngoscopy and he was successfully extubated. A swallow evaluation showed no defects and the patient was transitioned to a diet. The allergy list was updated to include hydralazine and ACEi class medications. The patient was discharged to a subacute nursing facility for rehabilitation on post-operative day 8. On follow up he was noted to have no airway or hernia complaints.

Discussion

Angioedema (AE) is defined as a rapid swelling of the deep dermal, subcutaneous, and submucosal tissues, and was first described in 1876. AE typically presents in areas possessing loose connective tissue such as the face, lips, tongue, pharynx, supraglottis, and the subglottic area, as well as the genital and gastrointestinal tissues.\(^2\) Early warning signs of airway compromise reported by patients include difficulty breathing, mouth and facial swelling, voice changes and difficulty swallowing.\(^2\) In rare cases AE can progress to complete airway compromise requiring emergent airway control.

Angioedema is divided into allergic and non-allergic subtypes. Allergic AE is associated with urticaria and responds well to antihistamines.\(^3\) These histamine-mediated events involve a type I IgE\(^4\) mediated hypersensitivity with mast cell degranulation and resolve within 24-36 hrs.\(^5\) The non-allergic forms of AE include hereditary AE, acquired AE, pseudoallergic AE, idiopathic AE and renin-angiotensin-aldosterone system blocker induced AE (RAE). Each subtype displays a unique mechanism of causing AE related to various interactions with bradykinin production and breakdown. Excess bradykinin acts on vascular smooth tissues which typically presents acutely and can progress to cause airway compromise and respiratory distress.1,2 Angioedema results from a broad range of etiologies including drugs such as angiotensin converting enzyme inhibitors (ACEi), histamine-mediated allergies, and hereditary mutations. While angioedema does not often affect surgical patients, when it does occur it is can be immediately life threatening. Here we describe an unusual presentation of life-threatening angioedema induced by a long-standing home medication, Lisinopril, which required prolonged mechanical ventilation and ICU stay immediately following an elective hernia repair.

An 83-year-old man presented to clinic with a large, chronic, and painful left inguinal hernia. The patient had a surgical history notable for prostatectomy and coronary stenting, and a past medical history significant for hypertension, coronary artery disease, severe COPD, chronic kidney disease and diabetes. His medications were appropriate for his comorbidities, including metformin, omeprazole, albuterol, aspirin, lisinopril and hydrochlorothiazide. He reported no known drug allergies. He was taken to the operating room for an uneventful elective hernia repair under monitored anesthesia care (MAC). The patient took both of his home medications, Lisinopril, which required prolonged evaluation showed no defects and the patient was transitioned to a diet. The allergy list was updated to include hydralazine and ACEi class medications. The patient was discharged to a subacute nursing facility for rehabilitation on post-operative day 8. On follow up he was noted to have no airway or hernia complaints.

Shortly thereafter the patient began reporting lingual swelling and dyspnea. On exam significant edema of his lips and tongue were noted with a respiratory rate below 20 and an oxygen saturation greater than 95%. He was placed on a non-rebreather mask and IV Benadryl and hydrocortisone were administered. Over the subsequent thirty minutes his lingual edema worsened, his respirations became sonorous with marked tachypnea, and the decision was made to intubate the patient. Intubation was accomplished on the first attempt by an attending anesthesiologist using a fiberoptic Glidescope who noted an edematous posterior oropharynx.

In the ICU he was easily ventilated with volume control ventilation, and he continued to receive IV antihistamine, corticosteroids, and famotidine. The otorhinolaryngology and medical critical care teams were involved in the patients care to assist with management. Surgical and anesthesia providers involved with the case reviewed the operative record in conjunction with records from the patient’s prior prostatectomy, noting that no new medications were administered in this case. Upon review, the patient had previously received oral and IV hydralazine without issue, however he began Lisinopril therapy 3 months prior and had been suffering from a dry cough at home since initiation. The patient demonstrated no noticeable response to antihistamine and steroid treatment for the first 48 hours, however, at 72 hours the patient demonstrated improvement in his lingual edema, had a positive cuff leak and minimal posterior oropharyngeal edema on nasopharyngoscopy and he was successfully extubated. A swallow evaluation showed no defects and the patient was transitioned to a diet. The allergy list was updated to include hydralazine and ACEi class medications. The patient was discharged to a subacute nursing facility for rehabilitation on post-operative day 8. On follow up he was noted to have no airway or hernia complaints.

Discussion

Angioedema (AE) is defined as a rapid swelling of the deep dermal, subcutaneous, and submucosal tissues, and was first described in 1876. AE typically presents in areas possessing loose connective tissue such as the face, lips, tongue, pharynx, supraglottis, and the subglottic area, as well as the genital and gastrointestinal tissues.\(^2\) Early warning signs of airway compromise reported by patients include difficulty breathing, mouth and facial swelling, voice changes and difficulty swallowing.\(^2\) In rare cases AE can progress to complete airway compromise requiring emergent airway control.

Angioedema is divided into allergic and non-allergic subtypes. Allergic AE is associated with urticaria and responds well to antihistamines.\(^3\) These histamine-mediated events involve a type I IgE\(^4\) mediated hypersensitivity with mast cell degranulation and resolve within 24-36 hrs.\(^5\) The non-allergic forms of AE include hereditary AE, acquired AE, pseudoallergic AE, idiopathic AE and renin-angiotensin-aldosterone system blocker induced AE (RAE). Each subtype displays a unique mechanism of causing AE related to various interactions with bradykinin production and breakdown. Excess bradykinin acts on vascular smooth tissues which typically presents acutely and can progress to cause airway compromise and respiratory distress.1,2 Angioedema results from a broad range of etiologies including drugs such as angiotensin converting enzyme inhibitors (ACEi), histamine-mediated allergies, and hereditary mutations. While angioedema does not often affect surgical patients, when it does occur it is can be immediately life threatening. Here we describe an unusual presentation of life-threatening angioedema induced by a long-standing home medication, Lisinopril, which required prolonged mechanical ventilation and ICU stay immediately following an elective hernia repair.

An 83-year-old man presented to clinic with a large, chronic, and painful left inguinal hernia. The patient had a surgical history notable for prostatectomy and coronary stenting, and a past medical history significant for hypertension, coronary artery disease, severe COPD, chronic kidney disease and diabetes. His medications were appropriate for his comorbidities, including metformin, omeprazole, albuterol, aspirin, lisinopril and hydrochlorothiazide. He reported no known drug allergies. He was taken to the operating room for an uneventful elective hernia repair under monitored anesthesia care (MAC). The patient took both of his home medications, Lisinopril, which required prolonged evaluation showed no defects and the patient was transitioned to a diet. The allergy list was updated to include hydralazine and ACEi class medications. The patient was discharged to a subacute nursing facility for rehabilitation on post-operative day 8. On follow up he was noted to have no airway or hernia complaints.

Discussion

Angioedema (AE) is defined as a rapid swelling of the deep dermal, subcutaneous, and submucosal tissues, and was first described in 1876. AE typically presents in areas possessing loose connective tissue such as the face, lips, tongue, pharynx, supraglottis, and the subglottic area, as well as the genital and gastrointestinal tissues.\(^2\) Early warning signs of airway compromise reported by patients include difficulty breathing, mouth and facial swelling, voice changes and difficulty swallowing.\(^2\) In rare cases AE can progress to complete airway compromise requiring emergent airway control.

Angioedema is divided into allergic and non-allergic subtypes. Allergic AE is associated with urticaria and responds well to antihistamines.\(^3\) These histamine-mediated events involve a type I IgE\(^4\) mediated hypersensitivity with mast cell degranulation and resolve within 24-36 hrs.\(^5\) The non-allergic forms of AE include hereditary AE, acquired AE, pseudoallergic AE, idiopathic AE and renin-angiotensin-aldosterone system blocker induced AE (RAE). Each subtype displays a unique mechanism of causing AE related to various interactions with bradykinin production and breakdown. Excess bradykinin acts on vascular smooth
Drugs are the predominant cause of non-allergic angioedema, and a variety of agents including fibrinolytic agents, estrogen, and nonsteroidal anti-inflammatory (NSAIDs) medications have been linked to AE. These drug reactions are classified as pseudoallergic AE and are mediated via their drugs typical mechanisms of action. For example, nonselective NSAID drugs increase cysteinyl leukotrienes by inhibiting cyclooxygenase-1.\(^1\) No reports of hydralazine induced angioedema were identified. RAE, however, results from ACEi and angiotensin II receptor antagonists inhibiting ACE, the enzyme responsible for bradykinin breakdown. RAE occurs in patients on these drugs who lack fundamental redundancy of peptidases other than ACE, such as aminopeptidase or neutral peptidase, which normally compensate and degrade excess bradykinin.\(^4\) ACEi drugs are the leading cause of angioedema in the United States accounting for 30-55% of all angioedema presentations.\(^2,3\) Currently it is estimated that more than 40 million people worldwide use ACEi medications, however of nearly 200,000 patients initiated on an ACEi in a VA study only 0.20% developed AE, speaking to the need for an underlying enzymatic predisposition.\(^6\) The timing of RAE presentation is unique in that it does not necessarily occur immediately after initiation. One large study reported 55% of cases occur within the first 90 days after drug initiation, yet the increased incidence of RAE in patients prescribed ACEi compared to other oral anti-hypertensive medications extended out beyond 360 days, suggesting presentation can occur at any time.\(^6\)

Populations at highest risk for RAE include those aged over 65, African American race, and female gender. Patients at high risk for severe and recurrent angioedema include those with an ASA score of III or greater, a positive smoking history, a history of cardiopulmonary disease, Hispanic race, and those edema of deeper portions of the aerodigestive tract at first presentation.\(^2,6,7\)

Management of angioedema is dependent upon the etiology. Allergic type angioedema responds well to conventional allergy interventions including antihistamines, H2 blockers and steroids. Approximately 90% of angioedema presenting to the emergency department are discharged 6 hours after administration of an intravenous antihistamine, H2 blocker, and steroids.\(^1\) More severe forms, including incidences such as the case reported here, are significantly less likely to respond to short courses of conventional therapy. New therapies including Ecallantide, a specific and reversible inhibitor or kallirenin, and Icatibant, a selective bradykinin B2 receptor antagonist, are under investigation for treatment of both HAE and RAE.\(^4\) Severe cases will require hospitalization, prolonged pharmacologic management including steroids and potentially ICU care for airway management.

**Conclusion**

Our case highlights the need for surgeons to be constantly vigilant, rapidly recognize early warning signs and willing to undertake prompt delivery of care in rare conditions that may present as life threatening emergencies in the peri-operative period. Patients with severe angioedema will often require ventilator support and may benefit from use of specialized treatments targeting kallirenin or bradykinin receptors in addition to classic allergic interventions.

**Lessons Learned**

Surgeons must be constantly aware and cognizant of potential crises affecting airway, regardless of etiology. Given the increasing number of patients who are prescribed ACEi for management of hypertension, it’s critical that surgeons understand the potential for life threatening ACEi induced angioedema in their patients and how to treat it.

**References**

