

Angioedema with Three Possible EtiologiesChancen Hall, D.O.¹, David Petrie, M.D.¹, John Crowley, D.O.², Justin Sandall, D.O.¹, Felecia Newton, Ph.D.¹¹University of Kansas School of Medicine-Wichita, Wichita, KS

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<https://doi.org/10.17161/kjm.voll5.16653>**INTRODUCTION**

Angioedema (AE) is the localized extravasation of fluid into skin or mucosa resulting from increased vascular endothelial permeability. It is self-limited, often asymmetrical, and can be life threatening if associated with airway compromise and/or anaphylaxis. While hereditary AE has been examined thoroughly in the literature,¹⁻³ there is much to be discovered of the acquired and idiopathic forms. This case reports a new onset unspecified postoperative angioedema, possible etiologies, and best treatment practices. Written, informed consent was obtained from the patient for publication of this case report.

CASE REPORT

A 72-year-old female patient presented for an elective venous port placement for recently diagnosed metastatic colon adenocarcinoma. She had undergone a video-assisted thoracic surgery for pulmonary wedge biopsy one month prior with no complications. She had allergies to lisinopril and atenolol, but had not been taking either for months.

Preoperative exam revealed an obese 80 kg female with Mallampati II and otherwise negative physical exam, with an American Society of Anesthesiologists (ASA) grade of III. The case proceeded uneventfully under monitored anesthesia care with standard ASA monitors. Perioperatively, she received Pepcid[®], ondansetron, cefazolin, lidocaine, propofol, and hydromorphone. The patient recovered well in the post-anesthesia care unit, but several hours post-operative she developed tongue swelling which progressed rapidly to her entire oropharynx, necessitating emergent transfer back to the operating room for airway management. Glidescope insertion, as well as oral fiberoptic intubation, were unsuccessful. After applying lidocaine jelly and a topical 5% lidocaine spray, an awake nasal fiberoptic intubation yielded successful placement of a 7.0 mm endotracheal tube through the left nare. No signs of anaphylaxis were noted. She was transported to the intensive care unit, received fresh frozen plasma, dexamethasone, and Benadryl[®] with gradual resolution of edema. Ultimately, she was extubated and discharged four days later.

Lab work revealed normal complement (C4, C1q, total complement and functional C1-INH), borderline low thyroid levels, and elevated thyroglobulin antibodies (77 nml < 5 IU/mL). It was discovered later that the patient had an episode of hand/lip/mouth swelling three weeks prior to the procedure associated with strawberry consumption that was treated with steroids and Benadryl[®], along with discontinuation of losartan. At the time of discharge, the patient was referred to immunology for additional diagnostic testing and management to reduce the risk of recurrence. On follow-up four weeks after discharge, no additional testing had been done, and the patient continued to have minor episodes of swelling (without strawberries) despite initiation of chemotherapy.

DISCUSSION

Angioedema is localized extravasation of fluid into skin or mucosa resulting from increased vascular endothelial permeability caused by vasoactive substances including histamine, bradykinin, proteases, tryptase, complement, and prostaglandin.⁴ AE is pertinent to anesthesia providers as acute airway compromise may occur any time throughout the perioperative period, as was demonstrated by our case. In fact, the lifetime risk for experiencing AE is estimated between 10-15%.⁵ Our case demonstrated the need for rapid decisive action in cases of AE involving the airway to avoid excessive surgical procedures, asphyxiation, or death. There are several possible causes of AE, along with typical empiric treatment which covers the broad etiologies of AE.

Angioedema can be categorized into three broad etiologies: mast cell mediated, bradykinin pathway mediated, and idiopathic.⁶ AE from mast cell degranulation can occur as an acute allergic reaction from the activation of sensitized immunoglobulin E receptors, or as direct stimulation, and presents with urticaria and/or pruritis.⁵ Direct stimulation of mast cells has been observed with narcotics (codeine and meperidine), neuromuscular blocking agents, and radiocontrast.⁶ Our patient received cefazolin and hydromorphone, but had no reaction on previous administrations, making either of these an unlikely cause of her AE. Her prior reaction attributed to strawberries was a reasonable consideration, although she still showed recurrence without strawberry consumption up to four weeks later. Treatment of mast cell mediated AE cases includes antihistamines, glucocorticoids and, if anaphylaxis is present, epinephrine.

Bradykinin is a potent natural vasodilator and alterations in its production and metabolism have the potential to cause AE.⁶ Most notably, it is well known that angiotensin converting enzyme inhibitors (ACE-I) downregulate the renin-angiotensin-aldosterone system and inactivate the degradation of bradykinin into its metabolites. While the mechanism has not been elucidated, angiotensin receptor blockers have been associated with AE.⁷ Dipeptidyl peptidase-4 inhibitors also may increase vasoactive substances, including bradykinin and substance P.⁸

Our patient did not receive an ACE-I due to her documented allergies and, while she previously was prescribed losartan (an angiotensin receptor blocker), it was unprescribed three weeks prior to surgery. However, AE can develop several years from the onset of ACE-I therapy⁹ with up to 46% of patients reporting AE recurrences long after the discontinuation of the ACE-I therapy.¹⁰

Another facet of the bradykinin pathway involves the enzyme C1 esterase inhibitor (C1-INH), which is responsible for inhibiting activation of the complement system. Deficiency or dysfunction of C1-INH allow inappropriate activity of bradykinin and is the mechanism for hereditary AE which affects approximately 1 in 50,000 people.² Treatment options for bradykinin mediated AE are centered around ceasing ACE-I or angiotensin receptor blocking medications and replacing C1-INH or ACE through fresh frozen plasma. Medications that specifically target the bradykinin pathway include Berinert[®], Ruconest[®], and Lanadelumab[®].^{2,6,11,12}

Acquired angioedema (AAE) is a rare form of AE that presents in the fourth or later decade and can be associated with lymphoproliferative and autoimmune disorders or gastrointestinal adenocarcinomas.^{6,13} There are two proposed mechanisms for AAE: Type 1 includes the consumption of C1-INH by immune complexes; and Type 2 have autoantibodies directed towards C1-INH.¹² Autoimmune disorders such as lupus or thyroiditis have long been associated with AE,^{4,14} as well as the relationship between AAE and lymphomas.

Data on the relation between AE and gastrointestinal tract cancers were limited, but there was a report of adenocarcinoma-associated AE.¹⁵ Our patient had a confirmed colon adenocarcinoma, and it was possible her AE may be explained by progression of the malignant process. However, AAE usually presents with altered complement levels, such as decreased C1-INH, C4 levels, or C1q assay, which was not seen in our patient.^{5,16} She did have elevated thyroglobulin levels despite having no thyroid disease diagnosis, which may have resulted in her acute case of AE.

A thorough understanding of the possible etiologies of AE aids in the successful prevention and treatment of this phenomenon. Our patient showed three possible explanations for her new onset nonhistaminergic AE including an atypical reaction to strawberries, a new onset AAE associated with her colon cancer, or an undiagnosed thyroid autoimmunity. Ultimately, the etiology of our patient was still unspecified. Upon discharge, we referred her to the immunology service for additional testing to seek a definitive diagnosis and treatment to optimize management and reduce the risk of AE recurrence.

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