Regional Anesthesia and Pain

Acute upper airway angioedema secondary to acquired C1 esterase inhibitor deficiency: a case report

[Angio-œdème aigu des voies respiratoires supérieures secondaire à une déficience acquise de l'inhibiteur de C1 estérase : une étude de cas]

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Purpose: Adverse reactions to local anesthetics are widely reported. We report a case of acute upper airway angioedema presumed to be due to the local anesthetic articaine, which was subsequently diagnosed as acquired C1 esterase inhibitor deficiency.

Clinical features: A 54-yr-old woman presented with a history of progressive facial and periorbital edema 24 hr after receiving articaine local anesthetic for a dental procedure. She was in mild respiratory distress but was not stridorous. After inhalational induction with sevoflurane in the operating room, direct laryngoscopy revealed marked edema of supraglottic structures including epiglottis, uvula and aryepiglottic folds and the larynx was not visualized. The patient's trachea was intubated under direct laryngoscopy. Seventy-two hours later, the endotracheal tube was removed and she made an uneventful recovery.

Initially, the angioedema was thought to be caused by a hypersensitivity reaction to articaine. Later investigations showed normal C3 complement level, very low C4 complement and C1 esterase inhibitor levels confirming a diagnosis of C1 esterase inhibitor deficiency. Subsequently, the patient was started on androgen therapy. Her C1 esterase inhibitor level normalized and she remained symptom free nine months after initial presentation.

Conclusion: We report a case of acute upper airway angioedema secondary to C1 esterase inhibitor deficiency requiring emergency airway management. Anesthesiologists should consider C1 esterase inhibitor deficiency in the differential diagnosis of patients with airway edema and be familiar with the acute and prophylactic treatment of patients with this diagnosis.

Objectif : *Des réactions indésirables aux anesthésiques locaux sont largement rapportées. Nous présentons un cas d'angio-œdème aigu des voies respiratoires supérieures, d'abord attribué à l'anesthésique local, articaïne, mais reconnu par la suite comme la conséquence d'une déficience en inhibiteur de la C1 estérase.*

Éléments cliniques : *Une femme de 54 ans a consulté pour un œdème facial et périorbital progressif 24 h après avoir reçu l'anesthésique local articaïne pour un traitement dentaire. Elle présentait une détresse respiratoire bénigne, mais pas de stridor. Après l'induction réalisée dans la salle d'opération par inhalation de sévoflurane, la laryngoscopie directe a révélé un œdème marqué des structures supraglottiques, y compris l'épiglotte, la luette et les plis aryépiglottiques, et le larynx ne pouvait être visualisé. L'intubation endotrachéale a été faite sous laryngoscopie directe. Soixante-douze heures plus tard, le tube endotrachéal a été retiré et la récupération s'est déroulée sans incident.*

On a d'abord cru que l'angio-œdème était causé par une hypersensibilité à l'articaïne. Mais l'examen ultérieur a montré un niveau de complément C3 normal, un complément C4 très faible et un niveau d'inhibiteur de C1 estérase confirmant un diagnostic de déficience d'inhibiteur de C1 estérase. Par la suite, la patiente a été traitée à l'androgène. Le niveau d'inhibiteur de C1 estérase s'est normalisé et aucun symptôme n'était revenu neuf mois après leur manifestation initiale.

Conclusion : *Nous avons présenté un cas d'angio-œdème aigu des voies respiratoires supérieures, secondaire à une déficience en inhibiteur de la C1 estérase, qui a nécessité une assistance respiratoire d'urgence. Il faut inclure la déficience en inhibiteur de C1 estérase dans le diagnostic différentiel à établir dans les cas d'œdème des voies respiratoires et se familiariser avec le traitement prophylactique et urgent qu'ils exigent.*

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ADVERSE reactions to local anesthetics are widely reported. These include dose-related toxic effects, subjective psychomotor symptoms, as well as true allergic reactions.[1,2] We report a case of acute upper airway angioedema presumed to be due to the local anesthetic articaine, which was subsequently diagnosed as acquired C1 esterase inhibitor deficiency.

Case report

A 54-yr-old, 68 kg, 160 cm previously healthy woman presented to the emergency room with facial swelling 24 hr following a dental procedure. One day prior to presentation she received an injection of the local amide anesthetic articaine by her dentist for the filling of an upper molar carie. Two hours later she began to experience perioral swelling. By the next morning the swelling had progressed to involve her eyes, cheeks, and neck. This prompted her to seek attention at our institution, where she was assessed by the anesthesiology and otolaryngology services. She complained of throat tightness and mild respiratory distress. Her vital signs showed a heart rate of 108 beats·min^{-1}, blood pressure of 178/96 mmHg, respiratory rate of 20 breaths·min^{-1}, oxygen saturation of 93% on room air and temperature of 36.5°C. She had marked swelling of her perioral, periorbital and neck regions. She was in mild respiratory distress but was not stridorous. The patient received diphenhydramine 50 mg *iv*, methylprednisolone 125 mg *iv*, and *sc* epinephrine 300 mg. The otolaryngologist performed an awake oral examination and nasopharyngoscopy which revealed major swelling of the uvula and moderate swelling of the epiglottis. The larynx was not visualized. As the working diagnosis at the time was angioedema secondary to a hypersensitivity reaction to an amide local anesthetic, a decision was made not to apply lidocaine topicalization for awake airway examination. The otolaryngologist requested an urgent examination under anesthesia, possible endotracheal intubation or tracheostomy.

One hour later, in the operating room, with equipment and personnel for tracheostomy available, she was given an inhalation induction using 8% sevoflurane. Direct laryngoscopy revealed marked edema of supraglottic structures including epiglottis, uvula and aryepiglottic folds. The larynx was not visualized due to marked supraglottic edema. Based on the serial examination results and evidence of progressive airway edema, a decision was made to intubate the patient's trachea. Under direct laryngoscopy, a gum elastic bougie was inserted through the supraglottic opening to a depth of 25 cm and a 7.0-mm cuffed oral endotracheal tube was directed over the bougie into the patient's trachea without resistance. Capnography and auscultation confirmed endotracheal tube placement. She remained intubated in the intensive care unit for three days while receiving *iv* corticosteroids. After satisfying extubation criteria including the presence of a cuff leak, she was extubated uneventfully and subsequently discharged home.

Further evaluation revealed a history of periorbital swelling one year previous, following a dental injection of the ester local anesthetic procaine. In addition, she had received prior local anesthetic injections by the same dentist multiple times without adverse effect. The patient also stated that she had experienced, four months prior to admission, three episodes of foot and labial edema, all unrelated to local anesthetic use.

Laboratory investigations showed normal hemoglobin, serum biochemistry, electrocardiogram and a normal C3 complement level. Her C4 complement level was very low at 0.02 g·L^{-1} (normal > 0.2 g·L^{-1}). Her C1 esterase inhibitor level was also very low at 0.06 g·L^{-1} (normal 0.21–0.39 g·L^{-1}), confirming a diagnosis of C1 esterase inhibitor deficiency.

Upon leaving the hospital, she was started on danazol therapy at 100 mg daily, which was later increased to 200 mg·day^{-1}. This treatment was well tolerated. Nine months after presentation the patient has no further episodes of angioedema. Her C1 esterase inhibitor level has normalized to 0.31 g·L^{-1} (normal 0.21–0.39).

Discussion

Management of acute angioedema secondary to C1 esterase inhibitor deficiency causing upper airway edema has varied from conservative observation to early tracheal intubation or tracheostomy. A review of the literature suggests that, in upper airway edema resulting in suspected or significant airway obstruction, it is prudent to undertake awake laryngoscopic examination and tracheal intubation or tracheostomy after adequate topicalization, the exception being in pediatric patients in whom an inhalational induction of anesthesia may be undertaken.[3] Life threatening airway obstruction can rapidly ensue either spontaneously or upon airway manipulation. It is imperative to have immediate availability of equipment and personnel skilled in insertion of an infraglottic airway in anticipation of the potential "cannot intubate, cannot ventilate" situation. Patients with minimal upper airway swelling can be observed carefully while those with significant swelling should be intubated prophylactically.[4,5]

We faced a dilemma in a patient with significant upper airway edema whereby topicalization with lidocaine was contraindicated due to a suspected hyper-

sensitivity reaction to amide anesthetics. After discussion between anesthesiology and otolaryngology, a decision was made to perform an inhalational induction and direct examination under general anesthesia with a double setup for infraglottic airway insertion. When examination revealed marked supraglottic edema, tracheal intubation was performed successfully under direct laryngoscopy and bougie guidance thereby avoiding the need for an infraglottic airway.

The differential diagnosis of airway edema includes hypersensitivity reactions and/or angioedema, inhalant allergic reactions, infection, physical trauma or chemical injury such as burns. Our initial diagnosis in this case was a hypersensitivity reaction to articaine. Articaine is an amide local anesthetic that, while only recently introduced in the United States, has been used extensively in Europe and Canada since the 1980s, primarily for dental procedures.[6] Patients receiving injections of local anesthetics may complain of a variety of side-effects, and may incorrectly assume or be told they have an allergy to the drug.[1,7] True reproducible allergies to amide local anesthetics such as lidocaine or articaine are exceedingly rare and difficult to find in the literature.[7,8] Most of the various adverse reactions patients experience with injection of local anesthetics can be attributed to dose-related neurotoxic or cardiotoxic effects of the drug, effects of intravascular injection of vasoconstrictor additives, and reactions caused by other allergens, such as latex.[1]

The patient we describe was diagnosed with C1 esterase inhibitor deficiency. This perturbation of the complement system can be either hereditary or acquired. The incidence of the hereditary form of the disease is approximately 1: 50,000 to 1: 150,000.[9] It is usually diagnosed in the first or second decade of life, and is associated with a less severe rate of catabolism of the C1 esterase inhibitor, and thus milder symptoms.[10] It is inherited as an autosomal dominant trait. Acquired C1 esterase inhibitor deficiency is probably less common than the hereditary form. However the exact incidence is unknown.[10] It is more common in women and is associated with autoimmune or low-grade lymphoproliferative disorders.[9,10] It is a rare clinical condition characterized by recurrent, localized *sc* swelling, most often affecting the extremities and/or the head and neck.[9,10] Most episodes occur spontaneously, although there is an increased incidence following surgical procedures, especially of laryngeal edema.[9,10] The patient presented in her 50's and she had no family history of hereditary angioedema. Therefore, she most likely has the diagnosis of acquired C1 esterase inhibitor deficiency. Due to the high concordance with malignancies, individuals diagnosed with the disorder should undergo screening, particularly for lymphoproliferative and gastro-intestinal cancers. In this case, follow-up colonoscopy, abdominal ultrasound and mammography were negative for malignancies. Latex skin testing was negative also.

In the setting of acute episodes of airway edema secondary to C1 esterase inhibitor deficiency, glucocorticoids alone or in combination with epinephrine have been reported to be effective.[9–11] However, anabolic steroids, antifibrinolytic drugs, epinephrine, steroids or antihistamines have not been shown to be effective in acute episodes in randomized control trials. Long-term prophylactic treatment is indicated for patients with significant airway edema or frequent debilitating attacks. Androgen therapy, which is thought to cause an increase in the production of C1 esterase inhibitor by the liver has been shown to be effective in reducing the frequency of attacks.[9,10] In this case, C1 esterase inhibitor level normalized with androgen therapy and there was no clinical recurrence. Our intention is to keep her on chronic prophylaxis indefinitely as she has experienced a severe episode of airway angioedema. Short-term prophylactic treatment is indicated for patients with C1 esterase inhibitor deficiency undergoing elective procedures traumatic to the airway.[9–11] Such therapy can be provided by a two- to seven-day course of androgen or provision of fresh frozen plasma or C1 inhibitor concentrate shortly before elective surgery. At least one case series suggests pretreatment with fresh frozen plasma may prevent such trauma-induced exacerbations.[11] Although the risk of infectious disease transmission is relatively low with human blood products, it cannot be totally eliminated. Therefore, from the infectious disease standpoint, the usage of short-term androgen prophylaxis may be preferable.

In summary, we report a case of acute upper airway angioedema secondary to C1 esterase inhibitor deficiency requiring emergency airway management. Anesthesiologists should consider C1 esterase inhibitor deficiency in the differential diagnosis of patients with airway edema and be familiar with the acute and prophylactic treatment of patients with this diagnosis. Patients diagnosed with this disorder should be advised to carry an information card or bracelet stating the condition.

References

1 *Gall H, Kaufmann R, Kalveram CM.* Adverse reactions to local anesthetics: analysis of 197 cases. J Allergy Clin Immunol 1996; 97: 933–7.

2 *McCaughey W.* Adverse effects of local anesthetics. Drug Saf 1992; 7: 178–89.

3 *Benumof JL.* Airway Management: Principles and Practice, 1st ed. St Louis: Mosby-Year Book Inc.; 1996: 258–9; 614–5.
4 *Pruet CW, Kornblut AD, Brickman C, Kaliner MA, Frank MM.* Management of the airway in patients with angioedema. Laryngoscope 1983; 93: 749–55.
5 *Ishoo E, Shah UK, Grillone GA, Stram JR, Fuleihan NS.* Predicting airway risk in angioedema: staging system based on presentation. Otolaryngol Head Neck Surg 1999; 121: 263–8.
6 *Malamed SF, Gagnon S, Leblanc D.* Efficacy of articaine: a new amide local anesthetic. J Am Dent Assoc 2000; 131: 635–42.
7 *Fisher MM, Graham R.* Adverse responses to local anaesthetics. Anaesth Intensive Care 1984; 12: 325–7.
8 *Chandler MJ, Grammer LC, Patterson R.* Provocative challenge with local anesthetics in patients with a prior history of reaction. J Allergy Clin Immunol 1987; 79: 883–6.
9 *Jensen NF, Weiler JM.* C1 esterase inhibitor deficiency, airway compromise, and anesthesia. Anesth Analg 1998; 87: 480–8.
10 *Markovic SN, Inwards DJ, Frigas EA, Phyliky RP.* Acquired C1 esterase inhibitor deficiency. Ann Intern Med 2000; 132: 144–50.
11 *Jaffe CJ, Atkinson JP, Gelfand JA, Frank MM.* Heriditary angioedema: the use of fresh frozen plasma for prophylaxis in patients undergoing oral surgery. J Allergy Clin Immunol 1975; 55: 386–93.