



Challenging Clinical Cases

Masqueraders of angioedema after a dental procedure

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A 4-year-old girl was in her usual state of health until the morning of June 13, 2019, when she presented with acute facial and lip swelling after completing a pulpectomy for a dental abscess over the left central incisor (Fig 1A). During the procedure, she received local lidocaine injection, sodium hypochlorite (bleach) root canal irrigation, calcium hydroxide/iodoform paste for pulpectomy, and chlorhexidine mouth rinse after the pulpectomy. She had also been exposed to latex material over her face and mouth during the dental procedure and was on day 5 of an amoxicillin course for the dental abscess. Nonsteroidal anti-inflammatory drugs (NSAIDs) were not given during the procedure. Within minutes after completing the procedure, the patient developed significant left-sided upper lip swelling. She did not have any urticaria (or rashes), pruritus, respiratory distress, difficulty swallowing, or gastrointestinal symptoms. An emergency code was called in the dental clinic, and the patient received 0.15 mg of intramuscular epinephrine and 25 mg of intramuscular diphenhydramine without any alleviation of the swelling. Subsequently, she was transferred to a nearby emergency department, where she was afebrile with normal vital signs and without any respiratory distress. She received 40 mg (approximately 2 mg/kg) of oral prednisolone and 150 mg of oral ranitidine without any improvement. Her left-sided upper lip swelling at this point had progressed to profound bilateral upper lip (left greater than right) and cheek swelling (Fig 1A) without any other symptoms or abnormal findings noted on examination. Given the progression of the swelling, she was admitted to the pediatrics inpatient unit, where she received a second dose of intramuscular epinephrine (0.2 mg) and 25 mg of oral diphenhydramine approximately 8 hours after her initial presentation, but no improvement was noted. At this point, the allergy/immunology service was consulted to evaluate for the cause of the facial and lip swelling and to recommend management. The patient had a history of intermittent asthma but had no history of other atopic diseases,

such as urticaria, angioedema, or drug allergies. She had no family history of angioedema or atopic diseases. On examination, the patient had significant swelling of the cheeks, eyelids, and upper lips. There was no appreciable oropharyngeal swelling, respiratory distress, wheezing, or abdominal tenderness.

Facial and lip swelling after dental procedures encompass a broad array of differential diagnoses that include allergic and nonallergic causes. Common allergic causes include immediate hypersensitivity and histaminergic vs bradykinin-mediated angioedema, whereas nonallergic causes include trauma, infection, and idiopathic conditions, such as cheilitis granulomatosa and cheilitis glandularis (Table 1^{1–13}). Given that this patient's facial and lip swelling occurred immediately after dental work, one of our initial differential diagnoses included allergic histaminergic angioedema secondary to immediate drug hypersensitivity to 1 of the medications that she received during the pulpectomy. Chlorhexidine allergy has been increasingly recognized in the perioperative setting and has been reported in the dental setting.¹⁴ Immediate hypersensitivity to lidocaine has also been reported, although it is very rare.¹⁵ Likewise, latex immediate hypersensitivity, although uncommon since the introduction of powder-free gloves, continues to be reported as a potential cause of allergic reactions.¹⁶ We did not consider amoxicillin to be a prominent potential cause of immediate hypersensitivity given that the patient was on day 5 of an amoxicillin course on the day of the dental procedure. Immediate hypersensitivity to drugs typically occurs within minutes to an hour of exposure.¹ Calcium hydroxide/iodoform paste is a commonly used material for root canal fillings in primary teeth. We could not find any reports of possible hypersensitivity to this material. Finally, sodium hypochlorite root canal irrigation does not contain any antigenic peptides or proteins that are typically necessary for eliciting hypersensitivity, and thus, we did not consider this material to be relevant to her presentation at this point (see Discussion section below). Factors that made immediate drug hypersensitivity less likely in the differential diagnosis, however, included the patient's lack of response to several medications, including intramuscular epinephrine (2 times), diphenhydramine (2 times), ranitidine, and prednisolone. By the time we were consulted (approximately 8 hours from initial presentation), we expected that her swelling should have improved or at least remained stable if she had an immediate drug

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Figure 1. Pictorial timeline of patient's clinical presentation and schematic of possible causes. (A) At day 0 (onset), the patient's bilateral upper lip and cheeks were swollen within minutes of completing a pulpectomy. (B) At day 6, the patient's cheek swelling had drastically decreased but her upper lip swelling (left greater than right) remained. (C) At day 16, all facial swelling, including the lips, were minimal to resolved. (D) An ulcer over the left inner upper labial mucosa (yellow arrow) was found near the treated left central incisor (asterisk). (E) Cartoon illustration of the passage of air (blue arrows) as the cause of possible subcutaneous emphysema. The patient's left central incisor dental abscess and associated tissue destruction expose the root canal, establishing an opening for air generated by air-driven dental handpieces to enter through the root canal into the adjacent soft tissues of the face. (F) Cartoon illustration of a possible route that sodium hypochlorite (yellow arrow) could have traveled in causing lip swelling and labial ulceration. As above, the root canal of the patient's left central incisor was exposed and could allow for sodium hypochlorite root canal irrigation to enter through the root canal, travel down, and exit out of the adjacent labial mucosa by gravity, causing tissue damage and associated swelling along the way.

hypersensitivity. Similarly, anaphylaxis was exceedingly unlikely given the patient's lack of response to epinephrine and the lack of cardiorespiratory or gastrointestinal symptoms.¹⁷

Our other differential diagnoses at this point include idiopathic (spontaneous) histaminergic angioedema vs bradykinin-mediated angioedema, which includes hereditary angioedema (HAE), acquired angioedema, and angiotensin-converting enzyme inhibitor (ACE-I)—associated angioedema.³ There are key features that distinguish whether angioedema is histaminergic vs bradykinin induced. Histaminergic idiopathic angioedema is thought to belong to the same clinical entity as spontaneous urticaria and can occur with or without urticaria.² Up to approximately 10% of histaminergic idiopathic angioedema presents with angioedema alone.¹⁸ In contrast, bradykinin-mediated angioedema never presents with urticaria but occasionally presents with erythema marginatum. Histaminergic angioedema is often pruritic, has a rapid onset and shorter duration (24–48 hours) of symptoms, and responds well to antihistamines, epinephrine, and corticosteroids.² In contrast, bradykinin-mediated angioedema is nonpruritic, generally has a slower onset and a longer duration (3–4 days) of symptoms, and only responds to medications that target the bradykinin pathway, including C1 esterase inhibitor, icatibant, and ecallantide.² Fresh frozen plasma can also be effective in abrogating HAE attacks but may acutely exacerbate some cases; therefore, caution is warranted.^{3,4} Tranexamic acid has been used as an on-demand and prophylactic treatment for HAE, but because evidence for its use is limited and efficacy appears to be low, it is not currently considered a first-line treatment.⁴

Given that our patient's symptoms did not improve with antihistamines, epinephrine, and corticosteroids, idiopathic histaminergic angioedema seemed unlikely, although we could not completely rule it out at this point given the possibility that she may respond to higher-dose antihistamines. Bradykinin-mediated angioedema

remained in the differential diagnosis at this point, although HAE less frequently presents *de novo* without a family history (approximately 25% of cases), acquired angioedema typically occurs in older individuals, and ACE-I–induced angioedema can be ruled out in this case because the patient has never received an ACE-I.²

We recommended obtaining a serum tryptase level to rule out anaphylaxis, C4 level and C1 inhibitor antigen and function to assess for HAE, a complete blood cell count with differential to look for eosinophilia, and a complete metabolic panel for general assessment. We also recommended transferring the patient to our hospital given the unavailability of rescue medications for HAE at the local hospital. After arriving at our hospital, the patient further received high-dose cetirizine, ranitidine, montelukast, and prednisone, which did not alleviate her swelling in the next 24 hours. Given the lack of response to various medications used to treat histaminergic angioedema and concerns for potential progression of the swelling to involve the upper airway, the patient was then empirically given icatibant for a potential first presentation of HAE. For children younger than 12 years, plasma-derived C1 esterase inhibitor is the only approved on-demand therapy for HAE in the United States.⁵ However, the only on-demand medication for HAE that our hospital had in stock at the time was icatibant, a bradykinin B2 receptor antagonist. Given that icatibant is approved in Europe as an on-demand medication for HAE in children 2 years or older, we decided to give our patient the recommended weight-based dose of 10 mg of icatibant.⁵ She received 10 mg of icatibant repeated 3 times during the next 12 hours without any significant improvement of her swelling. Given no worsening of her swelling and the lack of respiratory distress or difficulty with swallowing, she was discharged home 2 days later. The results of measurement of serum tryptase, C4, and C1 inhibitor antigen

Table 1
Differential Diagnoses and Masqueraders of Angioedema in Acute Facial or Lip Swelling

Symptom	Diseases	Associated symptoms			Physical findings		Family history	Onset; duration	Mechanisms	Diagnosis	Management	Other features
		Pruritus	Pain	Fever	Rash	Crepitus						
Acute histaminergic angioedema	Immediate hypersensitivity (eg, drug, food, venom) ¹	+/-	-	-	+/- Urticaria	-	+/- Atopy	Minutes to hour; <24 h	IgE and mast cell or basophil mediated	Skin or intradermal testing	Symptomatic treatment with antihistamines +/- epinephrine; avoidance of the offending agent	Anaphylaxis possible
	Acute histaminergic angioedema (non-IgE-mediated) ²	+/-	-	-	+/- Urticaria	-	+/- Atopy	Minutes to hour; <24 h	Mast cell/basophil related	Clinical diagnosis; response to antihistamines	Symptomatic treatment with antihistamines +/- epinephrine (rare)	Triggers: infection, NSAIDs, physical, idiopathic
Bradykinin-mediated angioedema	HAE ³⁻⁵	-	+/-	-	+/- Erythema marginatum	-	Approximately 75%	Hours to day; 3-5 d	Genetic deficiency/dysfunction of C1INH (types I and II); mutations in Factor XII, angiotensinogen 1, plasminogen, or unidentified gene (HAE with normal C1INH)	(1) Low C4 and low C1INH protein (type I); (2) low C4 and low C1INH function (type II); and (3) normal C4, C1INH protein level and function (HAE with normal C1INH)	Treatment of acute attack: C1INH (plasma derived or recombinant), icatibant, ecallantide	Triggers: invasive procedure, infection, stress, drugs (ACEI, estrogen), menstruation, pregnancy
	Acquired angioedema ³	-	+/-	-	+/- Erythema marginatum	-	-	Hours to day; 3-5 d	Excessive consumption of C1INH, leading to deficiency	Low C4, often low C1q, and presence of anti-C1INH antibodies	Treatment of the underlying cause; mixed results with rituximab	Often associated with autoimmune disorder, lymphoproliferative disorder, or MGUS
	ACEI-induced angioedema ³	-	+/-	-	-	-	-	Greatest risk in first week to month of exposure but can occur at any time	Inhibition of bradykinin catabolism	Clinical diagnosis	Avoidance of ACEI; icatibant (off-label)	More frequent in patients of African descent
Other processes	Episodic angioedema with eosinophilia (Gleich syndrome) ⁶	+/-	+/- Abdominal pain or arthralgia	+/-	+/- Urticaria	-	-	Cyclic recurrence; hours to days	Uncertain mechanism	Clinical features + eosinophilia +/- elevated IgM every 3- to 4-wk interval	Resolve spontaneously +/- diuresis in the absence of therapy	Weight gain, hypereosinophilia, +/- elevated IgM every 3-4 wk
	SVC syndrome ⁷	-	+/- Chest pain	-	+/- Cyanosis, distended vessels	-	-	Chronic persistent until treatment	Compression of the SVC from tumor, thrombus, infection, thyroid goiter	Venography, chest ultrasonography or radiography, or MRI	Treatment of underlying tumor or disease	Edema of the head, neck, arms; laryngeal or cerebral edema also possible
	Cheilitis granulomatosa ⁸	-	-	-	+/- Angular cheilitis, mucosal cobblestone, ulceration, fissures	-	-	Initial episode lasts hours to days; frequency and duration increase until becoming persistent or recurrent	Uncertain mechanism	Biopsy and histology: noncaseating granulomatous inflammation	Corticosteroids; antibiotic; TNF- α inhibitor; clofazimine	Reports of associated delayed hypersensitivity to food additives

(continued on next page)

Table 1 (continued)

Symptom	Diseases	Associated symptoms			Physical findings			Family history	Onset; duration	Mechanisms	Diagnosis	Management	Other features
		Pruritus	Pain	Fever	Rash		Crepitus						
	Cheilitis glandularis ⁹	–	+/-	–	Redness of the vermillion area +/- ulceration or crusting		–		Chronic persistent	Uncertain mechanism; chronic inflammatory disease involving minor salivary glands of the lower lips	Biopsy and histology: hyperplasia of the salivary glands and variable inflammation; important to rule out dysplasia/ carcinoma	Treatment unclear; if moderate dysplasia, surgical stripping, cryosurgery, laser surgery, or topical chemotherapy	More common in men; +/- mucopurulent fluid
Iatrogenic processes	Iatrogenic subcutaneous emphysema ^{10,11}	–	+/-	–	–		+	–	Minutes to hours; hours to weeks depending on amount of air and anatomic area affected	Iatrogenic/traumatic introduction of air into subcutaneous tissue	Crepitus finding +/- ultrasonography or radiography	Spontaneous resolution	Common causes: thoracotomy, esophageal surgery, laparoscopy, oral/ dental surgery, improper chest tube, endotracheal intubation
	Sodium hypochlorite toxicity ^{10,12,13}	–	+	–	+/- Ulceration, ecchymosis, hemorrhage		–	–	Seconds to minutes; weeks	Corrosive activity of sodium hypochlorite on contact with mucous membrane or skin	Clinical diagnosis	Typically heals with time; surgical debridement of necrotic tissue if necessary (rare)	Degree of tissue damage and possible associated swelling, ulceration, and ecchymosis depends on the extent of contact with sodium hypochlorite and the concentration

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; C1INH, C1 esterase inhibitor; HAE, hereditary angioedema; MGUS, monoclonal gammopathy of unknown significance; MRI, magnetic resonance imaging; NSAIDs, nonsteroidal anti-inflammatory drugs; SVC, superior vena cava; TNF, tumor necrosis factor.

NOTE. We did not include idiopathic angioedema that is unresponsive to high-dose antihistamines but improves with tranexamic acid prophylaxis. We also did not include angioedema associated with systemic symptoms such as drug rash with eosinophilia and systemic symptoms (DRESS), hypothyroidism, and systemic capillary leak syndrome.

and function all were negative. In addition, serum C1q level and Factor XII sequencing, both measured at a later time to assess for acquired angioedema and HAE with normal C1 inhibitor, respectively, were also unrevealing.

We started a therapeutic trial of high-dose H1 antihistamines along with a daily H2 histamine blocker and montelukast in this patient because if she responded clinically to this intervention, then histaminergic angioedema would have been the likely diagnosis. However, her complete lack of response to these medications raised suspicion for HAE because HAE does not respond to high-dose antihistamines. Surgical procedures, such as dental work, are also classic triggers of HAE.⁴ After seeing no response to 10 mg of icatibant, we decided to give 2 additional doses of icatibant (30 mg total) to more definitively rule out HAE because the maximum number of doses is 3 in 25 hours.¹⁹ Because the patient's swelling did not improve with a total of 30 mg of icatibant, we thought HAE was highly unlikely. Furthermore, our patient's HAE workup was unrevealing, and she had no personal or family history of angioedema. At this point, having minimized the likelihood of drug allergy, histaminergic angioedema, and HAE as causes of her presentation, given that therapeutic medications for these conditions had failed to alleviate her symptoms, we decided that it was safe for her to be discharged because her swelling did not progress further.

During the next 3 days after discharge (days 3–6 from initial presentation), the patient's facial swelling gradually subsided, but the swelling over her left upper lip persisted (Fig 1B) and took more than 2 weeks for near-complete resolution (Fig 1C). In addition, on day 10, the mother of the patient discovered an ulcer over the patient's inner left upper labial mucosa (Fig 1D), an area that could not have been examined at her initial presentation given the significant lip swelling that she had. The location of the ulcer precludes the possibility that it was caused by unintentional biting. At a subsequent clinic appointment, the patient underwent skin and intradermal testing to lidocaine and chlorhexidine, the results of which were negative. Latex IgE test results were also negative. These results, along with reasons described above, further decreased the probability that her reaction was due to immediate drug hypersensitivity.

The long duration of her facial swelling (6 days) further suggested against immediate hypersensitivity, histaminergic angioedema, and even HAE, which infrequently last more than 3 to 4 days.⁵ The duration of her upper left lip swelling (>2 weeks) and the discovery of an inner lip ulcer further suggested that we should actively consider differential diagnoses that can mimic angioedema²⁰ (Table 1). Disorders that typically present with a rash, such as contact dermatitis, urticarial vasculitis, Morbihan disease, and dermatomyositis, are unlikely given that our patient's epidermis was not affected. Systemic disease, such as drug rash with eosinophilia and systemic symptoms (DRESS), hypothyroidism, and systemic capillary leak syndrome, can also be ruled out given the patient had localized swelling without any weight changes or systemic symptoms. Infectious causes, such as soft tissue infection, were unlikely given the lack of pain, erythema, or systemic signs of infection. Gleich syndrome was unlikely given our patient did not have an elevated peripheral eosinophil count.⁶ Superior vena cava syndrome was unlikely given the patient's swelling was very acute, and she did not have any respiratory distress or hoarseness.⁷ Cheilitis granulomatosa is a rare, idiopathic disease that affects the lips, but the disease is chronic, persistent, and recurring and does not present with facial swelling.⁸ Cheilitis glandularis is a rare, idiopathic disease of the minor salivary glands that typically affects older men. It almost always affects the lower lip and not the upper lip or the face.⁹

Finally, we considered iatrogenic mimickers of angioedema, including subcutaneous emphysema and sodium hypochlorite toxicity. Iatrogenic subcutaneous emphysema occurs when air bubbles or other gas from air-driven devices becomes trapped in the subcutaneous tissue. Air can migrate through various fascial planes to

involve the thorax, abdominal wall, perineal region, extremities, and, most often, the neck or face, causing the condition to mimic angioedema. Subcutaneous emphysema has been reported to occur after endodontic dental procedures, including root canal therapy, such as pulpectomy.^{10,11} Air-driven dental equipment was used in approximately half of the cases and attributed to the source of the subcutaneous emphysema. Most cases of dental-related subcutaneous emphysema, although alarming, are painless and resolve spontaneously in 3 to 10 days with no complications or morbidity.¹¹ The diagnosis can be made clinically with the finding of crepitus, a characteristic crackling sensation created as gas is pushed through the tissue during palpation. In doubtful cases, ultrasonography or radiography can be performed to determine whether air is beneath the skin surface.¹¹ We suspect that our patient's cheek (and in part lip) swelling was due to subcutaneous emphysema given that her painless swelling lasted 6 days before spontaneous resolution. In addition, before her acute episode, the patient had a radiography-confirmed periapical (dental) abscess and accompanying tissue destruction that would allow air from dental devices to enter through an exposed root canal into the adjacent soft tissues of the face (Fig 1E). We cannot conclude this diagnosis with certainty, however, because we regrettably did not palpate or image the facial swelling to identify crepitus or air, respectively, at her initial presentation because of our biased preoccupation with identifying allergic causes of her swelling.

As with the patient's inner labial ulcer and left-sided upper lip swelling (Fig 1B–D), which lasted more than 2 weeks, significantly longer than her cheek and right-sided lip swelling, case reports are available in the dental literature of sodium hypochlorite root canal irrigation causing variable mucosal ulceration and lip and facial swelling during dental procedures.^{10,12} Many of these reports assumed that the swelling is attributable to hypersensitivity, but we believe that the swelling (and ulcer) is caused by necrosis and tissue injury because sodium hypochlorite is an oxidizing agent.¹³ Furthermore, sodium hypochlorite contains no peptides or proteins that are usually needed to elicit hypersensitivity. The amount of the tissue damage and associated potential swelling, ulceration, and/or ecchymosis caused by sodium hypochlorite depends on the extent of contact with sodium hypochlorite and the concentration of the sodium hypochlorite. The swelling typically lasts several weeks.^{10,12} The tissue damage by sodium hypochlorite is typically associated with pain, but local lidocaine could have masked the pain in our patient's case.¹⁰ We think that sodium hypochlorite toxicity is a peculiar but plausible explanation for our patient's longer-lasting left lip swelling and ulceration. Although trapped air or gas floats in the case of subcutaneous emphysema, sodium hypochlorite is a liquid that travels with gravity and thus could have flowed through the exposed root canal down onto the adjacent labial mucosa by gravity and caused a necrotic ulcer on its way out (Fig 1F). Alternatively, an unintentional direct spill of the sodium hypochlorite root canal rinse onto the inner labial mucosa during the dental procedure could have caused the ulcer, but this possibility seems less likely given a dental dam had covered the area during the procedure. Ultimately, though, we have no definitive way to prove that her longer-lasting left-sided upper lip swelling and inner labial ulcer were caused by sodium hypochlorite toxicity because no laboratory or physical examination findings are specific for this adverse event.

In summary, we hope that this complicated case illustrates the breadth of differential diagnoses to consider in patients presenting with acute facial and/or lip swelling after dental or oral surgery. Uncommon nonallergic causes must be considered in addition to ruling out allergic causes with laboratory workup and therapeutic trials. We recommend always performing palpation for crepitus and consider imaging even in cases where angioedema is strongly suspected and especially in cases of angioedema refractory to medications. We also recommend careful examination of the inner lips if the swelling does not preclude this.

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