



Lethal manifestations of angioedema

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Abstract

An 86-year-old woman with a history of angioedema was found dead at her home address. She had recently complained of a swollen tongue. At autopsy the tongue was grossly edematous, protruding from the mouth. There was also marked edema of the tonsillar fossae, epiglottis and glottic inlet, causing critical obstruction. Histology of the tongue and upper airway demonstrated marked submucosal edema. Death was attributed to upper airway obstruction due to angioedema of the tongue, oropharynx and glottic inlet. Angioedema is characterized by localized non-pitting edema of the deep dermis and subcutaneous/submucosal tissues. It may be acute or chronic, acquired or inherited. Sudden death may result from critical airway occlusion, although both stroke and ischemic heart disease are known to occur. Post mortem genetic testing for hereditary variants can be conducted for *SERPING1* gene and F12 gene/THR328 mutations.

Keywords Angioedema · Sudden death · Airway obstruction · Tongue swelling · Angioneurotic edema · Asphyxia

Case report

An 86-year-old woman was found dead at her home address. She had a past history of chronic renal failure, osteoporosis, depression, hypertension, hiatus hernia, previous cholecystectomy and an appendicectomy. She had also been diagnosed with angioedema 18 years previously for which she was prescribed an antihistamine and a steroid. The last contact she had made with anyone had been a telephone call to a friend when she had complained of a swollen tongue.

At autopsy the tongue was noted to be grossly edematous and protruding from the mouth (Fig. 1). Further examination of the upper airways showed marked edema of the tonsillar fossae, epiglottis and glottic inlet causing critical obstruction (Fig. 2). The true and false vocal cords were unremarkable. Histology of the tongue and upper airway demonstrated marked submucosal edema (Figs. 3 & 4). Incidental findings at autopsy included pulmonary edema and congestion, evidence of previous cholecystectomy and appendicectomy, moderate hypertensive changes of both kidneys, a benign

endometrial polyp and generalized osteoporosis. There were no other significant underlying organic diseases present which could have caused or contributed to death. Toxicology revealed a blood alcohol level of zero with perindoprilat, the active form of perindopril, an angiotensin-converting enzyme (ACE) inhibitor, which had been prescribed for her hypertension. There was no evidence of trauma. Death was attributed to upper airway obstruction due to angioedema of the tongue, oropharynx and glottic inlet.

Discussion

Angioedema is a condition characterized by non-pitting edema of the deep dermis and subcutaneous/submucosal tissues due to increased vascular permeability, with passage of fluid into the surroundings. Leaking vessels include subcutaneous or submucosal capillaries and post-capillary venules [1, 2]. It was first described in 1586 by Donati, and is also known as angioneurotic, giant or Quinke edema [3]. The swelling is usually a localized phenomenon and may be acute or chronic, acquired or inherited. It often manifests with enlargement of the tongue, sometimes with associated swelling of the lips, face, palate or uvula that develops over minutes to hours. Other areas that may swell include the genitals, buttocks and the backs of the hands and feet. Intestinal involvement may cause nausea, vomiting, diarrhea and colic [1]. If the upper

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Fig. 1 Marked swelling of the tongue with protrusion between the lips in an 86-year-old woman with a long history of angioedema

airway is involved there may be stridor with respiratory distress and acute airway compromise, as in the reported case. It usually resolves in 48–72 h and has an estimated incidence in the United States of approximately 1 in 50,000 [4], although the life-time incidence may be as high as 15% [2]. A severe episode of angioedema may indicate that systemic anaphylaxis is imminent [5].

Underlying mechanisms involve mast-cell derived mediators such as histamine, prostaglandins and leukotrienes, or bradykinin and complement-derived mediators. Mast-cell mediated cases usually have urticaria and pruritus compared to bradykinin-mediated angioedema which develops more slowly without allergic features [2, 6]. On occasion the cause and mechanism may be unknown.

Acute angioedema involves mast cells in over 90% of cases with IgE-mediated urticaria often triggered by allergens found in drugs, food and venom. In other cases mast cells may be directly stimulated by drugs and materials such as aspirin,



Fig. 2 Mucosal edema with narrowing of the glottic inlet



Fig. 3 A low power view of the tongue showing marked edema of the submucosa and muscularis (Hematoxylin & Eosin; H&E $\times 5$)

other nonsteroidal anti-inflammatory agents, radiopaque contrast media and opiates. ACE inhibitors cause a significant percentage of acute cases by increasing bradykinin levels [7]. This may occur after years of treatment and is not associated with urticaria. It is of note in the reported case that perindopril, an ACE inhibitor, had been prescribed for hypertension. The manufacturer's literature states that patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema if this is prescribed.

The etiology of chronic angioedema is often unknown and does not usually involve IgE-mediated mechanisms. Acquired and hereditary angioedema may relate to abnormalities in the

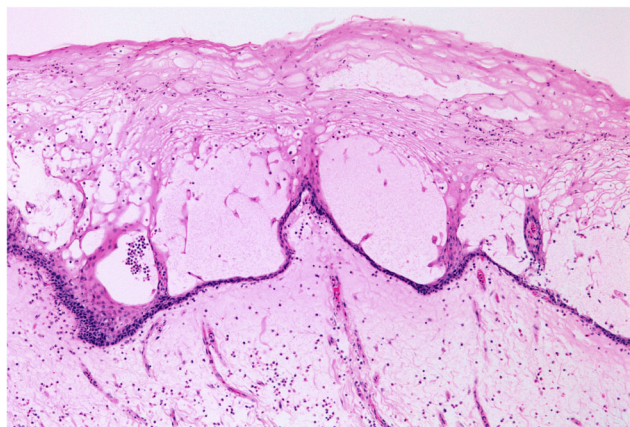


Fig. 4 A higher power view of the tongue showing marked edema of the submucosa with ballooning of the basal layers of the epidermis. A background inflammatory infiltrate of neutrophils and eosinophils was also present. (H&E $\times 150$)

Table 1 Categories of angioedema (adapted from LoVerde and Kaplan [1, 4])**ANGIOEDEMA WITH URTICARIA** (histamine- or immune-mediated)

1. Allergic (drugs, food, venom, latex)
2. Spontaneous acute and chronic
3. Other, associated with:
 - a. exercise
 - b. low temperature
 - c. vibration
 - d. vasculitis
 - e. eosinophilia
 - f. nonsteroidal anti-inflammatory drugs

ANGIOEDEMA WITHOUT URTICARIA (bradykinin-mediated)

1. C1-INH deficiency
 - a. Type I (defective function and reduced amount)
 - b. Type II (defective function but normal amount)
2. Normal C1-INH (Type III) with
 - a. factor XII mutation
 - b. unknown
3. Acquired with C1-INH deficiency with
 - a. autoantibodies
 - b. autoimmune disease e.g. systemic lupus erythematosus
 - c. lymphoproliferative disorders
4. Drug related
 - a. angiotensin converting enzyme inhibitor
 - b. recombinant tissue plasminogen activator
 - c. dipeptidyl peptidase 4 inhibitors
 - d. direct renin inhibitor aliskirin
 - e. combination of angiotensin converting enzyme and rapamycin inhibitors

ANGIOEDEMA OF UNKNOWN CAUSE (idiopathic)

1. histamine related
2. non-histamine related

complement pathway associated with reduced levels or abnormal function of C1 inhibitor. Hereditary angioedema was first described by Osler in 1888 and has three forms that activate the complement system [8, 9]. The condition occurs worldwide with no geographic or ethnic predilections [10]. Originally known as types I and II, these are autosomal dominant conditions caused by mutations in the *SERPINE1* gene which reduces C1-inhibitor protein in type I, or causes dysfunctional forms in type II. Type III is X-linked involving F12 gene/THR328 mutations without any discernible abnormalities in the C1-inhibitor protein [11]. Type I is the most common accounting for approximately 85% of reported cases [12]. The mean age of onset of the first episode of laryngeal edema is around 26 years, with a mortality rate in undiagnosed cases of 30–50% [13]. A classification of angioedema is found in Table 1. The laboratory characteristics of the various subgroups of angioedema and treatment options have been summarized elsewhere [4, 14].

Conditions which may mimic angioedema include superior vena caval syndrome, generalized edema due to cardiac, renal or hepatic failure, factitious illness, granulomatous cheilitis, Crohn disease or Melkersson-Rosenthal syndrome [1, 4]. The latter syndrome is a rare neurological disorder characterized by swelling of the face and lips. Macroglossia due to hypothyroidism, acromegaly or amyloidosis may also cause confusion [4].

Cases of angioedema may present for medicolegal assessment when there has been critical airway occlusion resulting in death, although both stroke and ischemic heart disease have been documented due to hypovolemia and hypoxia [4]. While acute laryngeal swelling is most often responsible for airway obstruction [15], similar effects may result from swelling of the pharynx or tongue [1] as in the present case. Post mortem genetic testing for hereditary angioedema can be conducted for *SERPINE1* gene and F12 gene/THR328 mutations [11].

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Compliance with ethical standards

Ethical approval This paper was approved by Forensic Science SA management.

Conflict of interest The authors declare that they have no conflicts of interest.

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