

## A slow and dangerous swelling of the tongue and the face

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A 91-year-old man presented at our emergency room complaining of sialorrhoea and facial edema, especially around his lips and palpebral region. The symptoms started in the morning and got worse over two hours. He had a history of hypertension and hypokinetic ischemic cardiomyopathy treated with ramipril, doxazosin, aspirin, furosemide, amiodarone, ranolazine, atorvastatin, and pantoprazole. He referred an allergy to clopidogrel. He did not introduce any novel medications or foods. His vital signs were BP 150/70, HR 57 bpm, sO<sub>2</sub> 97% in room ambient, RR 18/min, and BT 36.4°C. He presented a severe edema of the tongue with tirage and cornage. He was immediately treated IV with hydrocortisone 1 g chlorpheniramine maleate 10 mg, and icatibant 30 mg SC and he was intubated through the nose.

### Question

Given the patient's history, what is the most likely diagnosis?

1. Cellulitis
2. Angiotensin-converting enzyme inhibitor-induced angioedema (ACEI-AE)
3. Acute urticaria
4. Anaphylaxis

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## Answer

Considering the progressive, slow onset of the symptoms, the lack of urticaria, and the ACEI therapy, the correct diagnosis is ACEI-AE. After nasotracheal intubation, the patient was transferred to the ICU. Icatibant (30 mg sc) was repeated after six hours from the previous dose, and IV steroids and antihistamines were administered for ten days. After six days he was extubated, and he was discharged in good clinical condition two weeks later. The C1 esterase inhibitor resulted in the normal range (0.26 g/L, nv 0.21-0.38 g/L). C3 and C4 were 90 mg/dL (nv 93-188) and 22 mg/dL (nv 15-44), respectively.

AE is a clinical heterogeneous entity defined as self-limiting edema localized in the deeper layers of the skin or the upper respiratory or gastrointestinal mucosa and lasting for several days. Firstly described by Heinrich Quincke in 1882, it is often referred to as Quincke edema.<sup>1</sup> AE can occur at any age<sup>2</sup> and in any location. It is characterized by a vascular reaction of deep dermal, subcutaneous, mucosal, or submucosal tissues with localized increased permeability of blood vessels resulting in tissue swelling, affecting the face, lips, mouth, throat, larynx, uvula, extremities, and genitalia, with an asymmetric presentation.<sup>3</sup>

AE can be mediated by two different vasoactive peptides: bradykinin (nonhistaminergic AE) or histamine (histaminergic AE).<sup>4</sup> Clinical presentations may be similar, but the treatment is different. Urticaria is suggestive of histaminergic AE, whereas itching may not be present. Swelling can occur within minutes in the case of histaminergic AE and usually subsides within 24-48 hours, but relapses are common and unpredictable, in contrast with a typically slower and more progressive onset in bradykinin-mediated AE,<sup>5</sup> which usually reverts within 48-72 hours, although it can persist for up to five days.<sup>6</sup> Both the two forms can lead to an imminent upper airway obstruction and a life-threatening emergency. When the bowel wall is involved, AE can mimic an acute abdomen.<sup>7,8</sup> Histaminergic AE resolves with antihistamines, steroids, and epinephrine, while bradykinin-mediated AE is unresponsive to those treatments and can be successfully treated with plasma-derived human-C1INH concentrate or icatibant.

Patients with recurrent AE have a lower quality of life. For recurrent AE without urticaria, it is strongly recommended to rule out hereditary angioedema, ACEI-AE, and acquired C1 esterase inhibitor deficiency angioedema (C1-INH-AAE).<sup>9</sup> Only C1-INH-AAE is directly associated with other systemic diseases, such as multiple myeloma, chronic lymphocytic leukemia, rectal carcinoma, and non-Hodgkin lymphoma.<sup>10</sup> ACEI-AE is the most common form of AE typically presenting in the emergency department.<sup>11</sup> Diagnosis is based on the patient's medical history. ACEIs cause a reduction in bradykinin degradation. ACEI-AE most commonly involves the orofacial region, and up to 39% of the cases may involve the upper airway. It can develop years after the beginning of the treatment.<sup>12</sup> Despite the discontinuation of the ACEI, recurrent AE can occur over weeks to months. Additional therapies reported with various efficacies for the treatment of ACEI-AE include fresh frozen plasma, ecallantide, icatibant, tranexamic acid, and C1 inhibitor concentrate.<sup>3</sup>

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