Macroglossia

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THE CHALLENGE

A 59-year-old man sought treatment for swollen tongue and bilateral submandibular areas of 6-months' duration. The enlarged tongue led to dysphagia without pain. The patient reported that the swelling fluctuated between mild and severe. The patient had a history of hypertension and diabetes for 10 years. Calcium channel blockers controlled the hypertension, and glycemic status was well controlled via lifestyle intervention, with fasting blood glucose maintained at below 6 mmol/L. In addition, the patient had undergone cardiac surgery for myocardial infarction 5 years earlier and took aspirin regularly.

Oral examination showed an enlarged, somewhat inflexible tongue. No discrete mass was palpated. Scattered nodules were noted on the ventral tongue; when palpated, the nodules felt the same as the rest of the substance of the tongue (Figure 1). No changes were noted on the oral mucosa or the bilateral cervical and submandibular lymph nodes. The initial clinical diagnosis at a local hospital was angioneurotic edema. The patient was treated with antihistamines and 25-mg prednisone tablets daily. The symptoms were alleviated temporarily and slightly after 2 months of treatment but recurred 1 month later, accompanied by a decrease in urine volume.

No changes were found in liver or kidney function or in routine blood tests, except in total protein, albumin, and cholinesterase. Urine analysis revealed protein, ketone bodies, small round epithelial cells, and epithelial cells.

A tongue tissue biopsy was performed. Histopathologic examination of hematoxylin and eosin–stained sections revealed extracellular deposition of amorphous, eosinophilic, hyalinelike material in the submucosal connective tissue (Figure 2A). Congo red stained the extracellular deposition brick red under conventional light microscopy (Figure 2B) with apple green birefringence under polarized light (Figure 2C).

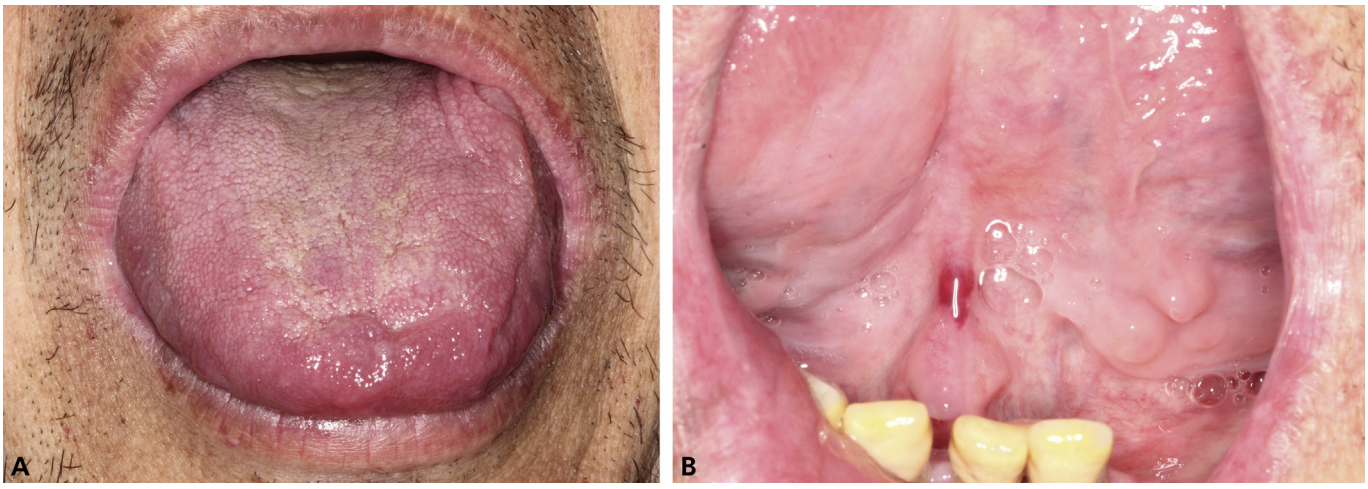

Figure 1. A. A severely swollen tongue fills the intraoral space. **B.** Scattered nodules on the ventral tongue.

(Please see next page for additional images.)

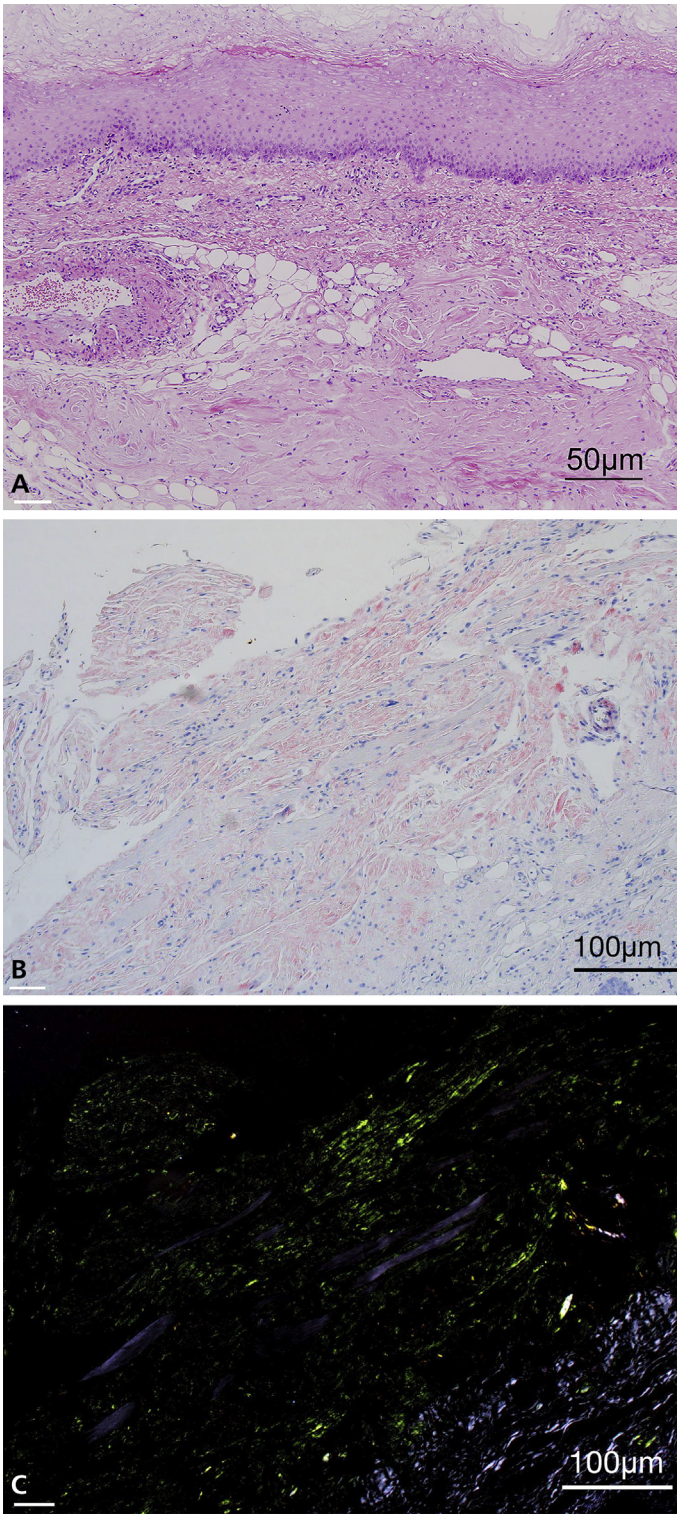

Figure 2. **A.** Histopathologic examination of hematoxylin and eosin–stained sections showing extracellular deposition of amorphous, eosinophilic, hyalinelike material in the submucosal connective tissue (×200 magnification). **B.** Congo red staining under conventional light microscopy revealed diffuse brick red staining in the submucosa of the purple, clustered cloudlike lesions and nodules (×100 magnification). **C.** Congo red staining under polarized light resulted in apple green birefringence, consistent with amyloids (×100 magnification).

Can you make the diagnosis?

A. angioedema
B. amyloidosis
C. adenoid cystic carcinoma (AdCC)
D. lymphangioma
E. neurofibromatosis (NF)

The diagnosis:

B. amyloidosis

A comprehensive review of the medical history and the clinical, laboratory, and histopathologic findings led us to diagnose the patient with systemic amyloidosis with kidney damage. Immunoglobulin- (Ig-) free light-chain analysis excluded multiple myeloma. Amyloidosis is a group of conditions caused by accumulation of abnormal protein (called amyloid fibrils) in the tissue.[1] Amyloidosis can be localized or systemic.[2]

Amyloidosis symptoms depend on the amyloid accumulation site. Oral amyloidosis manifests as macroglossia and nodules, purple bullae or blisters, ecchymosis, and ulcers that often involve the tongue, gingivae, and buccal mucosa. The submental and submandibular regions swell and harden, and the border of swelling becomes obscure. Dry mouth may occur if the salivary glands are involved.[3] Our patient only showed full-tongue enlargement, an early nonspecific symptom of oral amyloidosis, which posed great challenges for diagnosis. Fortunately, we noticed that the patient had kidney-related symptoms (oliguria, proteinuria). Seizing this lead, we reached the definitive diagnosis of amyloidosis that primarily affected the oral cavity and kidneys, after a multidisciplinary consultation. Amyloidosis may be associated with systemic disease. The kidney is one of the organs most commonly involved in amyloidosis. Kidney amyloidosis manifests with proteinuria, mild kidney dysfunction, edema, and hypoalbuminemia. It can cause nephrotic syndrome, resulting in increased concentrations of serum creatinine, blood urea, and biochemical markers of kidney injury.[4] Other organs involved include the heart, brain, liver, glands, skeletal muscle system, eyes, and mouth.[5]

The reference standard for diagnosis of amyloidosis is biopsy with use of Congo red stain, which produces apple green birefringence on polarized light microscopy.[6] Once amyloid deposits are identified, the clinician should determine whether they are localized or systemic and which organs are involved. Combined with the patient's general condition, assessment should include the kidney (urine routines, kidney function, 24-hour proteinuria) and liver functions.[7] Serum and urine immunofixation and Ig-free light-chain assays were used to screen for abnormal association of Ig and amyloid light chains.[8] Because most cases with amyloidosis manifest as a systemic disease and have poor prognoses, a comprehensive evaluation is needed to determine the underlying disease, such as multiple myeloma or Crohn disease, to guide treatment and prognostic evaluation.[3]

DIFFERENTIAL DIAGNOSIS

Angioedema

Angioedema can be acquired (AAE) or hereditary (HAE). AAE is an allergic reaction, particularly to certain insect bites, food, or medication. The facial skin and mucous membranes of the mouth, tongue, and throat show edema within a few minutes to several hours, accompanied by itching or pain. Paresthesia appears when the nerves are compressed.[9] There is no specific laboratory test for AAE diagnosis. The diagnosis can be based on clinical manifestations, and the trigger can be found through auxiliary means such as scratch testing or immunoglobulin E specificity to allergen testing.[10]

HAE is an autosomal dominant genetic disease with multiple hereditary forms, and HAE1 (Online Mendelian Inheritance in Man [OMIM] 106100) and HAE2 are associated with mutations in the C1 esterase inhibitor gene, whereas other forms (HAE3-HAE8) are associated with other genes.[10] In addition to facial swelling, HAE may cause swelling in other body parts such as the limbs, genitals, and neck. Edema resulting from HAE occurs within 12 through 36 hours and then subsides over 2 through 5 days. Symptoms range from mild discomfort to pain, depending on the location and severity of the edema. HAE sometimes is accompanied by abdominal pain, diarrhea, and weakness.[11] HAE diagnosis relies on positive family history of angioedema and laboratory findings of low (30% of normal) functional C1 esterase inhibitor titers and severely reduced C4 levels.[12]

AdCC

AdCC is the third most common malignant salivary gland tumor and is observed most often in women aged 50 through 60 years.[13] When AdCC involves the tongue, tongue swelling with or

without pain, accompanied by slurred speech and swallowing difficulty, may occur. Infringement of the hypoglossal nerve can cause paralysis and muscle tremor.[14] Typical clinical manifestations include slow growth, local recurrence, perineural infiltration, and distant metastasis.[15] Studies have shown that tongue lesions account for 3.4% through 11.8% of head and neck AdCC cases.[16]

Histopathology is still the reference standard for tumor diagnosis. The tumor is characterized by asymmetric and varying lobulated or invasive growth patterns. Histologically, AdCC may manifest in 3 patterns: glandular (cribriform), tubular, and solid. Histologic features and immunohistochemical markers such as smooth muscle actin, S100, MYB, vimentin, and CD117 (c-kit) can be used to confirm the diagnosis.[17]

Lymphangioma

Lymphangioma is a benign lesion formed by the growth and proliferation of primitive lymphatic vessels that can occur in any part of the skin and mucous membranes. Tongue lymphangiomas usually exist at birth, show no symptoms, and are easily missed.[18] Lymphangiomas may appear as a clear lump or huge tongue, accompanied by difficulties in speech and chewing and, in extreme cases, airway obstruction. Clinically, tongue lymphangioma is characterized by clusters of pebbles and vesicular nodules that may appear purple because of their blood and lymph components.[19]

Lymphangioma diagnosis is based on clinical history and examination results. Biopsy may be used to confirm the diagnosis. Magnetic resonance imaging or ultrasonography can be used to assess the depth and extent of the lesion.[20]

NF

NF is an autosomal dominant genetic disease, causing multisystem damage via abnormal neural crest cell development.[21] The 3 disease types are NF type I (NF1) (OMIM 162200), NF type II (OMIM 101000), and schwannomatosis (OMIM 162091).[22] Of these, NF1 is the most likely to manifest with tongue nodules, and oral soft-tissue lesions occur in 72% through 92% of patients with NF1. The tongue with neurofibroma is characterized by hemimacroglossia, with localized ridges or nodules, and soft texture.[23] NF1 symptoms include café au lait spots on the skin, armpit and groin freckles, Lisch nodules, and intellectual impairment.[24]

The diagnostic approach to NF differs according to the disease location and includes radiography, magnetic resonance imaging or computed tomographic scans, electroencephalograms, genetic testing, and histology.[24] The histopathologic characteristics of NF are primarily neurofibromas of various sizes that grow on peripheral nerves and are composed of spindle sheath cells.[25]

CONCLUSION

Amyloidosis is a rare metabolic disease in which misfolded proteins aggregate into oligomers and deposit outside cells, causing tissue and organ dysfunction.[26] Early signs of oral amyloidosis are often nonspecific, especially in patients with just an enlarged tongue. Furthermore, diseases such as lymphangioma, angioedema, and NF can all manifest as an enlarged tongue and can be confused easily with amyloidosis. Histopathology, Congo red staining, and apple green birefringence under polarized light microscopy are the reference standard for diagnosis of amyloidosis. Because of the poor prognosis associated with multiple underlying systemic conditions, amyloidosis should be investigated rapidly. Therefore, multidisciplinary cooperation, comprehensive review of the patient's medical history, and systemic investigation are needed to achieve timely and definitive diagnosis. ■

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