



Maintenance of Certification-CME Review

Angioedema of the tongue with an unfamiliar final diagnosis



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Release Date: April 1, 2015**Expiration Date:** March 31, 2017**Target Audience:** Physicians involved in providing patient care in the field of allergy/asthma/immunology**Learning Objectives:**

At the conclusion of this activity, participants should be able to:

- Describe the clinical and pathophysiologic presentation of angioedema as well as that of amyloidosis
- Recognize the need for and symptoms of deep brain stimulators

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Clinical Vignette

A 77-year-old white man with a medical history of hypertension, sleep apnea, Parkinson disease (PD), diabetes with mild neuropathy, and gastroesophageal reflux disease presented to the office with a sensation of tongue swelling for the past month. The symptoms were episodic in nature and lasted several days at a time and were not associated with symptoms of urticaria or anaphylaxis. Armodafinil was started 10 days before the onset of symptoms, but symptoms persisted after discontinuation. There were no obvious triggers, such as foods, medications, nonsteroidal anti-inflammatory drugs, heat, pressure, or stress. Diphenhydramine and fexofenadine and a prednisone course did not help with his symptoms.

The patient had a medical history of hypertension, diabetes, sleep apnea, PD, depression, and gastroesophageal reflux disease. Previous surgeries included brain surgery in 2010, heart stent placement in 2002, and repair of a hydrocele. Home medications included aspirin, atenolol, atorvastatin, glimepiride, lansoprazole, bupropion hydrochloride, rivastigmine, ramipril, insulin glargine, and methylphenidate. Allergies included clarithromycin; the patient denied any allergies to food, insects, or latex. The family history was not significant for any atopy.

Pertinent Physical Examination

Vital signs were within normal limits. The patient had a body mass index of 31 kg/m² and normal skin, eyes, ears, and nose. The tongue appeared slightly larger than average but without definite swelling or evidence of teeth indentation. Neck, thyroid, lymphatics, lungs, heart, and extremities were normal. There was no dermatographism.

Initial Impression and Plan

Intermittent tongue swelling that lasts a couple of days is consistent with angioedema, although at examination there was no definite objective evidence of swelling. A probable cause of angioedema without urticaria would be the patient's angiotensin-converting enzyme inhibitor (ACEI). We recommended discontinuation of the ramipril; ordered a complete blood cell count, liver function test, a thyroid panel, complement C4 level, and an erythrocyte sedimentation rate; and scheduled a follow-up in 1 month.

Introduction

Macroglossia can be a common complaint with a rather wide differential diagnosis. This case reviews the topics of angioedema, amyloidosis, and a final diagnosis not typically encountered in an allergist's office.

Angioedema Review

Angioedema is a transient swelling of a limited area in the deep dermis and subcutaneous tissue caused by localized blood vessel dilatation and increased permeability that results in tissue swelling. The lesions are asymmetric, nonpitting, and nondependent and resolve without scarring or bruising. Symptoms are usually that of pain or burning and not pruritus. The duration is often 1 day to several days but can be recurrent. Angioedema often occurs in highly vascular areas such as the face, oropharynx, genitals, and hands and feet.¹ Urticaria and angioedema occur together up to 50% of the time.² Angioedema occurs without urticaria infrequently, and then one must consider the various types of bradykinin-induced angioedema: hereditary angioedema (HAE) types 1 and 2, acquired C1-inhibitor (C1-INH) deficiency, and ACEI-induced angioedema.³

Hereditary angioedema is due to a gene defect in the C1 esterase inhibitor gene and often presents in childhood or teenage years.

Presentation after the fourth decade is less common and in such cases can be due to acquired C1-INH deficiency. The swelling can occur anywhere but is commonly found in the face, larynx, extremities, or abdomen. Attacks are often idiopathic but commonly triggered by trauma or emotional stress.

C4 levels are almost always low, even in asymptomatic states, so this is an excellent screening test for all forms of HAE except type 3. Type 1 HAE has a low C1-INH antigenic level and function. Approximately 85% of patients with HAE have type 1, making it the most common type. It occurs equally in men and women. In type 2 HAE, the C1-INH level is normal, but the existing C1-INH does not function properly, so the C1-INH function is low. Approximately 15% of patients have type 2 HAE, making it the second most common type of HAE. It occurs equally in men and women. In type 3 HAE, C4 and all C1-INH laboratory results are normal, but the patient has symptoms consistent with HAE. This is an extremely rare type of HAE and not entirely understood. Type 3 HAE occurs most often in women. In acquired C1-INH deficiency, C1q, C4, and C1-INH antigenic levels and functions are low. Acquired C1-INH deficiency occurs most commonly in the fourth decade of life or later and often is associated with an underlying lymphoproliferative or autoimmune disorder.⁴

The ACEI-induced angioedema also has a predilection for the face, lips, and tongue. The incidence is anywhere from 0.1% to 0.68%. It usually occurs in the first month of treatment but is notorious for occurring even years into treatment.³ Patients can have recurrences months after discontinuation, with 88% having a recurrence in the first month after discontinuing the ACEI.⁵ A meta-analysis of angiotensin II receptor blockers did not find an increased risk of angioedema compared with placebo, but a meta-analysis of the use of angiotensin II receptor blockers in patients with prior ACEI-induced angioedema found a risk of up to 6.6% for the occurrence of angioedema.^{6,7} Some of these cases of angioedema with angiotensin II receptor blockers in patients with prior ACEI-induced angioedema could be due to this newly described recurrence of angioedema shortly after ACEI discontinuation.

Continued Impression and Plan

The symptoms were extremely bothersome and distracting for the patient and we received multiple telephone calls from his wife during the preceding month regarding possible foods that would trigger swelling, prompting us to order laboratory tests to rule out food allergy. When the patient returned for a follow-up visit after discontinuing ramipril for 1 month, he complained of tongue swelling that was no longer intermittent but was constant and daily. All laboratory work was reviewed and was within normal limits, including radioallergosorbent tests for the foods. On physical examination, the tongue still did not appear enlarged; however, there were mild teeth indentations on the tongue that were new at this visit. The remaining physical examination did not differ from the previous examination.

Thus, this patient had macroglossia, not angioedema, and a history of a mild neuropathy judged to be from his diabetes. Additional laboratory testing showed an increased total urine protein at 104.2 mg/dL and mildly elevated free κ -light chain, and serum protein electrophoresis showed a possible band in the β -region. The patient was referred to hematology for a workup of possible amyloidosis.

Amyloidosis Review

Amyloidosis is a generic term used to describe the deposition of protein fibrils in an extracellular space. These protein fibrils are typically components of the circulating plasma in the body. Depending on the location of deposition, there can be a wide range of clinical manifestations.

Table 1
Comparison of AA amyloidosis and AL amyloidosis

Characteristic	AA amyloidosis	AL amyloidosis
Type	secondary	primary
Cause	chronic disease/inflammation	plasma cell dyscrasia
Deposition	acute-phase reactant serum amyloid A	monoclonal light chain fragments
Association	RA, infection, neoplasm	MM, WM

Abbreviations: AA, amyloid A; AL, amyloid light chain; MM, multiple myeloma; RA, rheumatoid arthritis; WM, Waldenstrom macroglobulinemia.

There are 2 major types of amyloidosis: amyloid light chain (AL; primary) and amyloid A (AA; secondary; Table 1). AA amyloidosis is typically associated with chronic inflammatory diseases such as chronic infections, inflammatory bowel disease, and rheumatoid arthritis. In the United States, 85% of patients with systemic amyloidosis have the primary AL type.⁸ AL amyloidosis is caused by plasma cell dyscrasia and is due to protein deposition derived from immunoglobulin light chain fragments. Because AL amyloidosis is a systemic disorder, patients can present with a wide range of symptoms, including proteinuria, heart failure, hepatosplenomegaly, carpal tunnel syndrome, and nonspecific symptoms, including fatigue, unintentional weight loss, edema, paresthesias, and change in voice.⁸ However, patients also can present with single organ involvement, including renal, cardiac, gastrointestinal, neurologic, pulmonary, musculoskeletal, hematologic, and dermatologic symptoms. Renal involvement typically leads to asymptomatic proteinuria; however, depending on the site of deposition within the renal system, patients can present with renal failure without significant proteinuria.⁹ Cardiac involvement can lead to diastolic or systolic heart failure. Syncope can result from arrhythmias, heart block, and even infarction brought on by amyloid deposits. An electrocardiogram can show a pseudo-infarction pattern in leads V₁ to V₃ most commonly, but the pattern also can occur in inferior leads II, III, and aVF.¹⁰ AL amyloidosis affecting the heart should be considered in patients with heart failure who have wall thickening on echocardiogram and low voltage on electrocardiogram (typically all limb leads <0.5 mV); this might be seen in approximately 46% to 71% of AL amyloidosis cases affecting the heart.¹¹ AL amyloid can lead to peripheral neuropathy if amyloid deposition occurs within the nerve. This can lead to focal or diffuse neuropathies affecting sensory, motor, and/or autonomic fibers. A common site of focal neuropathy in patients with amyloidosis includes the median nerve at the wrist, which can lead to symptoms of carpal tunnel syndrome.¹² Amyloid proteins also can infiltrate muscles and cause visible enlargement. When the tongue is involved (macroglossia), it is almost always secondary to systemic amyloidosis, whereas localized tongue amyloidosis is extremely rare.¹³ Although the oral cavity is an uncommon site when a patient has systemic amyloidosis, the tongue is the most frequent site when there is involvement.¹⁴

The diagnostic workup for amyloidosis includes, most importantly, a tissue biopsy examination with Congo red staining showing apple-green birefringence under polarized light; usually this is obtained through an abdominal fat-pad aspiration that carries a sensitivity of approximately 80% (increases to 93% with 3 smears examined) and a specificity of 92% to 100% in systemic amyloidosis cases.¹⁵ Abdominal fat-pad aspirations also are preferred because they carry a lower risk of complications compared with other tissue biopsy sites such as kidneys and liver. Other testing that can be performed to support the diagnosis include serum and urine immunofixation, bone marrow biopsy examination to look for plasma cell dyscrasia, an echocardiogram and/or additional imaging, and blood tests to look for other organ involvement.

Treatment of amyloidosis depends on the type and cause of fibril deposition. Only after a thorough workup on the extent of the disease should treatment be initiated. Patients with AL amyloidosis could be candidates for chemotherapy and/or autologous hematopoietic cell transplantation.

Continued Impression and Plan

Because this patient now had macroglossia, neuropathy, and proteinuria, a thorough workup for systemic amyloidosis was initiated. No evidence of amyloid deposition was found on Congo red staining of a fat-pad biopsy specimen. Echocardiographic findings were within normal limits. Computed tomogram of the chest and abdomen did not visualize any hepatosplenomegaly or lymphadenopathy. The mild increase in monoclonal protein could be monoclonal gammopathy of undetermined significance, and the increased urinary protein and mild neuropathy were likely secondary to his diabetes. The patient was referred to an ear, nose, and throat physician who determined that the signs and symptoms did not require tongue biopsy examination. At a follow-up visit with the patient's wife in attendance, she described the patient having similar subjective symptoms of tongue swelling when he had his brain surgery, consisting of placement of a deep brain stimulator for his PD. The patient was referred back to his neurologist for adjustment of the settings of his deep brain stimulator.

Deep Brain Stimulator Review

Levodopa is a common medication in the treatment of PD, but the benefits of its use can wane. To combat this, deep brain stimulation (DBS) is currently the most common surgical procedure in the treatment of advanced PD.¹⁶ According to Fasano et al,¹⁶ DBS of the subthalamic nucleus and globus pallidus internus improve motor features, whereas stimulation of the thalamic ventralis intermedius (VIM) predominantly lessens tremor in patients with PD. However, DBS is not without risks and complications. Aside from the rare surgical risks of implantation, there are numerous associated stimulation-related complications that could be related to the present patient. In a comparison of continuous thalamic stimulation vs thalamotomy for the suppression of severe tremor associated with PD, Schuurman et al¹⁷ found that 6 of 33 patients in the thalamic VIM stimulation group had side effects only while the pulse generators were on, suggesting a reversible etiology. Side effects from thalamic stimulation have included dysarthria, paresthesias, dystonia, balance disturbance, ataxia, and limb weakness.^{17,18}

After an in-depth review of the patient's medical history, it was noted that the patient underwent DBS of the VIM nucleus of the thalamus in June 2010 for tremor-predominant PD. Although a literature search did not turn up any results for the subjective symptoms of "macroglossia" secondary to DBS, relatable symptoms, such as dysarthria and paresthesias, as described for thalamic VIM DBS (the same type of procedure the present patient underwent), most likely played a role. This was supported by the fact that the patient's wife described the patient having experienced similar symptoms of subjective tongue swelling during the fine tuning process after the initial placement of the deep brain stimulator in 2010. All symptoms of tongue swelling resolved after his deep brain stimulator was adjusted.

Conclusion

This case illustrates the intriguing nature of medicine. Every day patients approach us with questions and problems about their health; sometimes our objective findings do not fall in line with the patient's subjective complaints. The present case is a good example of a rather straightforward complaint that did not have a reasonable explanation and that spread into a long and winding workup across many subspecialties. We hope by sharing this case that we

have provided a review of other topics (amyloidosis and deep brain stimulators) not typically discussed in the allergy office but that can one day provide an answer the next time a patient asks about a swollen tongue.

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