Macroglossia secondary to systemic amyloidosis: Case report and literature review

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Abstract
Amyloidosis is characterized by an abnormal extracellular deposition of amyloid in different tissues and organs, where it usually causes some type of dysfunction. Its cause is unknown. The two main forms of amyloidosis are systemic and localized; the latter is rare. No satisfactory treatment for systemic amyloidosis has been discovered, and mean survival is poor, ranging from 5 to 15 months depending on the presence or absence of multiple myeloma. We report a case of primary systemic amyloidosis in a 71-year-old man. The diagnosis of amyloidosis was established by tongue biopsy, and its systemic nature was identified by analysis of aspirated abdominal fat. At the 1-year follow-up, the patient's clinical condition had not changed, and he was thereafter lost to follow-up.

Introduction
Descriptions of amyloidosis date back to the 1840s.1 Amyloidosis is characterized by an abnormal extracellular deposition of amyloid in different tissues and organs.2 It is usually associated with tissue or organ dysfunction. Its cause is unknown.2 In a study of affected patients, Kyle and Bayrd3 reported a mean age of 61 years and a male preponderance, findings that were confirmed by Kerner et al.4

The diverse and unusual clinical manifestations of amyloidosis can involve a single anatomic site as well as multiple organs; as a result, signs and symptoms are varied.4 Because the clinical manifestations are so diverse, different classifications have been devised.2,5,6 The two main types of amyloidosis are systemic and localized:

- The systemic form is subclassified as primary, secondary, hereditary, and amyloidosis associated with multiple myeloma.7 Amyloidosis is designated as primary when no cause can be identified and secondary when it occurs in conjunction with a chronic disease such as tuberculosis, rheumatoid arthritis, Crohn's disease, etc.4 Some authors have reported that the incidence of amyloidosis in patients with multiple myeloma ranges from 10 to 20%,6,8 while others report a range of 6 to 15%.7 With or without multiple myeloma, however, survival is poor; Gertz and Kyle reported a mean survival of 15 months among patients without multiple myeloma and 5 months among those with it.6 No satisfactory treatment for systemic amyloidosis has been discovered.2

- The localized form is rare. Amyloidosis is classified as localized when there is no evidence of systemic involvement and no underlying chronic disease. When it does occur, it typically affects single anatomic sites. Patients with localized amyloidosis have a considerably better prognosis than do those with systemic disease.5 Based on their experience with a large series of patients at the Mayo Clinic, Kerner et al reported that localized amyloidosis can be successfully treated without major sequelae and that most patients remain symptom- and disease-free.4

In this article, we report a case of primary systemic amyloidosis of the tongue in an elderly man. We also review the literature on amyloidosis.

Case report
A 71-year-old white man who had been born in São Paulo presented with a 1-year history of swallowing difficulty. His dysphagia initially became evident when eating solid foods, but it soon progressed to interfere with his intake of liquids. He reported that his condition had caused him to lose approximately 25 lbs. Six months after the onset of his swallowing symptoms, he noted the appearance of an aching submandibular soft tumor. The mass had increased in volume to the point that it led to the development of macroglossia and tongue protrusion. His medical history was significant for systemic arterial hypertension, which was controlled by diuretic therapy. His brother had died of tongue cancer.

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MACROGLOSSIA SECONDARY TO SYSTEMIC AMYLOIDOSIS: CASE REPORT AND LITERATURE REVIEW

Physical examination confirmed the submandibular soft mass and the increase in tongue volume (figure 1). No color alterations or nodular lesions were noted on the tongue. Our differential diagnosis included a malignant tumor of the tongue, a vascular tongue or neck disorder, or a systemic condition such as hypothyroidism, a deficiency of vitamin B12 or folic acid, or amyloidosis. The patient was treated empirically with a corticosteroid and pentoxifylline pending the results of laboratory testing and other studies, but this did not result in a decrease of the tongue volume.

Laboratory tests detected anemia (hemoglobin: 10.3 g/dl) and abnormal renal function (urea: 103 mg/dl; creatinine: 1.7 mg/dl). Results of serology for hepatitis B and C were negative. Protein electrophoresis revealed an increase in immunoglobulin levels (total proteins: 5.8 g/dl; albumin: 2.8 g/dl; α1-globulin: 0.3 g/dl; α2-globulin: 0.6 g/dl; β-globulin: 0.6 g/dl; γ-globulin: 1.5 g/dl). Levels of thyroid-stimulating hormone (TSH) (3.5 μU/ml), vitamin B12 (192.0 pg/ml), and folic acid (2.7 ng/ml) in blood were within normal ranges. No abnormalities were seen on renal ultrasonography, urine culture, or measurement of 24-hour urinary protein level. Electrocardiography detected a left anterosuperior blockage, an inactive septal zone, left ventricular overload, and an anterior ventricular repolarization disturbance. No vascular disorders were diagnosed.

Cervical computed tomography (CT) confirmed the significant symmetrical increase in tongue volume, primarily in the posterior tongue. The enlargement led to a down-dislocation of all structures located below the tongue (figure 2, A and B). In fact, no submandibular mass or focal lesions were noted. The mass that had been palpated on physical examination actually represented an extension of the macroglossia. These findings were corroborated by magnetic resonance imaging (MRI) (figure 2, C).

Staining of tongue biopsy specimens revealed rose substances distributed among muscular fragments on hematoxylin and eosin (H&E) staining and apple-green birefringence under polarized light microscopy when...
stained with Congo red; both these findings suggest the presence of an amyloid substance (figure 3). Analysis of an abdominal fat aspirate also identified an amyloid substance, and this clinched the diagnosis of systemic amyloidosis. A myelogram detected no sign of multiple myeloma. In view of the nonspecific nature of the disease, no treatment was instituted.

At the 1-year follow-up, the patient’s clinical condition had not changed. Thereafter, he moved to another country and was lost to follow-up.

Discussion

Oral manifestations have been reported in 39% of patients with amyloidosis.8 Amyloid deposition in the tongue of patients with multiple myeloma occurs frequently and can result in macroglossia, which is the most common oral finding.8–10 An enlarged tongue resulting in apertognathia and tooth indentations along the lateral border can be the first clinical sign of primary amyloidosis.11–13 The tongue may be firm, dry, stony-hard, fissured, ulcerated, hemorrhagic, and/or painful. Its color is often a pale pink, but occasionally red.14 Macroglossia was the primary feature on the physical examination of our patient. What we originally believed was a submandibular mass was in fact an extension of the significant degree of macroglossia, which was probably the cause of his swallowing difficulties.

Of course, amyloidosis should not be the first consideration in a case of macroglossia. Other causes—such as a malignant tongue tumor, a vascular disturbance, or a systemic etiology (e.g., hypothyroidism or a deficiency of vitamin B12 or folic acid)—should be investigated first. Our patient’s weight loss and the presence of the submandibular mass initially led us to consider a malignant etiology, but this theory was not supported by imaging and laboratory findings. A systemic etiology was also discarded initially in light of his normal levels of TSH, vitamin B12, and folic acid. On the other hand, his individual characteristics (e.g., sex, age, and clinical signs) were consistent with amyloidosis.

Authors of previous articles on amyloidosis of the head and neck and the upper aerodigestive tract have reported that in all forms of amyloidosis, the frequency of head and neck manifestations ranged from 12 to 90%.15,16 In 1935, Kramer and Som published a literature review in which they identified 95 cases of local tumorlike amyloid deposits in the upper aerodigestive and lower respiratory tracts; specific sites included the larynx (36 patients), tongue (n = 16), trachea (n = 13), larynx and tongue (n = 8), nose (n = 6), tracheobronchial tree (n = 4), and a few other cases in the oral cavity, pharynx, and lung.17 In 1995, Kerner et al published the results of their retrospective review of 141 cases of biopsy-proven amyloidosis and reported that 19% featured head and neck manifestations, ranging from tongue involvement to amyloid deposits in the eyelids.4 The most common sites of head and neck involvement were the tongue (63% of cases) and the larynx (19%). Kerner et al also found that 44% of patients with amyloidosis of the head and neck and 59% of those with amyloid deposition in the tongue had multiple myeloma; the remaining patients with amyloidosis of the head and neck had primary, secondary, and localized forms of amyloidosis in equal proportions. Others have reported cases of localized amyloid deposition in the hard palate,18 Waldeyer’s tonsillar ring,19 and the peripheral nerves.20

In our patient, findings on analysis of tongue biopsy specimens led us to the diagnosis of amyloidosis, and analysis of the fat aspirate led us to the diagnosis of systemic amyloidosis. Distinguishing systemic from localized amyloidosis is important because of the considerable difference in associated survival rates. The differentiation...
can be made by either abdominal fat aspiration or rectal biopsy.21,22 We preferred abdominal fat aspiration because it is easier and safer to perform. In either case, findings are positive in 75 to 90% of patients with systemic amyloidosis.4 Because the abdominal fat aspirate in our patient contained amyloid deposits, we established the diagnosis with a high degree of confidence.

Amyloid deposits share certain key characteristics. They are eosinophilic on H&E staining, and they exhibit apple-green birefringence under polarized light microscopy when stained with Congo red. These are the strongest universally accepted criteria for diagnosing amyloidosis, and they are also the easiest to identify.6,13,23 These proteins have a fibrous appearance under electron microscopy and a cross-beta alignment on x-ray diffraction.15,16

After we established a diagnosis of systemic amyloidosis in our patient, we then tried to determine whether it was primary or secondary and whether it was associated with multiple myeloma. We were able to rule out secondary amyloidosis because the patient had no underlying chronic disease that is usually associated with amyloidosis. Moreover, although our patient’s protein electrophoresis revealed an increase in immunoglobin levels, which might be a sign of multiple myeloma, his myelogram detected no sign of this disease.

As many as half of all cases of systemic amyloidosis are associated with multiple myeloma.3 On the other hand, a significant percentage of cases of multiple myeloma are associated with amyloidosis.4,5,6 Kyle and Bayrd reported that 26% of patients with multiple myeloma exhibited amyloid macroglossia.3 Others have reported cases of oral amyloidosis that occurred as a result of multiple myeloma. These reports were summarized in 1994 by Reinish et al, who cited 54 cases dating back to 1979.14 They reported tongue involvement in 100% of patients with oral amyloidosis. In most of these cases, pain was the chief symptom, and many patients complained of dysphagia and speech difficulty. Xerostomia as a result of amyloid deposits in the tongue and salivary glands has also been seen, and it can also cause dysphagia.10

Renal and cardiac disease are seen in both primary and secondary amyloidosis, and renal failure is the most common cause of death.4 Our patient had already developed some signs of renal and cardiac failure by the time of his presentation.

In the literature, surgical reduction of the tongue has been suggested in cases of amyloid macroglossia.4,9,24,25 Kerner et al treated such patients by performing midline edge glossectomy; their patients healed well and enjoyed an improved quality of life as a result of the restoration of their ability to speak and eat.4 Dendy et al described the case of a 62-year-old woman with longstanding macroglossia secondary to primary amyloidosis; the anterior two-thirds of her tongue was successfully resected.25 However, Reinish et al advocated that surgical intervention be performed only in extreme cases of macroglossia with possible airway obstruction because the amyloid lesions frequently recur and require repeat excisions.14 We chose not to operate on our patient because there is no consensus in the literature that surgery would definitively improve his quality of life and because the morbidity of a glossectomy in this patient would have been substantial. More research on the benefits and consequences of the surgical treatment of macroglossia would be welcome.

References