Macroglossia reveals multiple myeloma

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Abstract

We present an eighty-year old man with a one year history of progressive macroglossia, dysphagia and loss of weight. He had a medical history of arterial hypertension and prostatic hypertrophy which he had under good therapeutic control. The entire tongue was swollen, had hard solidity and was slightly painful upon palpation. A tongue biopsy revealed an amyloid deposition as it coloured bright orange-red on Congo Red staining and lead us subsequently to the diagnosis of amyloidosis; then a bone marrow biopsy confirmed the diagnosis of multiple myeloma. The case was further evaluated by a multidisciplinary team who considered it appropriate to start a low-dose melphalan treatment combined with supportive care.

When macroglossia in the tongue is confirmed to be amyloidosis the differential diagnosis should include systemic amyloidosis deposition and multiple myeloma.

Introduction

Acquired macroglossia has a wide spectrum of etiologies, from metabolic disorders to inflammatory conditions, from neoplastic diseases to lymphangioma.[1] Amyloidosis should always be considered in the differential diagnosis of macroglossia. It is important to consider amyloidosis in the diagnostic process on account of its association with multiple myeloma, found in 15-20% of the cases,[2] though macroglossia has been rarely reported as first sign of multiple myeloma (MM).[3]

MM is a malignant neoplasm of the bone marrow which is characterized by the proliferation of bone marrow plasma cells producing monoclonal immunoglobulins or light chains. These light chains are known as Bence-Jones proteins, which are excreted in the urine and are a diagnostic feature of multiple myeloma. This uncontrolled production can lead to renal failure, immunosuppression, skeletal destruction and anemia of chronic disease. The disease predominantly affects older adults, and, because of the multiple manifestations of this disease, patients can present with vague and confusing symptoms.

It is thought that 5-15% of patients affected by multiple myeloma will develop amyloidosis, an extra-cellular deposition of insoluble fibrous protein aggregates (known as amyloid) in different tissues and organs. Oral localized amyloidosis can easily be found on the tongue,[4] which can be enlarged diffusely due to macroglossia or as nodular deposits. The most featured sign of intraoral deposition of amyloid is macroglossia.[5]

Case Report

An eighty-year old man presented with a one year history of progressive macroglossia, dysphagia and loss of weight. He had a medical history of arterial hypertension and prostatic hypertrophy which he had under good therapeutic control. The entire tongue was swollen (Figure 1), had hard solidity and was slightly painful upon palpation.

A magnetic resonance imaging (MRI) of the oral cavity was performed, and no focal lesions were detected. A tongue biopsy was carried out which resulted in neoplastic syndromes being excluded; however, a histological sample showed a complete disruption of the muscle tissue structure (Figure 2) and revealed itself positive for Congo Red staining, leading to the diagnosis of tongue amyloidosis.

Serum and urinary examinations were performed, though these investigations did not provide for any diagnostic certainty, having only detected a slight increase in urinary kappa light chains (k-LC). Furthermore, any possible cardiac and renal involvement was ruled out.

Following a hematological assessment, a bone marrow biopsy was performed which identified a plasma cell infiltrate, producing k-LC, which constitutes 15% of the whole cellularity (Figure 3), leading us to the diagnosis of multiple myeloma. A skeleton x-ray and a total body computed tomography (CT) scan excluded other secondary localizations.

The case was further evaluated by a multidisciplinary team who considered it appropriate to start a low-dose melphalan treatment. Additionally, to ensure adequate nutritional intake, a nasogastric tube was initially positioned, after which the option of a percutaneous endoscopic gastrostomy was seemed more appropriate, due to the irreversibility of the dysphagia.

Discussion

The term *macroglossia* defines a painless and long-term tongue enlargement, which can be recognized by the observation of a resting tongue protruding over the dentoalveolar structures.[6] Macroglossia is classified into two major categories: pseudo and true-macroglossia. Pseudo-macroglossia refers to a normal-sized but large-appearing tongue and it is usually due to anatomical abnormalities of the oral cavity.[7]

True macroglossia is associated with definitive histological changes in the tongue and it is frequently observed due to hypertrophy of the tongue muscles or due to infiltration of normal tissue with abnormal proteins or glycogen.[8] The size of the tongue may be assessed either by direct measure-

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ment or indirectly by measuring its impression on an appropriate impression material; a more accurate alternative is MRI.[9] An early and correct diagnosis can be difficult, clinical diagnosis of macroglossia is not always easy, for this reason it is generally required a tissue biopsy. The treatment of macroglossia depends on its etiology.[1] The consequences of macroglossia usually include a possible malfunction of the stomatognathic system, breathing and speech problems, increased mandible size, tooth spacing, diastema and other orthodontic abnormalities.

True macroglossia is common in amyloidosis which is a rare progressive disorder that includes a group of diseases characterized by aggregation of at least 31 different amyloid proteins[10] and subsequently the accumulation of pathologic deposits of amyloids in the tissues.[11] The amyloids are protein polymers made of identical monomer units. Pathological amyloids usually consist of misfolded proteins. The deposits of amyloids, situated either intracellularly or extracellularly, alter the normal function of organs;[12] they can aggregate between cells and cause atrophy which can have a direct toxic effect on cells leading to eventual cell death.[13]

The clinical manifestations may be heterogeneous and unusual. Clinically, amyloidosis is divided into two types: systemic and localized.

Systemic amyloidosis affects different organs and tissues; tongue involvement is common (10-40% of the cases), either with diffuse or nodular enlargement of the tongue.

Amyloidosis is classified as localized when there is no evidence of systemic involvement and no underlying chronic disease. It typically affects single anatomic sites, and it usually occurs in the head or neck region (larynx and trachea). Localized amyloidosis is rare[14] (approximately 9 to 15% of amyloidosis[15]). Patients with localized amyloidosis have a considerably better prognosis than those with systemic disease.[16]

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*.[17] Diagnosis of amyloidosis is usually made associating the clinical features with histopathological exam, which reveal the presence of acellular eosinophilic deposits. These hyaline deposits typically show a perivascular distribution, and they are positive for the Congo red staining and apple-green birefringent under polarized light.[18]

Systemic amyloidosis may be primary, and it can occur in association with multiple myeloma (15-20% of cases), typically in older adults.[19] Amyloidosis as a complication of multiple myeloma carries with it grave prognostic implications, and the median survival of myeloma patients following a diagnosis of amyloidosis is only 4 months.[20]

Primary amyloidosis in multiple myeloma is due to production of excess of lambda or kappa fragments of abnormal immunoglobulins by malignant bone marrow plasma cells, which accumulate in various tissues.

MM accounts for 1% of all cancers and ~10% of all hematological malignancies. The incidence in Europe is 4.5-6.0/100,000/year with a median age at diagnosis of 72 years; the mortality is 4.1/100,000/year.

Myeloma is a disease of the bone marrow characterized by uncontrolled prolifer-

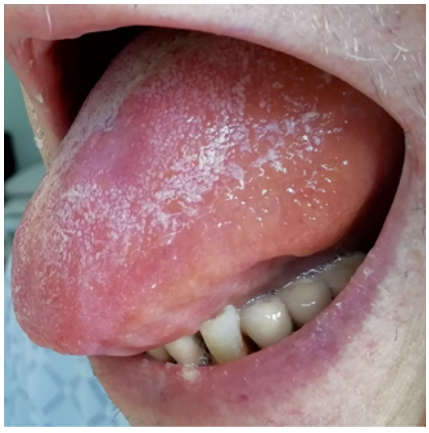

Figure 1. Patient's tongue presented excessive swelling causing dysphagia and dental problems.

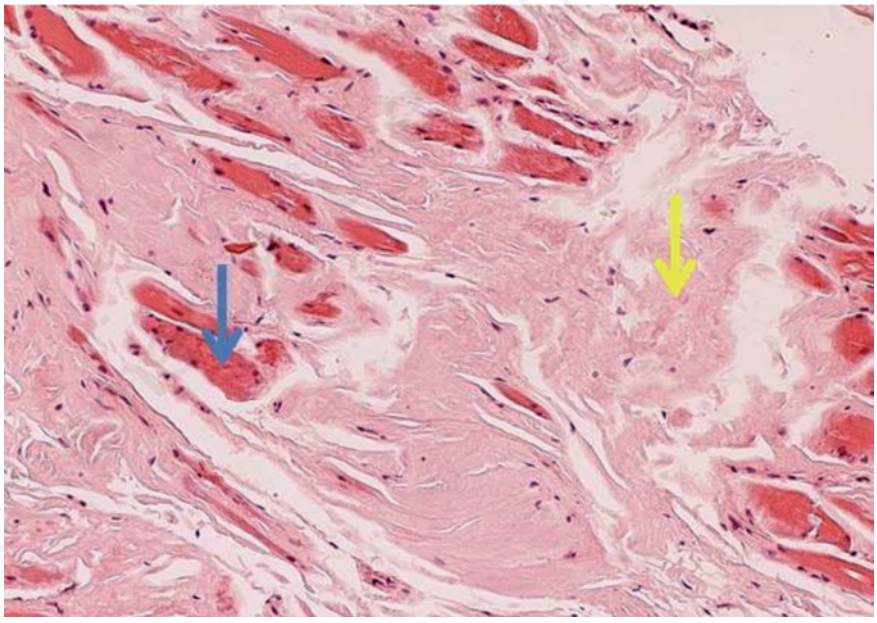

Figure 2. Histological sample of patient's tongue: muscle tissue (blue arrow) appears disrupted by the accumulation of amyloid substance (yellow arrow).

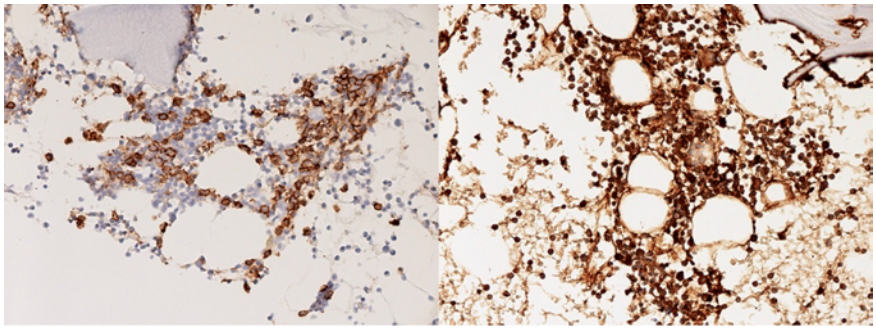

Figure 3 Histological sample of patient's bone marrow: plasma cell infiltrate detected with anti-CD138 monoclonal antibodies (left image); plasma cells produce k-LC detected with anti-k-LC monoclonal antibodies (right image).

ation of plasma cells in the bone marrow, monoclonal protein (monoclonal means that all proteins produced by this cell line have the same identity and the same impaired function), osteolytic bone lesions and hypercalcemia, renal disease, immunodeficiency and anemia. A pathognomonic feature of multiple myeloma is the Bence-Jones protein found in two-thirds of affected patients. These are immunoglobulin light chains produced by the neoplastic plasma cells, in either 'kappa' or 'lambda' forms (they are never produced simultaneously). They are found in urine and are contributory to renal failure.

Diagnosis[21] of multiple myeloma should be based on the following tests:

- Detection and evaluation of the monoclonal component by serum and/or urine protein electrophoresis (concentrate of 24 h urine collection); nephelometric quantification of immunoglobulins (IgG, IgA and IgM); characterization of the heavy and light chains by immunofixation; and serum-free light-chain measurement.
- Evaluation of bone marrow (BM) plasma cell infiltration: BM aspiration and/or biopsies are the standard options to evaluate the number and characteristics of plasma cells in BM.
- Evaluation of lytic bone lesions: whole-body low-dose CT (WBLD-CT) is the new standard for the diagnosis of lytic disease. Conventional radiography can also be used if WBLD-CT is not available. MRI provides greater details and is recommended whenever spinal cord compression is suspected. Either whole-body MRI or MRI of the spine and the pelvis may be used, according to their availability, to assess the BM plasma cell infiltration, in particular the presence of bone focal lesions. 18F-fluorodeoxyglucose positron emission tomography with CT can be done to evaluate bone lesions, according to availability and resources.
- Complete blood cell count, with differential serum creatinine, creatinine clearance and calcium level. The criteria for diagnosis of MM were updated in 2014 by the International Myeloma Working Group (IMWG)[22] (Table 1).

Once the diagnosis is confirmed, it is necessary to define the disease's stage. Both staging systems, Durie/Salmon and International Staging System (ISS), are based on three stages. Durie/Salmon, up until now, has been the most used staging system worldwide for multiple myeloma. It defines the disease's progression based on different factors such as: the amount of myeloma cells, the amount of damage the myeloma cells have caused to the bone, levels of protein in the blood or urine, blood calcium levels, albumin and hemoglobin levels. ISS staging system is based on albumin levels, B2-microglobulin levels and lactate dehydrogenase levels and it predicts survival at diagnosis. The higher the stage, the poorer the outcome.

Multiple myeloma is not a curable disease and not all stages require treatment. Consensus is to adopt a 'wait and see' policy for most stage 'I' patients and for those who do require treatment the first line therapy includes high-dose chemotherapy followed by autologous stem cell transplantation, which is currently the treatment of choice for those who are young (under the age of 60-65) and fit enough. Drug therapy is used for the treatment of symptomatic myeloma. Advances in treatment have been made with the introduction of bortezomib (a protease inhibitor), thalidomide and lenalidomide (immunomodulatory drugs), and these agents are now the main stay of therapy. Most patients do respond to initial therapy and are able to enter a period of disease stability. Relapse, however, is inevitable, with each relapse likely to become increasingly less responsive to treatment, until refractory end stage disease ensues.

Table 1. Criteria for diagnosis of multiple myeloma.

Multiple myeloma
Clonal BM plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events:
• *Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:*
- hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- renal insufficiency: CrCl <40 mL/min or serum creatinine >177 mol/L (>2 mg/dL)
- anemia: hemoglobin value of >20 g/L below the lower limit of normal or a hemoglobin value <100 g/L
- bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET-CT
• *Any one or more of the following biomarkers of malignancy:*
- ≥60% clonal BM plasma cells- involved/uninvolved serum-free light chain ratio ≥100
- >1 focal lesion on MRI studies (each focal lesion must be ≥5 mm in size)

BM, bone marrow; CrCl, creatinine clearance; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; MRI, magnetic resonance imaging.

Conclusions

Macroglossia is an important physical sign which requires investigation. When macroglossia in the tongue is confirmed to be amyloidosis the differential diagnosis should include systemic amyloidosis deposition and multiple myeloma.

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