J Stomatol Oral Maxillofac Surg 119 (2018) 514–517

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Case Report

# Macroglossia, the first manifestation of systemic amyloidosis associated with multiple myeloma: Case report

A. Maturana-Ramírez [a,b], A.V. Ortega [a], F.C. Labbé [c], Ê. de Moraes [d], J.P. Aitken-Saavedra [a,d,e,*]

[a] Department of Oral Pathology and Medicine, School of Dentistry, University of Chile, Santiago, Chile
[b] Therapeutic Diagnostic Center Odontology and Pathological Anatomy Service, Hospital Complex San José, Santiago, Chile
[c] Clinical Hospital of the University of Chile, Santiago, Chile
[d] School of Dentistry, Federal University of Pelotas, Pelotas, Brazil
[e] Center of Diagnosis of Diseases of the Mouth, Federal University of Pelotas, Pelotas, Brazil

ARTICLE INFO

*Historique de l'article :*
Received 16 April 2018
Accepted 17 June 2018
Available online 25 June 2018

*Keywords:*
Multiple myeloma
Amyloidosis
Macroglossia

ABSTRACT

Amyloidosis is a group of diseases characterized by an irreversible and extracellular deposition of fibrillar, amorphous protein known as amyloid in different organs and tissues. Amyloid deposits may occur locally in tissues or may involve various organs, resulting in a wide range of clinical manifestations. Amyloidosis of the head and neck is rarely seen and can reflect some plasma cell dyscrasia that affects B lymphocytes. Deposition of amyloid on the tongue is very rare and accounts for less than 9% of all types of amyloidosis. Amyloid involvement of the tongue is almost always secondary to systemic amyloidosis. We report a 73-year-old female who presented with weight loss and macroglossia. Firstly, she was diagnosed only with amyloidosis of the tongue. Her general health condition was evaluated, revealing renal dysfunction, anemia, hypercalcemia, and hyperphosphatemia. The final diagnosis was systemic amyloidosis with multiple myeloma. The patient was referred for emergency hemodialysis and chemotherapy. Her condition progressed to congestive heart failure and recurrent urinary and respiratory infections. After 100 days from diagnosis, the patient died by pulmonary infection as a consequence of her weakened state of health. It is important to highlight role of the dentist especially oral pathologist to the evaluation of local alterations that may reflect systemic deterioration of patients.


## 1. Introduction

Amyloidosis is a term used to describe a group of diseases characterized by extracellular and insoluble deposition of fibrillar, amorphous protein known as amyloid in different tissues and organs [1,2]. These deposits are identified by apple-green birefringence when stained with Congo red and seen under polarized light. More than 25 different proteins have been associated with amyloidosis. Amyloid deposits may occur locally in tissues or may involve various organs, resulting in a wide range of clinical manifestations. There are four categories of amyloidosis: primary systemic amyloidosis, secondary systemic amyloidosis, hereditary systemic amyloidosis, and localized amyloidosis [3,4]. In Western countries, the incidence of amyloidosis is approximately nine cases per million people per year, and amyloidosis occurs more often in men than in women [5].

In systemic amyloidosis, amyloid deposits can be present in many organs. When the deposition affects the kidney, those affected can present severe and irreversible renal failure [6]. Moreover, systemic amyloidosis can reflect plasma cell dyscrasia, which affects B lymphocytes (as in cases of multiple myeloma, lymphoma, and macroglobulinemia). Deposition of amyloid on the tongue is very rare, accounting for less than 9% of all types of amyloidosis and is almost always secondary to systemic amyloidosis [7].

We report a 73-year-old female with weight loss and a sensation of a large and rough tongue. Firstly, she was diagnosed with only amyloidosis of the tongue. Subsequently, her general health condition was evaluated, revealing renal dysfunction, anemia, hypercalcemia, and hyperphosphatemia. The diagnosis was systemic amyloidosis associated with multiple myeloma. The patient was referred for emergency hemodialysis and chemotherapy. Her condition progressed to congestive heart failure and recurrent urinary and respiratory infections. After 100 days from diagnosis, the patient was hospitalized with a pulmonary infection and died.

* Corresponding author. R. Gonçalves Chaves, 457 Centro, 96015-560, Pelotas, RS, Brazil.
*E-mail address:* juanpabloaitken@gmail.com (J.P. Aitken-Saavedra).

https://doi.org/10.1016/j.jormas.2018.06.009
2468-7855/

## 2. Case report

The patient was a 73-year-old female in treatment for diabetes and hypertension. She sought care for a painful increase in tongue volume within 1 month of symptom onset. After consulting 3 general practitioners who pointed out that clinical estate of patient was due to stress, the patient consulted with an oral pathologist at the Oral Medicine Clinic of the Dentistry Faculty of University of Chile. On intraoral examination, this increase in diffuse volume was associated with multiple ulcerated areas with hardened borders, as well as other ulcers in the bilateral jugal mucosa (Fig. 1A and B). The patient reported weakness and weight loss. Serum laboratory examination was requested and revealed anemia, uremia, hypercalcemia, and hyperphosphatemia. An incisional biopsy of the tongue was performed for which a medical authorization was requested. Histopathological examination revealed an ulcerated oral mucosa with deposits of proteinaceous material in the cell matrix. Histochemistry with Congo red staining was used and showed positivity. Immunohistochemical staining with the anti-amyloid A antibody was performed, which was also positive, establishing the diagnosis of amyloidosis (Fig. 2). The patient was referred for multidisciplinary medical care to Clinical Hospital of the University of Chile. New serum exams revealed the continued presence of anemia, uremia, hypercalcemia, and hyperphosphatemia, in addition to the same oral lesions, which were now more extensive (Fig. 1C and D). Serum levels of immunoglobulins (Ig) G, A, M, and beta-2 microglobulin (B2M) were also requested. Levels of IgM were especially reduced (9 mg/dL; normal range is between 40 and 230 mg/dL). B2M was also altered (13.8 mg/dL; normal range is between 0.61 and 2.37). Moreover, levels of plasmatic creatinine and creatinine clearance were 2.24 mg/dL and 11.5 mg/dL, respectively, revealing altered renal function. The patient was diagnosed with systemic amyloidosis associated with multiple myeloma. It was referred for emergency hemodialysis and chemotherapy, presenting each time with a greater number and severity of oral ulcers. After 100 days of initial evaluation, the patient died due to complications of the disease (pneumonia).

## 3. Discussion

We present a case of systemic amyloidosis associated with multiple myeloma, where the first clinical manifestation was macroglossia. After patient was referred for emergency hemodialysis and chemotherapy, her condition progressed to congestive heart failure and recurrent urinary and respiratory infections, and she died from a pulmonary infection after 100 days. In view of these findings, although it is a rare pathology, systemic amyloidosis should be considered in the differential diagnosis of the causes of macroglossia and progressive renal failure with or without proteinuria, especially because its diagnosis in the initial stages can substantially improve the survival and quality of life of those affected.

Amyloidosis is a heterogeneous group of diseases characterized by extracellular deposition in the organs and tissues of a series of fibrillar proteins, which are not biochemically related to each other but share common characteristics including apple-green birefringence with polarized light after staining with Congo red and a beta-laminated folded sheet configuration observed with X-ray diffraction. In the case of systemic amyloidosis, amyloid deposits can be formed in many organs, especially the kidney [7]. Patients with this disease have an average survival of 3 years. The most severe form of amyloidosis can be idiopathic or associated with dyscrasia of monoclonal B cells, including multiple myeloma, as our clinical case presented, lymphomas, and macroglobulinemia [8]. Multiple myeloma is a malignant proliferation of plasma cells that usually secrete large amounts of monoclonal immunoglobulins. Amyloidosis is common in patients who suffer multiple myeloma and leads to cardiac and renal dysfunction, malabsorption syndromes, and peripheral neuropathies [9].

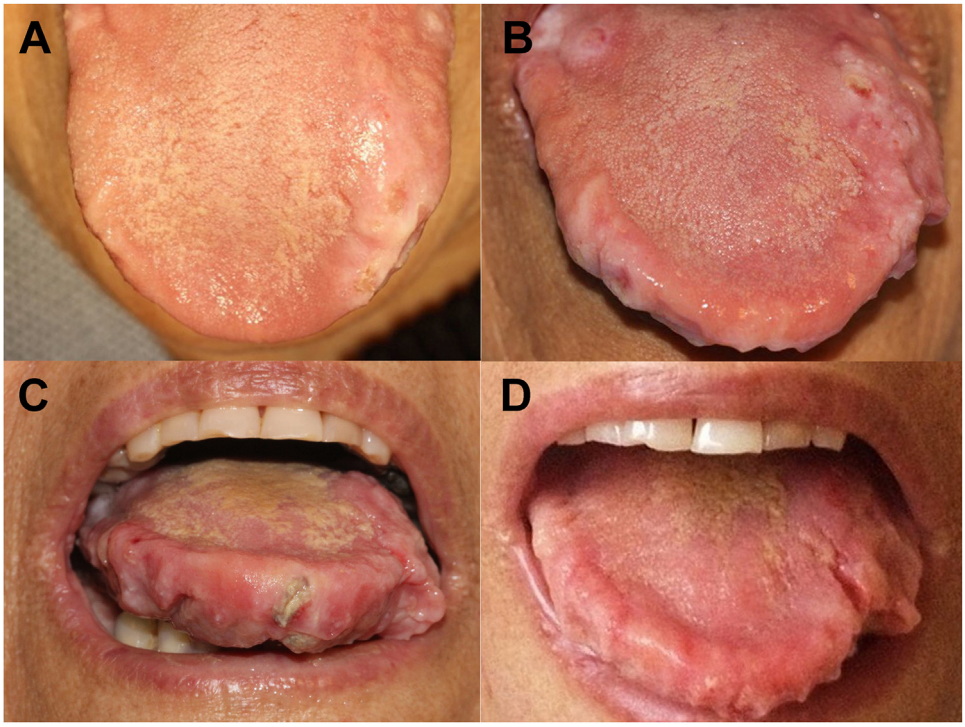


**Fig. 1.** Aspect of the patient's oral lesions. A shows the clinical aspect ulcers and the diffuse volume increase of tongue that the patient presented in the first evaluation. B shows oral lesions that the patient presented 30 days after the initial evaluation when an incisional biopsy was performed and C, the aspect of tongue after 60 days. D show frontal view of the tongue in the last month of life. As the systemic disease progressed, the lesions increased in number and severity.

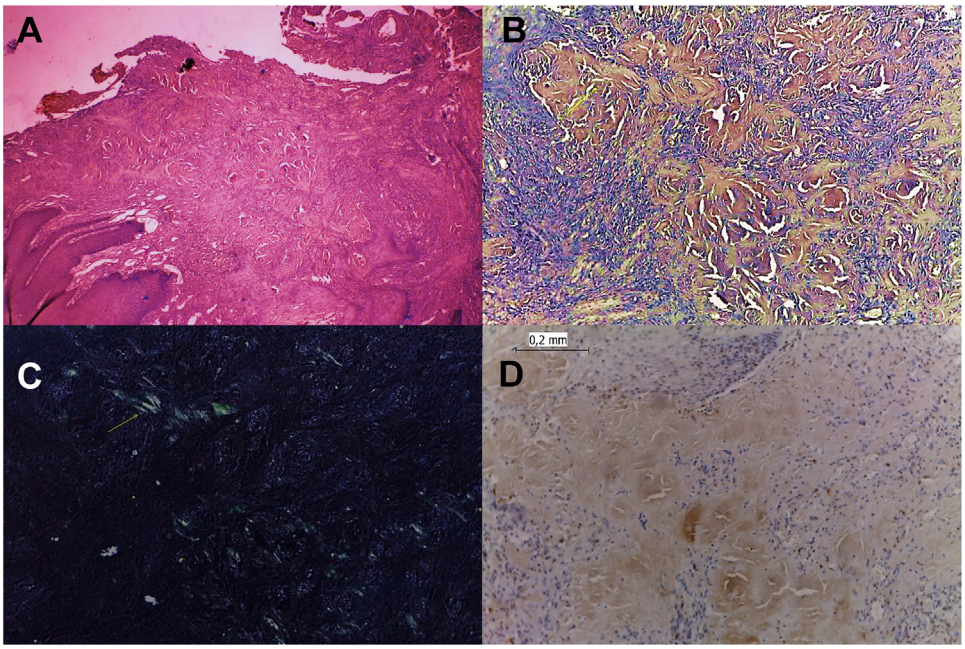


**Fig. 2.** Histopathological images. A shows fragment of the oral mucosa coated with parakeratinized stratified squamous epithelium. Underlying dense, fibrous connective tissue containing localized hyaline extracellular deposits and focal areas of chronic inflammatory infiltrate [4× hematoxylin and eosin (H&E)]. B shows metachromasia characteristic of amyloid (10× Congo red with polarized light). C shows microscopic appearance of amyloid under polarized light exhibiting apple-green birefringence (10× Congo red with polarized light) and D, anti-amyloid antibody, showing positivity in the hyaline areas (10× anti-amyloid antibody).

Systemic amyloidosis presents with a wide variety of signs and symptoms, the kidney being an organ often affected, giving it an unfavorable prognosis. It can lead to rapid progression of renal failure with the need for replacement therapy within a few months. In the present case, the patient showed anemia, uremia, hypercalcemia, and hyperphosphatemia, indicating renal failure, which was related to the amyloidosis initially diagnosed only on the tongue [4,10]. Nevertheless, to establish a definitive diagnosis, other systemic variables were also considered. The patient, for example, presented reduced serum levels of immunoglobulin M, which can indicate the presence of certain malignancies, such as leukemia or multiple myeloma. To complement this information, a B2M test was requested, which is a tumor marker usually expressed in blood cells. The levels of this marker in our patient were high.

A deeper understanding of the pathophysiology that links amyloidosis of the tongue and renal failure would open doors to the development of more effective therapies. This is very important because, generally, affected patients die from renal or cardiac failure or autonomic neuropathy, with an estimated survival of approximately 6–15 months [8]. In the present case, the patient had to undergo an urgent dialysis treatment, which extended her life. Nevertheless, an unsatisfactory response to treatment is usually reported. A safe and effective intervention is not yet available to treat most types of amyloidosis. All treatment planning should be directed at two objectives: to decrease the amyloid precursor protein and prevent amyloid fibril deposition in the organs [11].

Finally, the role of the dentist especially oral pathologist is fundamental to the evaluation of local alterations that may reflect systemic deterioration. In our case, macroglossia was the first manifestation of systemic amyloidosis. In addition to its larger size, the tongue can be smooth or dry and can have papules, nodules, plaques, or bullae, accompanied by ulceration, hemorrhage, and painful dysphagia [12,13]. For this reason, once the diagnosis of amyloidosis of the tongue has been established, the patient's systemic status must be evaluated. The diagnosis of amyloidosis is not the first to be raised when we are faced with a case of macroglossia; however, it must be considered. Early diagnosis and the development of an appropriate comprehensive management strategy is fundamental to the treatment of systemic amyloidosis, which can even eventually save the life of the patient if administered in the early stages. Unfortunately, in the present case, such a timely intervention did not occur.

### Disclosure of interest

The authors declare that they have no competing interest.

## Acknowledgments

Fellowship OAS-GCUB.

## References

[1] Sayuri Matsuo F, Barbosa de Paulo L, Silva Servato J, et al. Involvement of oral tissues by AL amyloidosis: a literature review and report of eight new cases. Clin Oral Invest 2016;20:1913–20.
[2] Milani P, Palladini G, Merlini G. New concepts in the treatment and diagnosis of amyloidosis. Expert Rev Hematol 2018;11:117–27.
[3] Sipe JD, Benson MD, Buxbaum JN, et al. Amyloid fibril protein nomenclature: 2010 recommendations from the nomenclature committee of the International Society of Amyloidosis. Amyloid 2010;17:101–4.
[4] O'Reilly A, D'Souza A, Lust J, Price D. Localized tongue amyloidosis: a single institutional case series otolaryngology. Head Neck Surg 2013;149:240–4.
[5] Desport E, Bridoux F, Sirac C, et al. AL amyloidosis. Orphanet J Rare Dis 2012;7:54.
[6] Demirkan S, Şavk E, Alp A, Doger FK, Kadikoylu G, Gunduz O. Macroglossia as a presenting feature of multiple myeloma. J Family Med Prim Care 2017;6:146–7.
[7] Babburi S, Ramya B, Subramanyam RV, Aparna V, Srivastava G. Amyloidosis of the tongue - Report of a rare case. J Clin Diagn Res 2013;7:3094–5.

[8] Lachmann HJ, Hawkins PN. Systemic amyloidosis. Curr Opin Pharmacol 2006;6:214–20.
[9] Wong SW, Toskic D, Warner M, Varga C, Moreno-Koehler A, Fein D, et al. Primary amyloidosis with renal involvement: outcomes in 77 consecutive patients at a single center. Clin Lymphoma Myeloma Leuk 2017;17:759–66.
[10] Touart DM, Sau P. Cutaneous deposition disease. Part I. J Am Acad Dermatol 1998;39:149–71.
[11] Lee MY, Byun JY, Choi YW, Choi HY. Multiple myeloma presenting with acquired cutis laxa and primary systemic amyloidosis. Eur J Dermatol 2017;27:654–5.
[12] Murthy P, Laing MR. Macroglossia. BMJ 1994;309:1386–7.
[13] Matsuo FS, Barbosa de Paulo LF, Servato JP, de Faria PR, Cardoso SV, Loyola AM. Involvement of oral tissues by AL amyloidosis: a literature review and report of eight new cases. Clin Oral Investig 2016;(20):1913–20.