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CASE REPORT

Oral localized amyloidosis: a literary analisys and case report

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Abstract:

Introduction: Amyloidosis is a condition related to aggregates of proteins in several organs of the body and can be systemic or localized. Amyloidosis localized in the oral cavity is extremely rare, being the tongue the more prevalent region. **Objective:** The aim of this present study is to describe a case of localized amyloidosis on the tongue and surgically removed. **Methods:** Also, a review of English-language literature of oral localized amyloidosis from 1946 to 2021 was performed. **Results:** A total of 52 cases of oral localized amyloidosis were found in the literature. The majority of the cases was observed in female patients (53,84%), with an average age of 55,4 years (range 9 to 90 years) and the tongue being the most common localization (49,12%). **Conclusions:** Amyloidosis is a rare condition with atypical sign and symptoms. The systemic involvement should be evaluated due to worse prognosis of this condition and the possibility of organs failures. There is no standard treatment for local amyloidosis, but surgical excision is indicated to reduce the functional prejudice and pain, in symptomatic cases.

Keywords: Oral amyloidosis; Oral amyloid; Localized amyloidosis; Diagnosis

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INTRODUCTION

Amyloidosis is a rare, progressive and variable group of complex diseases caused by extracellular deposition of pathological insoluble fibrillary proteins in organs and tissues and may result in severe organ dysfunction. These deposits are identified by apple-green birefringence when stained with Congo red and viewed under polarized light[1,2].

Regarding the aetiology, over 25 different human proteins have been described as precursor of amyloidosis and can develop due to unknown reasons or genetic factors[2,3]. This condition can occur locally, when the amyloid protein is produced and deposited only in one small area of the body or systemically, when amyloid protein can involve several organs of the body, being this latter, most commonly, related to heart and renal failure, paresthesia, carpal tunnel syndrome and gastrointestinal disturbances. It is essential to rule out systemic involvement since the aetiology, treatment and outcome between localized and systemic amyloidosis are different[3,4].

Amyloidosis is classified, mainly, into four types: primary systemic amyloidosis, secondary systemic amyloidosis, hereditary systemic amyloidosis, and localized amyloidosis. The primary amyloidosis, also known as amyloid light-chain (AL) amyloidosis, is related to monoclonal gammopathies, often associated with lymphoid or plasma cell dyscrasias, with or without an overt lymphoma (typically MALT lymphoma, Waldenstrom's macroglobulinemia) or multiple myeloma, with predilection for kidneys, liver, heart and nerves. Secondary or reactive systemic amyloidosis, known as Amyloid A (AA) amyloidosis, is a complication associated with chronic inflammatory systemic disease or chronic dermatosis such as rheumatoid arthritis, multiple myeloma, chronic suppuration, Hodgkin's lymphoma, tuberculosis, osteomyelitis and syphilis. Hereditary or familial amyloidosis occurs due to gene mutation, leading to the production of an abnormal protein and this type is most common in some countries, like Portugal, Japan and Israel. Localized amyloidosis is a rare type of amyloidosis without association with either multiple myeloma or other relevant systemic diseases and involve a limited site[5,6,7,8,9].

The treatment options for localized amyloidosis varying between excision and observation, being the first, usually, the treatment of choice and the latter, more commonly, undertaken in asymptomatic lesions. Although, the surgical removal be, generally, curative in cases of localized amyloidosis in the head and neck, recurrence can occur. The mean survival of patients with the systemic forms is between 5 to 15 months. However, the localized form have an excellent prognosis without increased risk of developing systemic involvement[4,10,11,12].

The aim of this present study is to describe a case of localized amyloidosis on the tongue surgically removed, associated with a review of the English-language literature of localized amyloidosis in oral cavity, from 1946 to 2021.

METHODS

A comprehensive literature review was performed using electronic databases (PubMed, Scopus and Cochrane Library) to identify relevant publications in the English language, between 1946 and 2021 that described cases of localized amyloidosis affecting the oral cavity. The following search terms were used: Oral amyloidosis OR Oral amyloid AND Localized amyloidosis.

The studies related to systemic amyloidosis; amyloidosis in another organs or regions of the body; major salivary glands involvement; presence of systemic disease related to amyloidosis, as well as letter to the editor and comments were excluded.

Oral localized amyloidosis was described as presence of the lesion just on oral cavity, without other organs involvement, confirmed by complementary exams, and without presence of systemic diseases related to amyloidosis (ex: multiple myeloma, rheumatic disease and others).

The data collected were: authors; number of cases; age (years); gender; clinicopathologic findings; localization; realization of incisional biopsy; red Congo analysis and light microscopy; treatment; time of follow up (months); presence of recurrence.

CASE REPORT

A 65-year-old female was referred to the Stomatology Clinic of the Dentistry Department of Pontifical Catholic University of Minas Gerais in Belo Horizonte, Brazil, with complain of multiple nodules in the tongue, with 3 years of evolution, causing traumas during the chewing and the speech. Her medical history included hypertension and *hypercholesterolemia*, both controlled with appropriate medicamentous treatment.

Clinical examination revealed multiple nodules in the dorsum of the tongue measuring from 8 to 30 mm, all of them well delimited, sessile, with firm rubbery consistency. The major nodule, located posteriorly in right lateral of tongue, presented yellowship coloration, and the other nodules presented the same coloration of tongue tissue (Fig. 1a and 1b).

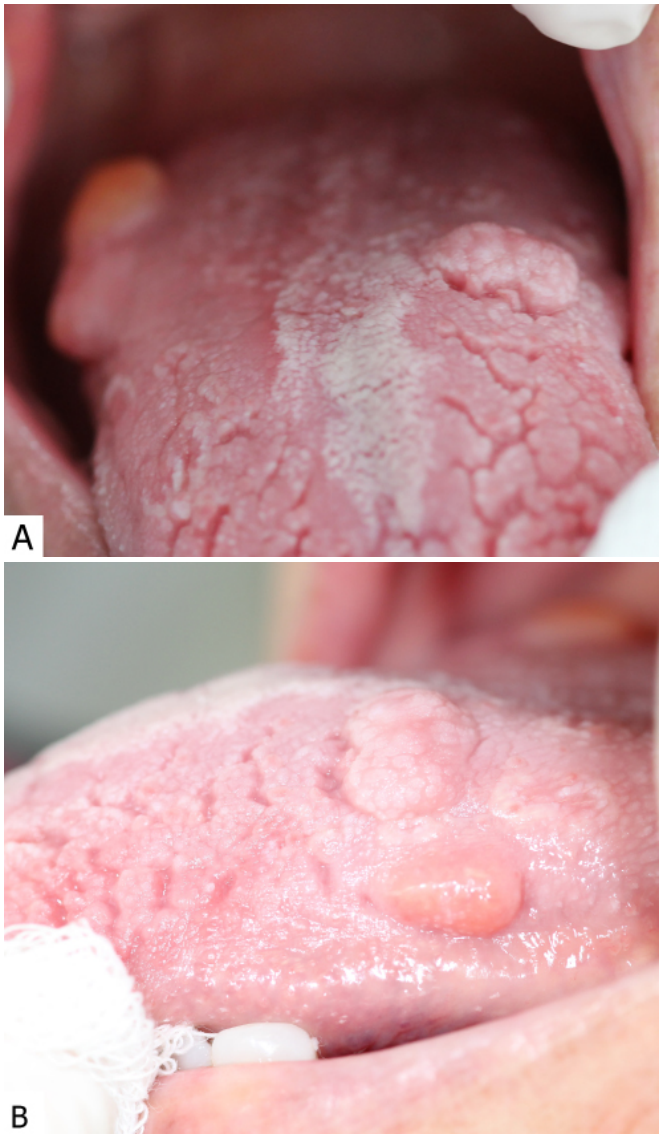

Figure. 1. (a) Frontal view of the tongue lesions; (b) Lateral view of the longue lesions.

The clinical diagnostic hypothesis were: multiple neuromas: fibrous hyperplasia; and, due to the color, multiple lipomas and oral amyloidosis. The excision of one of the nodules was performed for histopathological diagnostic (Fig. 2a, 2b and 2c).

Histopathological examination of haematoxylin and eosin (HE) stained sections demonstrated surface squamous epithelium and extracellular deposition of amorphous eosinophilic material in the submucosal fibrous connective tissue, consistent with amyloid. Furthermore, was observed dense inflammatory infiltrate. The diagnostic of amyloidosis was confirmed after the amorphous material presents positive staining for Congo red, showing a reddish color under light microscopy and apple green birefringence on polarized light microscopy (Fig. 3).

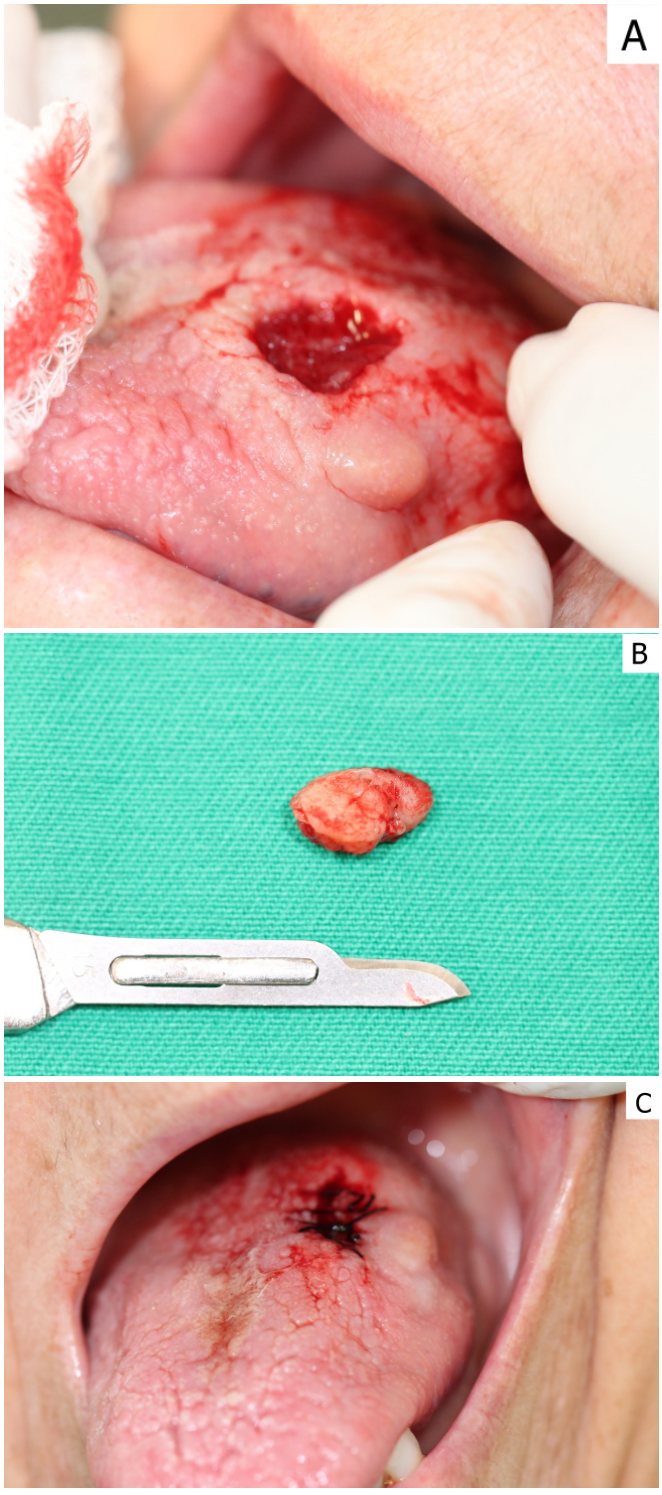

Figure. 2. a: Excisional biopsy of the lesion; b: Macroscopical view of the removed specimen; c: Suture of the surgical defect.

The others nodules were surgically removed and microscopically analyzed using the same procedure (HE stains and Congo-red stain under polarized light microscopy). For all of them, the final diagnosis was amyloidosis.

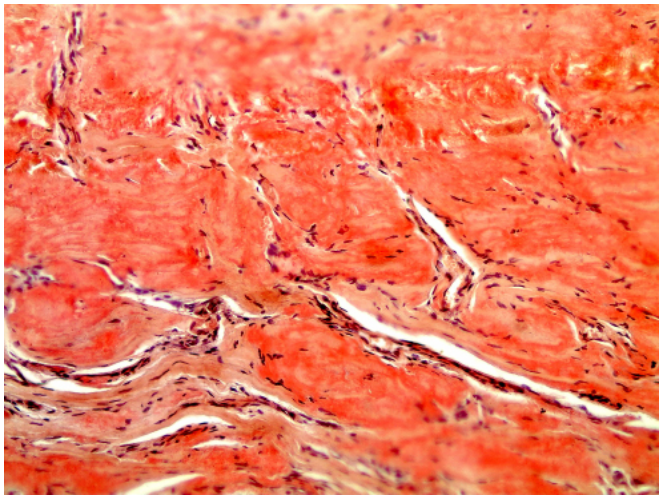

Figure. 3. Microscopical analysis through Congo red stain

The patient was referred for medical evaluation to verify others deposition focus of amyloid content. The systemic evaluation did not reveal systemic involvement of amyloidosis. Therefore, this patient was diagnosed with localized amyloidosis of tongue. She has four years of follow up, without local recurrence on the tongue or in any other region of the oral cavity and without systemic involvement by amyloidosis (Fig. 4).

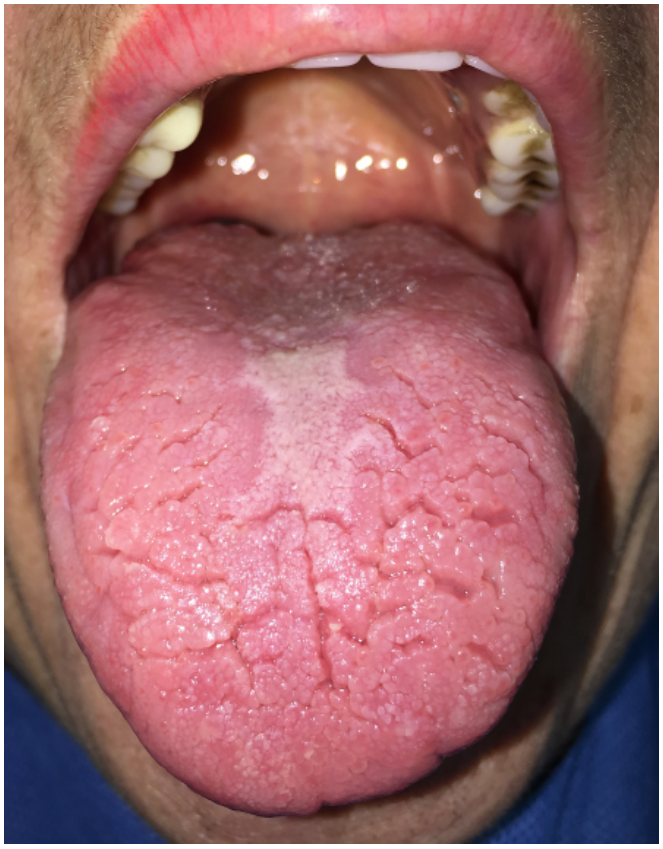

Figure. 4. Fourth year of follow up

RESULTS

After analysis and final decision, 30 studies was included involving 52 patients. All data are shown in Table 1.

Twenty-eight (53.84%) of the 52 patients included in this study were female, with F / M ratio = 1.21/1 and age ranging from 9 to 90 years (mean age, 55.4 years). In the oral cavity, the tongue was most commonly affected (49.12%), followed by palate (28.70%) and lip (10.52%).

The incisional biopsy was performed in 39 patients (75%). The specimen was analyzed in Congo red stain under light microscopy in 50 cases (96.15%), being the gold standard for an adequate diagnosis.

The treatment modalities varying between excision (34.61%), observation (23.07%) and use of colchicine (1.92%). As to follow up, the time ranging from 1 to 156 months, with median in 12 months. The recurrence was found in just 4 cases (7.69%), but in 31 patients (59.61%) the presence of recurrence or no was not reported.

DISCUSSION

Amyloidosis is a condition related to aggregates of misfolded proteins that cannot be broken down easily and may precipitate at the location where they were synthesized, resulting in localized form, like Alzheimer's disease. Due not to be biodegradable, the body finds it difficult to remove these proteins and leads to the formation of oligomeres and fibrils[2,4].

Localized amyloidosis in the head and neck region is uncommon, being the most common reported sites in the thyroid, the larynx and subglottis, whereas in the oral cavity, amyloidosis usually involves the tongue and can be related to worsening deglutition, respiration and cosmetic appearance[5,10]. Together with this present review, a total of 52 cases of oral localized amyloidosis were found in the literature. The majority of the cases was observed in female patients (53.84%)[10,11,13,14,17,18,20-22,24-26,28-30,32,34-36], with an average age of 55,4 years (range 9 to 90 years) and the tongue as the most common localization (49.12%)[4,10,16,19-22,26-28,30,33-36,38]. All data of this review are consistent with the present case reported.

The diagnosis of localized amyloidosis, generally, consists of clinical, laboratorial and histological analysis, being this later performed after biopsy of the involved organ or tissue (with sections of at least 5 µm in thickness, due to the possibility of loss of amyloid deposits in thin sections)[3].

Table 1. Clinical features of localized oral amyloidosis between 1946 to 2021

Author & Year of publication	Number of Cases	Age (years)	Gender	Clinicopathologic findings	Localization	Incisional biopsy	Congo red stain	Light microscopy	Treatment	Follow-up (months)	Recurrence
Kaiser-Kupfer et al., 1977[13]	1	9	F	Tonsillitis	Hard palate	NR	NR	NR	Excision	12	N
Timoşca & Gavrilisă, 1977[14]	1	10	F	Painless nodule, discomfort during mastigation and deglution	Soft palate	Y	+	AGB	Excision	1	N
Takeda et al., 1987[15]	1	58	M	Swelling of the floor of mouth	Floor of mouth	Y	+	AGB	Excision	36	N
Madani et al., 1991[16]	1	63	M	Nodular lesion in the tongue	Tongue	NR	+	AGB	NR	NR	NR
Dominguez et al., 1996[17]	1	13	F	Oral bleeding, yellowship oral polypoid mass	Soft palate	Y	+	AGB	Excision	9	N
Maulin et al., 1997[18]	2	55	M	Frenum linguae sweeling	Tongue	Y	+	AGB	Colchicine	10	N
		46	F	Gingival hypertrophy	Gingival	Y	+	AGB	NR	11	N
Koren et al., 1998[19]	1	33	M	Solitary lesion in the tongue, painfull	Tongue	NR	NR	NR	Excision	NR	NR
Asaumi et al., 2001[20]	1	84	F	Painless sweelinf of the tongue	Tongue,lower lip and cheek	Y	+	AGB	NR	NR	NR
Kojima et al., 2006[21]	1	64	F	Soft palate mass	Soft palate, tongue and lip	Y	+	AGB	Excision	156	Y
Penner e Muller, 2006[22]	1	69	F	Multiple tongue nodules	Tongue	NR	+	AGB	Excision	NR	NR
Pentenero et al., 2006[11]	1	68	F	Reddish mucosa of the palate	Hard palate	Y	+	AGB	Observation	24	N
Yoshida et al., 2006[23]	1	63	M	Small oral hard palate tumor	Hard palate	Y	+	AGB	NR	NR	NR
Henley, et al, 2007[24]	1	63	F	Palatal soreness	Hard palate	Y	+	AGB	Observation	36	N
Aono et al., 2009[25]	1	74	F	Painless mass of the hard palate	Hard palate	Y	+	AGB	Observation	17	N
Angiero et al., 2010[26]	4	36	M	Lesiono on the tongue	Tongue	Y	+	AGB	NR	NR	NR
		82	F	Multiples nodules on the tongue	Tongue	NR	+	AGB	Excision	36	N
		57	M	Lesions on the tongue	Tongue	Y	+	AGB	NR	NR	NR
		63	F	Nodular lesions of the tongue	Tongue	Y	+	AGB	NR	NR	NR
Cengiz et al., 2010[27]	1	67	M	Painfull tongue	Tongue	Y	+	AGB	NR	NR	NR
Andreadis et al., 2011[28]	1	30	F	Painless nodular mass on the tongue	Tongue	NR	+	AGB	Excision	6	N
Rowczenio et al., 2011[29]	1	51	F	Enlarging mass on the palate	Palate	Y	+	AGB	NR	NR	NR
Gouvêa et al., 2012[30]	2	33	F	Isolated nodules on tongue dorsum	Tongue	Y	+	AGB	Excision	NR	NR
		55	F	Multiple nodules in hard palate	Hard palate	Y	+	AGB	Excision	NR	N
Babburi et al., 2013[4]	1	54	M	Sweeling of tongue	Tongue	Y	+	AGB	Observation	NR	NR
Gabali et al., 2013[31]	1	11	M	Lower lip nodule	Lower lip	Y	+	AGB	Excision	12	N

Continuation **Table 1.**

Author & Year of publication	Number of Cases	Age (years)	Gender	Clinicopathologic findings	Localization	Incisional biopsy	Congo red stain	Light microscopy	Treatment	Follow-up (months)	Recurrence
O'Reilly et al., 2013[10]	6	43	F	Dorsal tongue mass	Tongue	Y	+	AGB	Excision	NR	NR
		72	M	Dorsal tongue mass	Tongue	Y	+	AGB	Observation	NR	NR
		73	F	Dorsal tongue mass	Tongue	Y	+	AGB	Observation	36	NR
		74	M	Tongue mass	Tongue	Y	+	AGB	Observation	NR	NR
		64	M	Tongue mass	Tongue	Y	+	AGB	Observation	24	NR
		90	F	Several lesions on tongue base	Tongue	Y	+	AGB	Excision	12	Y
Bucci et al., 2014[5]	1	73	M	Nodular mass in upper gingiva	Gingiva	N	+	AGB	Excision	24	N
Folkard et al., 2014[32]	1	23	F	Sweeling in the labial mucosa	Lower lip	N	+	AGB	Excision	12	Y
Anaya-Saavedra et al., 2015[33]	2	51	M	White reticular patch with transverse treaks accompanied by brown hyperpigmented areas in the dorsum of his tongue	Tongue	Y	+	AGB	NR	NR	NR
		19	M	Greyish-white patch on the right side of the hard palate	Hard palate	Y	+	AGB	NR	NR	NR
Matsuo et al., 2015[34]	4	54	M	Diffuse mass in tongue	Tongue	NR	+	AGB	Observation	12	N
		36	M	Diffuse gingivitis	Upper and lower gingiva	NR	+	AGB	Observation	NR	NR
		77	F	Hard mass located in tongue	Tongue	NR	+	AGB	Observation	2	NR
		64	F	Diffuse masses in tongue and hard palate	Tongue and hard palate	NR	+	AGB	Observation	2	N
Kubota et al., 2017[35]	1	70	F	Mass in tongue	Tongue	Y	+	AGB	NR	36	Y
Binmadi et al., 2018[36]	9	80	F	NR	Tongue	Y	+	AGB	NR	NR	NR
		NR	F	NR	Lip	Y	+	AGB	NR	NR	NR
		NR	NR	NR	Palate	Y	+	AGB	NR	NR	NR
		46	M	NR	Lip	Y	+	AGB	NR	NR	NR
		79	F	NR	Gingiva	Y	+	AGB	NR	NR	NR
		61	F	NR	Buccal mucosa	Y	+	AGB	NR	NR	NR
		58	F	NR	Tongue	Y	+	AGB	NR	NR	NR
		75	M	NR	Palate	Y	+	AGB	NR	NR	NR
		66	M	NR	Palate	Y	+	AGB	NR	NR	NR
Turiak et al., 2019[37]	1	62	M	Mass in palate	Palate	NR	+	AGB	Excision	NR	NR
Adamo et al., 2020[38]	1	49	M	Mass localized over the dorsum of the tongue	Tongue	Y	+	AGB	Excision	18	N

Abbreviatures: NR: No related; F: Female; M: Male; Y: Yes; N: No; +: positive; AGB: Apple-green birefringence;

This disease also can be classified, immunohistochemistry, according to protein type, being the more common types the AL (amyloid derived from immunoglobulin light chain); AH (amyloid derivated from immunoglobulin heavy chain); ASem1 (Semenogelin 1); ATTR (amyloid derived from transthyretin); AA ((Apo) serum amyloid A); ALECT2 (Leukocyte chemotactic factor-2); AFib (Fibrinogen A α chain variants); AI, AII, CII, CIII (Apolipoprotein variants); ALys (Lysozyme variants); AGel (Gelsolin variants); Aβ2Mv (β2 microglobulin variant); AApoAIV (Apolipoprotein AIV). However, only the three firsts are more related to the localized form, but also can be present in systemic form[39].

Although the immunohistochemical analysis allows a more accurate diagnosis, the gold standard histological diagnostic procedure for amyloidosis is the demonstration of Apple-green birefringence from Congo red stained tissue sections[1]. In the present case report, the Apple-green birefringence under polarized microscopy was positive and the immunohistochemical tests, for evaluate the protein type, were not performed.

In addition to local biopsy, a systemic evaluation should be performed when amyloidosis is suspected, including the following baseline examinations: complete blood count, serum electrolyte measurements, renal, liver and heart function tests, β2-microglobulin assay, prothrombin time, activated partial prothrombin time, urinalysis, 24-h urinary protein, Bence Jones protein analysis, electrocardiography and skeletal survey[1,4,10], biopsy of a surrogate site such as the abdominal fat, bone marrow, or minor salivary gland[3]. After exclusion of systemic involvement, amyloid lesions may be observed or excised, in symptomatic forms and eliminate a functional prejudice, even though recurrences have been described. Therefore, follow-up is mandatory[11].

In the review performed through this work, the median time of follow up is 12 months, being this case reported associated with 48 months of follow up, without signals of recurrence or progression and without systemic involvement.

The most adequate situation is an early and accurate diagnosis of amyloidosis in the initial stage, and education efforts should be made to elicit awareness among health professionals about this condition[2].

CONCLUSION

Oral localized amyloidosis is a rare condition and the early diagnosis is a challenge due to atypical sign, symptoms and clinical aspects, requiring the clinical, laboratorial and histologycal evaluation. The systemic involvement should be analyzed due to worse prognosis of this condition and these systemic evaluation can be made through blood tests, bone marrow biopsy, echocardiography, digestive endoscopy and other tests as listed in this study. Yet, there is no standard treatment for local amyloidosis, but surgical excision is indicated to reduce functional damage and pain, in symptomatic cases.

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