

Amyloid Deposition in the Tongue: Clinical and Histopathological Profile

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Abstract. *Aims: Oral amyloidosis is a rare and debilitating disease that, whether primary or secondary, may severely impact the quality of a patient's life. The study investigated the characteristics of amyloid deposition in the tongue from the clinical and histopathological profiles. Materials and Methods: Biopsy specimens were received from five patients: 2 female, 3 male. All biopsies were taken from the tongue, and all had amyloid deposition in the subepithelial connective tissue, conclusive for a diagnosis of amyloidosis. All patients showed macroglossia and difficulty in eating and impairment of speech. Results: In three cases there was no evidence of systemic involvement or associated disease; these were characterized as localized amyloidosis of the tongue. The other two cases revealed multisystemic involvement. Histologically, the disease was diagnosed through specific staining with Congo red, which examined under polarized light revealed the amyloid deposits as apple-green birefringence. Conclusion: The findings show the tongue to be the site most frequently affected in forms of localised amyloidosis, and that a tongue biopsy possess a highly diagnostic value for amyloidosis. There is still no consensus regarding the management of lingual amyloidosis, although numerous therapies have been proposed, including surgical excision and pharmacological treatment. However lesions often persist or recur. The prognosis is uncertain, owing to the rarity of the condition, requiring regular follow-up and monitoring.*

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The term *amyloid*, meaning starch or cellulose, was introduced by Virchow in the mid-19th century to describe abnormal extracellular material seen in the liver at autopsy (1). At present, the term amyloidosis is used to describe a group of diseases characterized by extracellular deposition of fibrillar proteins in organs and tissues (2). The classification is based on the nature of the precursor plasma proteins that form the fibril deposits and is divided into primary and secondary amyloidosis (3). The pathogenesis is multifactorial. Nonetheless, the common final pathway is identical in all forms of the disease: the production of amyloid fibrils in the extracellular matrix. All amyloid deposits have a common fibrillar structure consisting of linear, aggregated fibrils with an approximate diameter of 7.5-10 nm and a cross β -pleated sheet conformation, evidenced by x-ray diffraction (4).

The commonest types of primary amyloidosis are immunoglobulin/light-chain related (AL) and familial transthyretin-associated (ATTR)(2). Secondary amyloidosis due to chronic diseases (*e.g.* rheumatoid arthritis and chronic infections) is caused by amyloid derived from serum amyloid A, an acute-phase protein produced in response to inflammation. In the past, tuberculosis was one of the commonest causes of amyloidosis associated with inflammatory conditions (*i.e.* AA amyloidosis) (3, 5, 7).

In a small percentage of AL amyloidosis cases, the bone marrow plasma cells show the clonal dominance of a light-chain isotype, and the light-chain variable region of the immunoglobulin represents the main constituent of AL amyloid deposits. These patients commonly produce urinary free monoclonal light chains, referred to as *Bence Jones proteins*, of the K or λ isotype (2). Unlike multiple myeloma and monoclonal gammopathies, in which K chains are more frequent, in AL amyloidosis the ratio of K to λ light chains has been found to be 1:3 (3).

The familial transthyretin-associated (ATTR) type of amyloidosis is derived from a group of autosomal-dominant diseases in which, beginning in midlife, a mutant protein

forms amyloid fibrils (8). In this case, the aberrant protein is transthyretin, a transport protein for thyroxine that is capable of retinol binding. Other hereditary forms of amyloidosis involve mutations in other serum proteins, such as apolipoprotein A1, fibrinogen, and gelsolin (3). In secondary amyloidosis, the acute-phase protein formed, serum amyloid A, is produced under the regulation of cytokines, including tumour necrosis factor α 3. The amino acid sequence in the AA protein is highly conserved, in contrast to the high variability of the amino acid sequence in the AL protein (9).

AA amyloid deposits consist of fragments of at least 5 different molecular forms (10, 11) and are most commonly seen in patients with rheumatoid arthritis or inflammatory bowel disease (12). Another type of secondary amyloidosis may occur in patients undergoing dialysis. In these patients, the β 2 microglobulin, part of the Class I major histocompatibility complex antigen, fails to cross the dialysis membrane, resulting in the formation of amyloid fibrils (13). These fibrils may deposit in the joints, periarticular tissue and bones (3).

Clinically, AL amyloidosis has the widest spectrum of tissue and organ involvement. The initial symptoms are most frequently fatigue and weight loss, but the diagnosis is usually not made until signs and symptoms involved with a particular organ appear (2). The organs most commonly involved are the kidney and the heart, either alone or in combination. Renal amyloidosis may manifest as proteinuria, which may be clinically evident as mild renal dysfunction. Normal serum creatinine and blood urea nitrogen concentrations may mask massive proteinuria, which may be accompanied by profound oedema and hypoalbuminemia. Cardiac complications of amyloidosis are most likely to manifest as congestive heart failure, which is rapid in onset and progressive. Electrocardiographic results vary and may be normal, demonstrate a pattern of myocardial infarction in the absence of coronary artery disease (2), or reveal a thickened ventricle and an ejection fraction that ranges from low normal to mildly reduced (14, 15). Furthermore, autonomic and sensory neuropathy are relatively common features (2). Hepatomegaly can transpire (1) and rarely, splenomegaly. Infiltration of soft tissue by amyloid may occur elsewhere, resulting in the "shoulder-pad sign," nail dystrophy or, in rare instances, alopecia (2).

The clinical manifestations of ATTR amyloidosis differ from those of the AL variant. The most striking differences are the decreased frequency of renal disease and the absence of macroglossia. In addition, peripheral sensory/motor and autonomic neuropathy are more prevalent in ATTR amyloidosis, as are gastrointestinal symptoms such as diarrhoea and weight loss (2, 7, 17, 18).

Amyloidosis affecting the oral cavity tends to involve the buccal mucosa, tongue and gingiva. Involvement of the palate is rare (19, 20). We report five cases of amyloidosis localized at the tongue.

Case 1. A man 36-years-old presented in October 1994 after the appearance, approximately one month previously, of a neof ormation of the dorsum on the tongue similar to that of a median rhombic glossitis. Neither remote nor recent medical history revealed anything significant. A biopsy was taken and the histological examination indicated the presence of amyloid in the tissues. Screening tests were performed to search for amyloid in other organs, but findings were negative. A diagnosis of localized amyloidosis was therefore formulated.

Case 2. A man 57-years-old presented in October 1994 due to the onset of a hyperplastic lesion of the dorsum of the tongue. Medical history was significant only for chronic kidney failure, which was treated by dialysis. A lingual biopsy was taken, and tests for AB2M protein (Beta 2-microglobulin amyloid) were positive. A monoclonal IgG λ component was detected, with light chain λ isotype and Bence Jones proteinuria, however no bone alterations were revealed by skeletal radiography, and medullary plasmocytosis. Periorbital purpura, macroglossia and tumefaction of the sub-mandibular area were present, with a drop in the voice tone (Figure 1A-B). The outcome of the collective examinations enabled a diagnosis to be made of multiple myeloma with AL amyloidosis (light chain λ isotype and Bence-Jones proteinuria) with prevalent involvement of soft tissues, heart and kidneys. A diagnosis of amyloidosis in a patient undergoing dialysis was thus formulated.

Case 3. A woman of 82-years-old presented, in February 1995 due to the presence of multiple nodules on the dorsum and underside of the tongue, dyskinesia of the tongue; with serious problems of swallowing and speech (Figure 1C-D). She also had palatal lesions. She suffered from chronic kidney failure but was not undergoing dialysis. After excision of two of the lingual nodules, histological analysis was performed and a senile amyloidosis was diagnosed.

To determine histopathology, incisional biopsies were taken from different sites of the tongue and a diagnosis of amyloid deposition was rendered. The patient was referred to a rheumatologist. Chest X-ray was normal. Laboratory findings showed normal full blood count, liver and renal function. Serum protein electrophoresis was normal and serum amyloid-associated (SAA) protein was not detected. The patient was managed conservatively. After three years, CT scans showed that the palate and maxillary sinuses remained intact, and the palatal lesion did not increase in size. Follow-up ceased after 3 years and no further assessment was possible to be made.

Case 4. A man 57-years-old presented in January 1998 about 4 months after the onset, on the dorsum of the tongue, of a hard neof ormation with a diameter of about 1 cm (Figure 1E). Remote and recent medical history revealed nothing significant. A biopsy was taken for histological examination, which was indicative of localized amyloidosis.

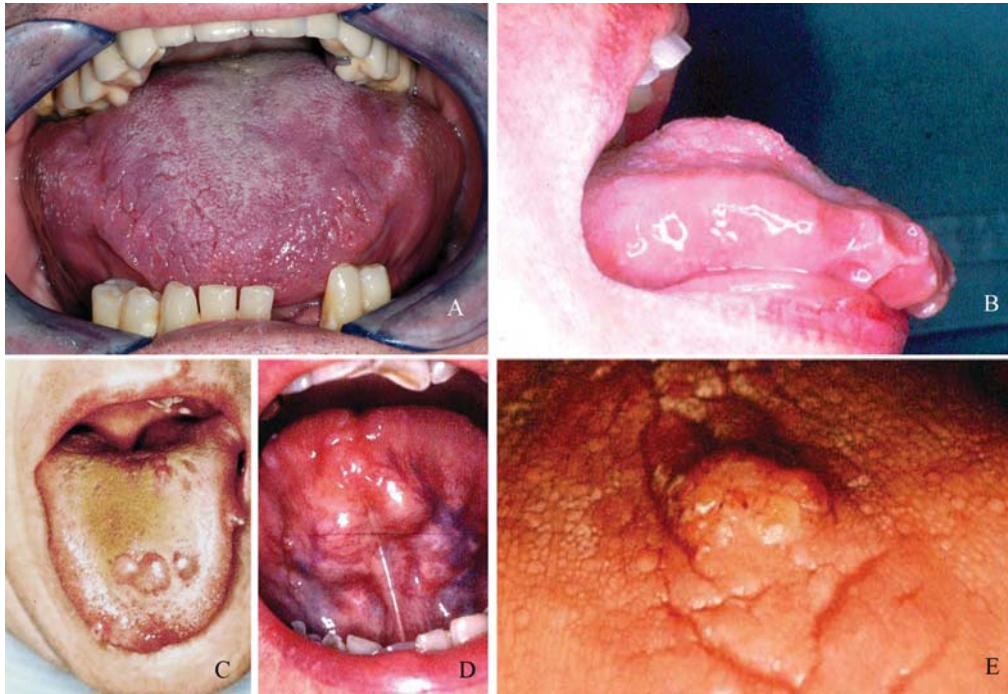


Figure 1. A-B. Clinical photograph of the oral cavity showing the macroglossia (A) and the presence of a neoformation having a diameter of about 1 cm on the tongue (B). C-D. Clinical photograph showing the presence of multiple nodules on the dorsum (C) and underside of the tongue (D). E. The superficial mucosa of the tongue, appeared thickened and erythematous, purple and a nodular lesion is visible.

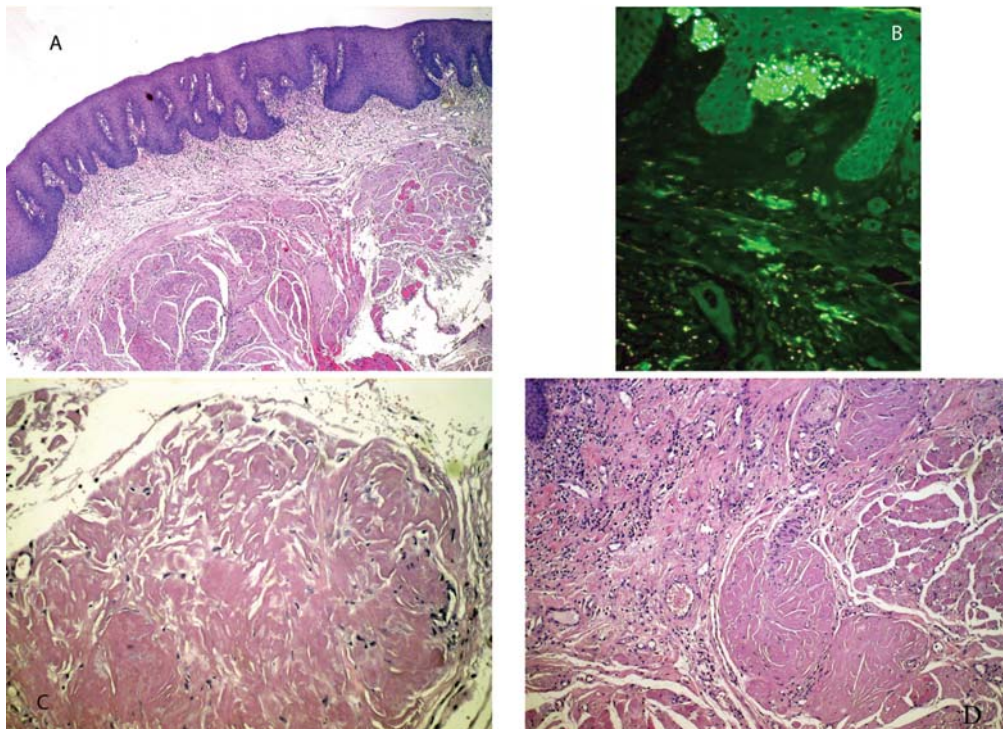


Figure 2. A. Biopsy of the dorsum of the tongue. The amyloid appears as homogenous, eosinophilic material within connective tissue cells and scattered capillaries (hematoxylin-eosin, original magnification $\times 100$). B. The same area showing apple green birefringence under polarized light. (Hematoxylin and eosin, original magnification $\times 150$). C. Microphotograph showing eosinophilic amorphous material in the connective tissue beneath the intact epithelium. (Hematoxylin and eosin, original magnification $\times 200$). D. Microphotograph showing homogenous material in a nodular pattern (original magnification $\times 150$).

Table I. Clinical data of the current cases.

Case	Gender	Age	Site	Systemic signs	Diagnosis
1	male	57	tongue	Chronic kidney failure, dialysis	amyloidosis undergoing dialysis
2	male	36	tongue	negative	localized amyloidosis
3	female	63	tongue	negative	localized amyloidosis
4	male	57	tongue	negative	localized amyloidosis
5	female	82	tongue, palate	Chronic kidney failure, no dialysis	senile amyloidosis

Case 5. A women 63-years-old was referred in 2009 to the Oral Pathology Department at the University of Milan by her maxillofacial surgeon, with a 6-month history of nodular lesions of the tongue. The patient's medical history included hypertension, treated by furosemide and atenolol. On examination she appeared to be in good general health. There was clinical swelling of the tongue with no cervical lymphadenopathy. The superficial mucosa appeared thickened and erythematous, with discoloured and congested areas. On palpation, the mucosa felt pliable and oedematous. The only painful area of the tongue identified by the patient was at the margin. A computed tomography (CT) scan of the maxillary sinuses and mandible did not show any abnormalities. Histological examination was thus performed, and given that there was no evidence of systemic involvement or associated disease, the case was diagnosed as localized amyloidosis of the tongue.

Histopathology

The study comprised 5 patients with amyloidosis, all of whom underwent surgical biopsy, and were subsequently followed up at the Institute of Oral Pathology of the University of Milan-Bicocca at San Gerardo Hospital, Monza between September 1994 and May 2009. All clinical data are shown in Table I.

Histological examination showed interstitial deposition of hyaline material in the lamina propria and submucosa, which in many areas involved the walls of small blood vessels and occasionally surrounded the salivary parenchyma. The deposits were moderately reactive to periodic acid-Schiff, and stained with Congo red, showing apple-green and red birefringence (Figure 2 A-D). Tissue sections were examined under polarized light and the amyloid deposits showed apple-green birefringence. This is a routine procedure to confirm amyloid deposition. All features of these cases were consistent with infiltration of the lingual mucosa and submucosa by amyloid.

Discussion

A diagnosis of amyloidosis is usually made on the basis of clinical presentation; a tissue biopsy is used subsequently to establish a definitive diagnosis. Bennhold introduced the Congo red stain in 1922, and showed the characteristic red staining of amyloid in normal light. Apple-green birefringence with polarized light microscopy, however, is the gold standard for diagnosis (3).

The nature of amyloid deposition in the oral cavity has long been the subject of controversy. In the absence of clinical symptoms of amyloidosis, biopsy of oral tissues has been advocated to confirm amyloid deposition. The tongue is the most frequently reported intraoral location of amyloid deposition (21-23). If the deposition is extensive, macroglossia may develop, which may cause difficulty in speaking and chewing.

There is also some controversy over diagnosis. Some researchers, including Keith (24), suggest taking a biopsy of the tongue, whether or not this organ is causing symptoms. However, other authors have reported tongue biopsy to be diagnostic in only 60% of cases (25). Other areas of the oral cavity may be involved: the palate which is involved very rarely, with only six cases having been reported to date (19, 20) and the maxillofacial complex. However, not all of these areas are possible biopsy sites. Localized amyloidosis has been reported in the nasal septum and maxillary sinus (26) and an unusual case has been documented involving the parotid gland (25). These sites would be difficult to biopsy because of their surgical accessibility. Delgado and Mosqueda (27) have reported that the labial minor salivary glands are another intraoral site of amyloid deposition which conversely are suitable for biopsy. Others suggest taking random tissue biopsies (28, 29).

In our cases, amyloid deposition in the oral cavity manifested itself as macroglossia; the largest amyloid deposits were in the tongue, and in one case also in the palate, in the form of nodular lesions. Clinical correlation with the lesion is very important; immunofixation electrophoresis of serum or urine will detect monoclonal immunoglobulins or light chains

in of patients with AL amyloidosis. With patients in whom light chains are not detected, a bone marrow biopsy can be used to detect the clonal dominance of plasma cells by immunohistochemical staining techniques. If no evidence of plasma cell dyscrasia is noted, other types of amyloidosis should be considered, such as the ATTR type. A mutated transthyretin should be investigated and may be identified by isoelectric focusing of the patient's serum, which will separate variant and wild-type transthyretin (30). Serum of patients suspected of having AA amyloidosis should be sent for immunohistochemical staining to detect the AA protein.

With regard to treatment of AL amyloidosis, many pharmacological agents have been advocated, starting with colchicine, which was first used to treat familial Mediterranean fever, a genetic disorder associated with a high incidence of AA amyloidosis (31, 32). Intermittent oral melphalan, a chemotherapeutic agent, and prednisone, a corticosteroid, have also been used and are more efficacious than colchicine on its own in treating AL amyloidosis (33-36). Other chemotherapeutic agents that have demonstrated evidence of response are vincristine and adriamycin, when used in combination with dexamethasone (3). Treatment with high-dose intravenous melphalan with autologous blood stem cell support produces complete remission of plasma cell dyscrasia (2). Organ transplantation has had limited success in treating cardiac amyloidosis (3); however, kidney transplantation is extremely successful, providing symptomatic relief for patients with dialysis-related amyloidosis (35).

Surgical management may also be required if airway obstruction is anticipated (36). Surgical excision has been considered (37, 38, 39) but the lesions often persist or recur.

Treatment of forms of amyloidosis with systemic involvement targets both the affected organ and the specific disease type (40). Kidney involvement may necessitate the use of diuretics and dialysis, while cardiac involvement may dictate the need for diuretics. Calcium channel blockers may exacerbate amyloid heart disease (41), and are also to be avoided because of their negative inotropism (3). Digoxin is contraindicated in cardiac amyloidosis because at therapeutic levels it may cause toxicity, as it binds to amyloid fibrils (3, 41, 42).

In regard to other therapeutic options, thalidomide has been shown to be effective in treating refractory multiple myeloma, and is now being considered for use in treating AL amyloidosis (43). Eternacept, a tumour necrosis factor receptor antagonist, has shown some early success in treating the symptoms of cardiac amyloidosis (3): The definitive therapy for ATTR amyloidosis is liver transplantation, on account of the production of transthyretin by this organ.

In localised forms, surgical intervention is usual; however if this is problematic, the laser treatment may be employed. Alternatively, the patient may simply be kept under observation (44, 45). The prognosis for patients with localised forms is good, but there is still a paucity of data.

Our patients with the localised form were kept under observation; they had no known progression of the lesion and systemic amyloidosis did not develop. Patients with systemic involvement were treated: one case with anti-hypertensive therapy and the other for the severe kidney failure. For AL amyloidosis, prognosis depends on the extent of organ involvement. Generally, the prognosis of a patient with this condition is poor if left untreated, with a median survival of 1 to 2 years. Seven patients with ATTR amyloidosis usually have a shorter survival time the earlier their age at disease onset.

To conclude, amyloidosis, whether primary or secondary, can be debilitating and may decrease significantly the quality of a patient's life. The data reported here, which are confirmed by the results of other studies, indicate that, within the oral cavity, the tongue may be of superior diagnostic value than the other locations in obtaining a diagnosis of amyloidosis.

In three cases there was no evidence of systemic involvement or associated disease; these were characterised as localised amyloidosis of the tongue. Histologically, the disease may be diagnosed through specific staining of a biopsy specimen with Congo red, which is an established feature of amyloidosis. There is no consensus as to the management of lingual amyloidosis. Surgical excision has been considered, but the lesions may persist or recur. The prognosis is uncertain, owing to the rarity of the condition, and regular follow-up and monitoring are recommended.

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