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Localized Amyloidosis of the Oral Cavity: A Rare Clinical Entity

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Received: 15 January 2025 | **Accepted:** 25 March 2025

Funding: The authors received no specific funding for this work.

Keywords: amyloid | Congo red | electrophoresis | fibrils | immunofixation

ABSTRACT

Amyloidosis is a complex disease which rarely affects the oral cavity. While localized and systemic variants have a similar clinical presentation, these entities differ vastly in their natural history and prognosis. There is a need for practitioners to be aware of the diverse presentation of this disease and the need for further workup. We present two cases of localised oral amyloidosis, outline their investigation and management and review the related literature.

1 | Introduction

The amyloidoses are a heterogeneous group of metabolic diseases, characterized by the progressive, aberrant deposition of fibrillar protein in beta-pleated sheets [1]. These misfolded proteins, denominated amyloid, are insoluble and ultimately become extracellular, collecting in any organ or tissue in the body [2].

Amyloid is derived from several precursor proteins that are deposited in the interstitium of organs and tissues, resulting in pressure atrophy and eventual organ dysfunction [3]. The contemporary classification of amyloidosis is determined by the organs/tissues affected (systemic/localized) and the type of precursor protein responsible for the amyloid fibrils [4]. Over 40 types of amyloids have been identified thus far [5].

Systemic amyloidosis is an uncommon but life-threatening multisystem disease, resulting in multiorgan impairment and eventual failure if not diagnosed and managed appropriately [6]. Amyloidosis can also be limited to one area of the body, termed localized amyloidosis, in which the amyloid proteins are made and deposited in the same organ or tissue [6]. Both forms of the disease can present with head and neck manifestations [7]. However, localized amyloidosis in the oral cavity is rare, with most cases being secondary to systemic amyloidosis.

A histopathological diagnosis of amyloidosis in the oral cavity warrants further investigation to determine whether the amyloidosis is systemic or localized and to further classify the subtype of amyloid, which will ultimately guide further treatment and determine prognosis. We herein present two cases of localized oral amyloidosis, documenting each case from initial presentation to the multisystem investigations conducted to reach a definitive diagnosis.

1.1 | Case 1

1.1.1 | Case History/Examination

A 40-year-old male was referred to the oral surgery department of the Dublin Dental University Hospital concerning an incidental finding of a polypoid, pedunculated lump of the right palatopharyngeal arch. The lesion was detected during a planned

wisdom tooth extraction procedure. The patient was unaware of this pathology previously and was asymptomatic.

The patient's medical history was significant for previous cardiac investigations in 2021. The patient suffered from long COVID and subsequently experienced fainting episodes. Cardiac ECHO and MRI were carried out at the time and were found to be normal. The patient had a tonsillectomy as a child but recently reported a history of odynophagia several times per year. He was a lifelong nonsmoker and consumed 14 units of alcohol per week.

Physical examination revealed no cervical lymphadenopathy, swelling, or asymmetries. Intraorally, there was a pedunculated 10 × 6 mm lump of the right palatopharyngeal arch. The lump was soft to palpate, with normal overlying mucosa (Figure 1).

1.1.2 | Differential Diagnosis, Investigations, and Treatment

The differential diagnosis was residual tonsillar tissue. Investigations included a conservative excisional biopsy of the lesion under local anesthetic and intravenous sedation. The histopathology reported squamous mucosa with underlying focal tonsillar tissue; the adjacent sub-epithelium was expanded by amorphous eosinophilic material. Congo red staining showed apple-green birefringence under polarized light. There was no significant inflammatory component. The features were consistent with amyloid deposition.

This unexpected finding prompted further investigation to determine the extent of amyloidosis (localized or systemic) and to subtype the amyloid. This case was sent to the National Amyloidosis Centre Royal Free Hospital in London. The original biopsy was re-examined, and the presence of amyloid was demonstrated by the staining of amorphous material with Congo red (Figure 2) that displayed apple-green birefringence when viewed under high-intensity cross-polarized light (Figure 3). Amyloid deposits were present throughout the section. The amyloid deposits were extensive, substantially replacing the normal structure.

Immunohistochemical staining of the amyloid deposits was performed using monospecific antibodies that reacted with serum amyloid A protein, transthyretin, kappa, and lambda immunoglobulin light chains. The amyloid stained with antibodies to lambda light chains. The interpretation of the case was amyloid of AL type lambda subtype.

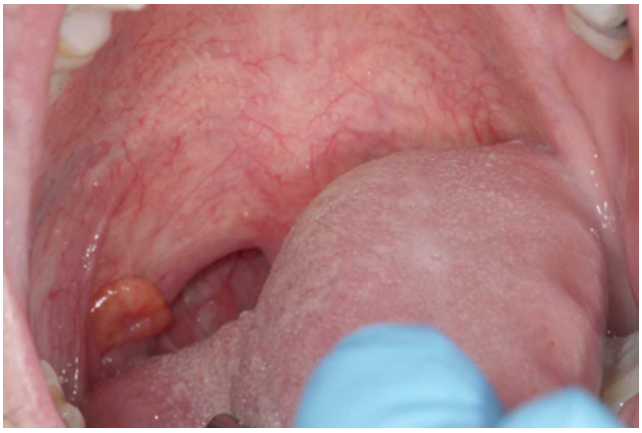

FIGURE 1 | Case 1 Amyloid deposit of the right palatopharyngeal arch.

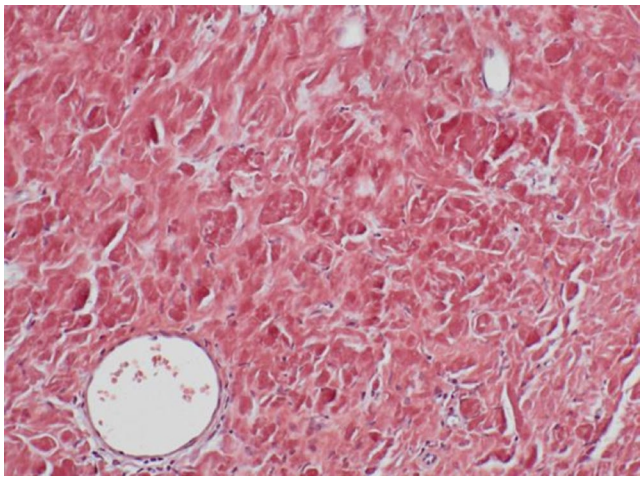

FIGURE 2 | Congo red staining of amyloid fibrils.

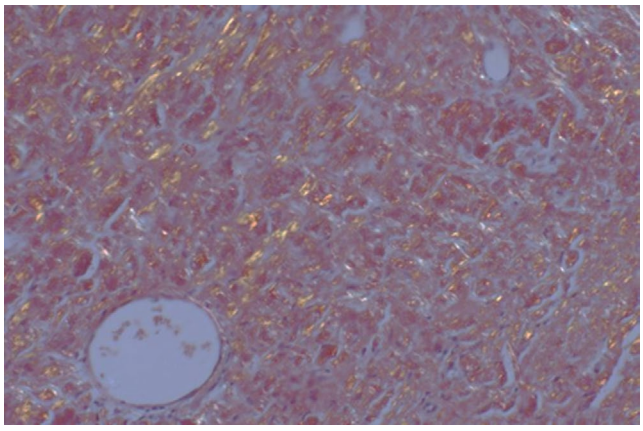

FIGURE 3 | Apple green birefringence of amyloid fibrils under polarized light.

The diagnosis of oral amyloid prompted further patient workup to evaluate for any underlying or associated systemic diseases and other possible sites of amyloid involvement. The patient was subsequently referred to the Hematology/Oncology department in St James's Hospital, Dublin. The results of the panel of laboratory tests (full blood count, glomerular filtrate rate (GFR), ESR, CRP, albumin, bone and renal profile, connective tissue diseases screen) were unremarkable. Serum-free light chain (SFLC) estimation, immunofixation, and serum protein electrophoresis of the blood and urine were unremarkable. Bence Jones protein test was clear. A full-body MRI was recommended, but the patient refused further investigations.

1.1.3 | Conclusion and Results (Outcome and Follow-Up)

The overall result of these investigations was confirmatory for localized oral amyloidosis with no evidence of systemic disease. The patient was asymptomatic with no recurrences at the 6-month follow-up. The patient refused further investigations

but remains well and under review with the Hematology Department.

1.2 | Case 2

1.2.1 | Case History/Examination

A 34-year-old female was referred to the oral medicine department concerning a yellow patch on the dorsal surface of the tongue. The patient reported a 3-month history of the above entity and could not associate the onset of the patch with any particular event. The patch/lump did not fluctuate, and there was no history of any overlying ulceration or discharge. She did not report feeling unwell systemically and had no dyspnea, paresthesia, weight loss/change of bowel habits, or dizziness. Her medical history was significant for a penicillin allergy and use of the oral contraceptive pill. She was a nonsmoker and an infrequent consumer of alcohol.

On examination, there was a 12×10 mm swelling on the posterior dorsum isolated to the left side, well defined with normal overlying epithelium, extending deep within tissues and firm (Figure 4).

1.2.2 | Differential Diagnosis, Investigations, and Treatment

The differential diagnosis for this was a lipoma, hemangioma, or lymphangioma. Management for this case initially involved an incisional biopsy under local anesthetic. The histology demonstrated squamous mucosa showing subepithelial deposits of acellular eosinophilic material (Figure 5). Congo red staining for amyloid showed pink to red staining of the subepithelium compared to light pink of the underlying collagen. The true apple green birefringence classically seen in polarized light was not identified here. However, the overall spectrum of anomalous color in polarized light could represent amyloid. The other alternative was that this represents a disturbed collagen due to trauma. Immunohistochemistry indicated amyloid of AL type lambda subtype.

The histology results prompted further investigations including screening bloods (full blood count, renal, liver and bone profile, thyroid function tests, antinuclear antibodies, rheumatoid factor, immunoglobulins, HbA1c). These results returned slightly reduced calcium of 2.15 (2.20–2.60 mmol/L), elevated creatinine of 81 (44–80 umol/L), and IgA of 4.32 (0.62–2.9). The plan was to refer the patient to hematology for further investigations. The patient was also subsequently referred to the National Amyloidosis Centre in London to rule out systemic amyloid.

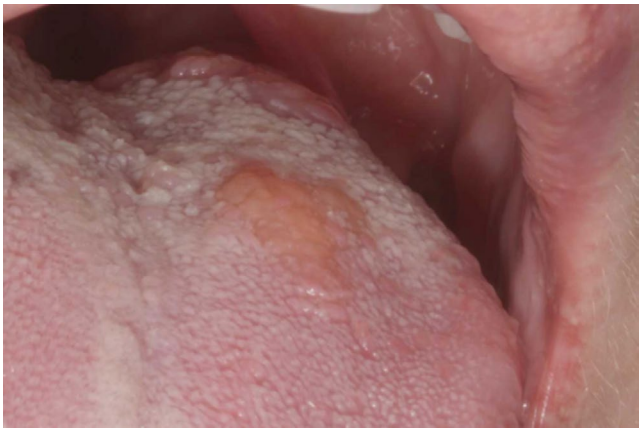

FIGURE 4 | Amyloid deposit of the left dorsum of the tongue.

Electrophoretic examination of the plasma proteins was unremarkable. Bence Jones proteins were not found in the serum or urine. The ECG was normal, and the ECHO showed no evidence of amyloid but slight enlargement of the right ventricle with flattening of the septal wall in diastole, possibly consistent with a patent foramen ovale. A serum amyloid protein scintigraphy (SAP) scan showed no visceral amyloid deposits. A biopsy of the bone marrow was also carried out to assess for a clonal dominance of plasma cells. This showed no evidence of plasma cell dyscrasia on immunohistochemistry.

1.2.3 | Conclusions and Results (Outcome and Follow-Up)

The patient's diagnosis was confirmed as localized AL amyloidosis of the oral cavity. The patient was followed up for 7 years with no change in the size of the swelling. No further surgical excisions of the deposit were conducted. She was subsequently discharged back to the care of her general dentist.

2 | Discussion

Amyloidosis is a rare and debilitating condition characterized by protein misfolding and auto-aggregation into highly ordered fibrils in a quaternary structure [8]. Fibrillogenesis, the process of amyloid formation, results in a conformational change in protein structure to a beta-pleated sheet secondary structure. This conversion results in the formation of degradation-resistant, nonfunctional fibrils which, resistant to catabolism, progressively accumulate in tissues and organs, ultimately contributing to organ dysfunction [6].

The currently accepted classification for amyloidosis considers the type of precursor protein and the distribution of that protein (localized or systemic). To allow for consistent and uniform classification, the Nomenclature Committee of the International Society of Amyloidosis classification system involves the use of the prefix A for amyloid followed by a suffix of the abbreviated precursor. Of the identified amyloid precursor proteins, 17 have been associated with systemic amyloidosis [9].

Amyloidosis is a rare disease. There are few published epidemiological studies on amyloidosis, which lack large population databases to determine its true incidence. Based on retrospective data from referrals to the National Centre for Amyloidosis in London, the incidence of amyloidosis was estimated to exceed 8 per million of the population [10]. Of the different subtypes, AL is the most common form, accounting for over 70% of cases [3]. Demographically, amyloidosis is more common in individuals above 65 years old. Males are at a slightly higher risk of developing the disease compared to females [11]. In our case series, both individuals were under the age of 40.

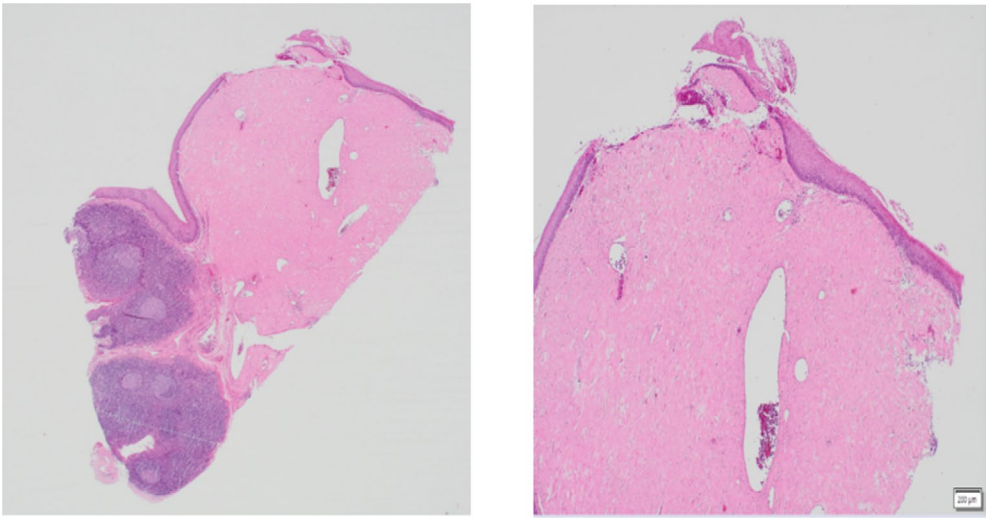

FIGURE 5 | Hematoxylin and eosin staining of histological specimen in Case 1.

The pathogenesis of amyloidosis is poorly understood. The reason for fibril deposition is hypothesized to be associated with several factors, including a genetic predisposition, defective proteolysis, an amyloidogenic precursor, and an amyloid-promoting factor in the extracellular matrix [12].

Amyloidosis is not a single entity but rather a spectrum of diseases. According to the different kinds of precursor protein forming amyloid fibrils, amyloidosis is mainly classified into four subtypes, including immunoglobulin light chain amyloidosis (AL), amyloid A amyloidosis, transthyretin amyloidosis, and B2 macroglobulin amyloidosis [13].

Light chain or AL amyloidosis, previously known as primary amyloidosis, is characterized by deposits of immunoglobulin light chain and the presence of paraprotein in urine and serum [12]. AL is most commonly associated with a low-grade benign gammopathy, or rarely a B-cell neoplasm. AA, previously known as secondary amyloidosis, is reactionary in nature and is associated with chronic infection or inflammatory diseases.

A major challenge in the management of amyloidosis is early diagnosis, which is impacted by the fact that clinical manifestations are variable and determined by precursor protein and involved organs. Approximately 37% of individuals with systemic amyloidosis are not diagnosed until a year after presentation [14]. Of clinical relevance, oral involvement may be the first sign of the disease in cases of systemic amyloidosis, with one study showing oral manifestations in two-thirds of a cohort of patients with systemic amyloidosis [15]. Therefore, clinicians must be alerted to the oral manifestations of this disease to facilitate prompt diagnosis and treatment [16].

Amyloidosis of the oral cavity is extremely rare and can be seen in both systemic and localized forms of the disease. In most cases, amyloid deposits in the oral mucosa occur secondary to systemic amyloidosis [17]. Over 90% of individuals with systemic amyloidosis develop amyloid deposits in various regions of the head and neck, including the larynx, pharynx, salivary glands, orbit, and oral cavity [12, 18].

Localized amyloidosis is an uncommon disorder of idiopathic etiology that can occur in the absence of systemic amyloidosis or other associated diseases, in which amyloid fibrils are produced and deposited in the same localized anatomic site. The oral cavity represents 9% of localized amyloid cases [19]. According to criteria from the National Amyloidosis Centre in the UK, localized amyloidosis requires a biopsy showing amyloid that stains with Congo Red, alongside an absence of renal, hepatic, cardiac, and neurological involvement, with no visceral amyloid detected on scintigraphy [20].

Localized oral amyloid can typically have a variable presentation in the oral cavity, [7] including tongue infiltrations and nodules [21–24] as seen in Case 2, salivary gland infiltrations, [25] gingival [26] and palatal nodules, [27, 28] as well as flat patches [27]. Less commonly, amyloid can present as hemorrhagic bullae [5] and widespread oral ulceration [29]. In contrast, systemic amyloidosis most often presents as macroglossia and rarely presents in other locations in the head and neck region [30].

Localized amyloidosis of the tonsillar region, as seen in Case 1, is an extremely rare entity, with few reported cases in the literature [31–40].

Oral amyloid is most commonly secondary to systemic disease [17]. Given that both forms of the disease can affect the oral cavity, the detection of amyloid on a biopsy sample from the oral mucosa necessitates investigations to rule out the systemic form of the disease. While localized amyloidosis of the oral cavity rarely causes serious consequences, systemic amyloidosis is a progressive disease with a high degree of patient morbidity and mortality [41]. Therefore, given that both forms of the disease can affect the oral cavity, the presence of amyloid in the oral cavity necessitates judicious and thorough investigations for systemic disease or an underlying disorder driving the amyloidosis process. This is important as the extent of the disease, as well as the subtype of amyloidosis, have therapeutic as well as prognostic implications.

Workup for cases of oral amyloid is threefold and includes initial tissue biopsy, followed by confirmation of the amyloid fibril type, followed by systemic investigation [7].

Amyloid in all forms has a characteristic gross pathologic and microscopic appearance. Amyloid fibrils stained with Congo red appear red in normal light and demonstrate birefringence with polarized light microscopy (Figure 2). This can demonstrate a characteristic "apple-green" dichroic appearance (Figure 4) [13]. Sections stained with hematoxylin and eosin show a homogeneous, eosinophilic amorphous substance with metachromasia with crystal violet (Figure 5).

Confirmation of the type of precursor amyloid fibril is a crucial step since this will guide subsequent therapy. This is accomplished routinely by immunohistochemistry [42]. Mass spectrometry is now considered the most accurate means of subtyping amyloid fibrils, with a sensitivity of 88% and specificity of 96% [13, 43]. However, this technique is not widely available. Both Case 1 and Case 2 were amyloid of the AL type.

Amyloidosis detected on biopsy of the oral tissues requires investigations to ascertain the extent of amyloidosis (localized or systemic). Multisystem investigations are necessary, including clinical assessments of the heart (ECG, ECHO, cardiac MRI, NT-proBNP, and troponin), kidneys (urinalysis, proteinuria, renal function tests), liver (liver function enzymes), and the nervous system (physical examination, nerve conduction, and autonomic nerve function).

Screening for plasma cell dyscrasias in patients with diagnosed localized amyloidosis is also required [7]. Serum-free light chain (SFLC) estimation, blood, and urine immunofixation and electrophoresis can be employed to detect paraprotein, and the Bence Jones protein test can detect the free immunoglobulin light chain in the urine. Bone imaging such as SAP scintigraphy can be employed to detect visceral organ involvement and can negate the need for biopsies in certain cases. Bone marrow aspirate and biopsy can also be employed, as was seen in Case 2, to analyze plasma cells quantitatively. The examinations were employed in both of the above cases, with no evidence of systemic involvement. According to the diagnostic criteria of localized amyloidosis as per the National Amyloid Centre, both cases were deemed localized in nature and treated as such. In cases of AA, investigations are necessary to identify the underlying condition driving the amyloidosis process.

There is no consensus on the management of localized amyloidosis. Treatment for localized amyloidosis of the oral cavity is usually simple excision, provided it can be safely resected from the surrounding tissues. In Case 1, the amyloid deposit was completely excised. In Case 2, the amyloid deposit of the tongue was not surgically removed as it did not cause any functional impairments. In cases of systemic disease, treatment is not curative. Instead, management is focused on reducing the level of amyloid and preventing and treating organ impairment. Treatment will depend on the subtype of amyloidosis; AA amyloidosis is managed through treatment of the underlying inflammatory disease. AL amyloidosis management may include chemotherapy, immunotherapy, and hematopoietic stem cell transplantation [3].

Systemic amyloidosis is a progressive disease with high mortality. However, with more effective therapies and the development of methods for earlier detection, the median survival rate has increased considerably over the past 15 years [44]. All organs except the central nervous system can be involved in progressive dysfunction [8]. The aggregation of amyloid fibrils within tissues and organs impedes function and ultimately results in end-organ failure, with mortality as high as 20% within 6 months of diagnosis [45]. Cardiac involvement is the leading cause of morbidity and mortality, responsible for 50% of deaths in patients with AL-type amyloidosis [46].

In comparison, localized amyloidosis of the oral cavity follows a benign natural history. While recurrences can occur [41], it has been demonstrated over protracted follow-up that these cases do not progress to the systemic form of the disease or multiple myeloma [19, 47–49] and do not impact patient life expectancy [47]. Long-term follow-up is still suggested for localized amyloidosis to monitor for progression to systemic amyloid or plasma cell dyscrasias [50]. Neither case in our series demonstrated recurrence or progression, over a period of months in Case 1 and over 7 years in Case 2.

3 | Conclusion

Amyloidosis is a rare and complex disease. Involvement of the oral cavity may be the first presentation of the disease; thus, clinicians must be aware of its diverse and multitudinous oral manifestations. Systemic and localized forms of the disease can present similarly in the oral cavity but have a vastly different natural history and prognosis. Therefore, the diagnosis of localized amyloidosis should be integrated with the results of multisystem investigations to intercept systemic disease. Despite its benign course, long-term follow-up is suggested for localized disease to detect systemic progression.

Author Contributions

Brian Maloney: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, visualization, writing – original draft, writing – review and editing. **Veronica Fisher:** conceptualization, data curation, formal analysis, methodology, supervision, validation, writing – review and editing. **Claire M. Healy:** formal analysis, investigation, methodology, supervision, validation, writing – review and editing.

Ethics Statement

The study did not require ethical approval.

Consent

Written informed consent was obtained from both patients to publish this report in accordance with the journal's patient consent policy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon request.

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