Localised oral amyloidosis in the context of oral epithelial dysplasia: Literature review and report of two cases

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Abstract
Amyloidosis is a group of rare progressive diseases that occur as a result of abnormal protein folding and aggregation. Systemic amyloidosis is a serious disease with high mortality, and prompt diagnosis is key to improving prognosis. Conversely, localised amyloidosis does not reduce life expectancy and can often be treated with simple surgical excision. Amyloid deposits can be found in the oral cavity, usually in the context of systemic amyloidosis. We present two cases of localised oral acquired immunoglobulin light chain (AL) amyloidosis that were detected in oral biopsies taken for the management of oral epithelial dysplasia (OED). Both patients underwent thorough multisystem investigations by haematology in conjunction with the NHS National Amyloidosis Centre (NAC) in order to exclude systemic amyloidosis and confirm the diagnosis. Localised oral amyloidosis is rare, and to our knowledge, localised oral AL amyloidosis has not been reported in the context of OED before. We discuss important learning points from these cases as well as hypothesising on the pathophysiology involved.

CLINICAL RELEVANCE

Scientific rationale for study
Two patients with localised acquired immunoglobulin light chain (AL) amyloidosis in the context of oral epithelial dysplasia (OED) in our department prompted us to report these unusual cases and conduct a literature review on amyloidosis in the context of oral surgery/oral medicine.

Principal findings
To our knowledge, localised AL amyloidosis has not been reported in the context of OED before.

Practical implications
Demonstrated by two clinical cases, the investigations that need to be undertaken to exclude systemic amyloidosis when oral amyloidosis is detected in the oral cavity are highlighted.

1. INTRODUCTION
Amyloidosis is a group of rare progressive diseases that occur as a result of abnormal folding of various proteins; this leads to the formation of amyloid fibrils that aggregate in sheets. The degradation of these amyloid deposits is slow, and thus, extracellular accumulation occurs. Previously classified as primary, secondary or familial, amyloidosis is currently classified depending on the fibril type and also whether the amyloidosis is systemic or localised. There are numerous different types of amyloid precursor proteins; for example, immunoglobulin light chain (AL amyloidosis), transthyretin (ATTR amyloidosis), serum amyloid A (AA amyloidosis), polypeptide hormone (endocrine-related amyloidosis) and cytokeratins1,2 (cytokeratin derived amyloidosis), in this article, we will review the most common types.

Systemic amyloidosis affects tissues throughout the body and has high morbidity and mortality, whereas localised amyloidosis affects a single site and rarely has serious consequences. Presentation, prognosis and treatment vary significantly between each type—both of which can affect the oral cavity5—and it is therefore important that clinicians...
understand how to manage these cases appropriately. All patients diagnosed with amyloidosis should be referred to haematology for multisystem investigation and management in conjunction with the NHS National Amyloidosis Centre (NAC) based in London, on a shared-care basis.6

We present two cases of localised oral AL amyloidosis as incidental findings from biopsies taken for the management of oral epithelial dysplasia (OED). Both patients were referred to the NAC, and the diagnoses confirmed to be localised amyloidosis. To our knowledge, localised oral AL amyloidosis has not been reported in this circumstance before.

2. BACKGROUND

Amyloidosis is a group of rare diseases caused by deposition and build-up of proteins in tissues and organs throughout the body. It can be classified by the organs and tissues that it affects (systemic or localised) or by the type of protein precursor that forms the amyloid fibrils (over 30 subtypes).

2.1. Systemic amyloidosis

In systemic amyloidosis, the accumulation of amyloid deposits in various organs and tissues around the body progressively affects their function. There is significant morbidity and mortality, particularly due to cardiac involvement but other sites can be affected (e.g., head and neck region, kidneys, liver, spleen). There can also be nervous system involvement, meaning that peripheral and autonomic neuropathy commonly present.

2.2. Localised amyloidosis

Localised amyloidosis (amyloidoma) is a rare form of amyloidosis where the amyloid fibrils form a discrete lesion affecting one site (often mucous membranes or skin). Localised amyloidosis has been reported to affect the urogenital tract, gastrointestinal tract, skin, respiratory tract (including the larynx), nasal mucosa, and tonsils and is most common in the head and neck region.5 Whilst localised amyloidosis can recur,13 it is generally accepted that it does not progress to systemic disease14 and does not reduce life expectancy.4 However, depending on the location of the amyloidoma, it can be associated with significant morbidity.14 Treatment is usually simple excision but given that localised amyloidosis can affect the same sites and tissues as the systemic type, thorough investigation must be undertaken to exclude systemic amyloidosis.

2.3. Acquired immunoglobulin light chain amyloidosis

Acquired immunoglobulin light chain (AL) amyloidosis is the most common form in both systemic and localised amyloidosis, with 55% cases in the United Kingdom presenting with this type. The prevalence of systemic AL amyloidosis in the United Kingdom is around 20 per million of the population.15 The male:female ratio is 1:3:1 in western countries and has been shown to be higher in China.15 In systemic disease, it develops in patients with an underlying plasma cell dyscrasia (e.g., multiple myeloma or monoclonal gammopathy of unknown significance (MGUS)), where proliferation of monoclonal bone marrow plasma cells results in light chain gammopathy.16 Therefore, monoclonal immunoglobulin light chains are produced in the bone marrow, carried around the body and deposited as amyloid fibrils in distant organs. AL is most likely to be the subtype in a case of localised amyloidosis, but due to the limitations of immunohistochemistry, it cannot always be confirmed or excluded.7 A study examining patients who were assessed at the NAC found that 98% [n = 606] with localised amyloidosis likely had this type.4 Whilst not fully understood, the pathophysiology of localised AL amyloidosis is different to that of systemic AL. Localised AL amyloidosis is caused by clonal expansion of a B cell or plasma cell in the affected tissue resulting in production of the light chain expressed by that B cell (monoclonal); the precursor to the amyloid fibrils. Therefore, the amyloid is produced in the same place as it is deposited.

2.4. ATTR amyloidosis

In ATTR amyloidosis, amyloid deposits accumulate from abnormal folding of the protein transthyretin (TTR), which is produced in the liver. There are two subtypes: hereditary ATTR (hATTR) amyloidosis, where family members inherit the mutated TTR gene and experience onset of symptoms in the fourth decade, and wild-type ATTR amyloidosis, which is not inherited and primarily causes cardiomyopathy in patients over 65.17 This type appears to be increasing in the population but this may be due to the increased use of cardiac MRI scans.18

2.5. Systemic AA amyloidosis

Systemic AA amyloidosis occurs in patients with underlying inflammatory conditions (e.g., Crohn’s disease, certain types of cancer, rheumatoid arthritis and even periodontal disease19), and most often affects the kidneys. A systematic review published in 2019 listed 48 diseases that were found to be strongly associated with AA amyloidosis.20 The protein precursor involved is serum amyloid A (SAA), which is usually present in blood but rises significantly in the presence of inflammation. It is not as common as previously due to developments in treatment for associated inflammatory conditions; approximately 5% cases referred to the NAC are diagnosed as this type. Although not fully understood, there have also been reports of AA amyloidosis occurring in association with multiple myeloma.21
2.6. Diagnosis

Diagnosis involves three stages: initial tissue biopsy, confirmation of amyloid fibril type (which can often be difficult) and systemic investigation. Amyloid deposits in a tissue biopsy will stain positively with Congo red and show classic apple green birefringence under polarised light. This is the gold standard for histological diagnosis and is true for all types of amyloidosis because of the common nonfibrillar components of all the amyloid fibril types; glycosaminoglycans (GAGs) and serum amyloid P component (SAP). Following a tissue diagnosis of amyloidosis, immunohistochemistry is undertaken to confirm the amyloid fibril type.

Assessment for underlying systemic disease is of paramount importance in patients with AL and AA amyloid deposits and abdominal subcutaneous fat aspirate, rectal biopsy and bone marrow biopsy may be examined; however, false negatives have been reported. It has been suggested that biopsies of the buccal mucosa or labial minor salivary glands may aid diagnosis of systemic amyloidosis.

Multisystem investigations should be carried out including: echocardiogram (ECG), blood tests, computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, serum free light chain (SFLC) estimation, blood and urine immunofixation and electrophoresis to detect paraprotein. The use of mass spectrometry in identifying the serum monoclonal light chain component in systemic AL amyloidosis is increasing in use. Bone imaging (e.g., scintigraphy) may also need to be performed to rule out myeloma. In systemic AL amyloidosis, the plasma cell dyscrasia can range from MGUS to serious malignancies (e.g., multiple myeloma). Patients who have MGUS should have regular monitoring tests including N-terminal B-type natriuretic peptide (NT-proBNP) levels (elevated levels are associated with severe disease in multiple myeloma) and testing urine for albuminuria. A SAP full body scan involving the injection of a radioactive tracer to confirm which tissues and organs are affected can be offered at the NAC, and this can negate the need for biopsies in some patients.

Genetic testing is important where hereditary amyloidosis is suspected.

Diagnosis of systemic amyloidosis is challenging and may be delayed due to the varied presentation. Clinicians should therefore consider amyloidosis early as a differential; a late diagnosis has a detrimental impact on prognosis and survival.

2.7. Management

There is currently no cure for amyloidosis. Management involves slowing the accumulation of amyloid whilst treating any resulting organ dysfunction and can be managed locally.

Treatment of systemic AL amyloidosis is underpinned by controlling the plasma cell dyscrasia (and thus reducing the amyloidogenic light chains). Treatment often involves combination chemotherapy agents and steroids but is not standardised for all patients. However, newer immunomodulatory drugs with lower toxicity and fewer side effects are being used. Some patients may also be suitable for high-dose chemotherapy and stem cell transplantation.

hATTR can be managed in a small number of cases with a liver transplant but this is rare in the United Kingdom. The National Institute for Health and Care Excellence (NICE) published Highly Specialised Technologies guidance [HST] 9 and 10 in 2019 and recommended use of Inotersen and Patisiran respectively for stages 1 and 2 polyneuropathy in adult patients.

Treatment of AA amyloidosis is primarily aimed at controlling the underlying inflammatory disease and thus reducing levels of SAA.

3. CASES

3.1. Case 1

A 54-year-old male attended the oral surgery (OS) dysplasia clinic in 2016 for management of multiple dysplastic white patches of the oral mucosa. He was a lifelong nonsmoker who consumed 15–18 units of alcohol per week and had diet-controlled type 2 diabetes mellitus, hypertension and back pain, for which he took losartan, bendroflumethiazide and dihydrocodeine. Biopsy-proven mildly dysplastic lesions affecting the buccal gingivae in the upper right molar and upper left premolar regions were excised fully and a separate lesion on the left maxillary tuberosity (Figure 1) was reported as moderate dysplasia; as no clinically evident white patch was present at review, no further excision was performed in this site. In 2018, the lesion in the upper left premolar region recurred and the histopathology report confirmed the presence of amyloid deposits with no evidence of OED (Figures 2 and 3). Retrospective examination of previous oral specimens found that all contained small amyloid deposits. The patient was referred to haematology and underwent investigations...
including bone marrow biopsy, which was normal. Other investigations included full blood count (FBC), haematinics, renal function, liver function tests (LFTs), bone profile and calcium which were normal, as were an ECG and random troponin. He had no monoclonal band, immune paresis or urine Bence Jones Proteins (BJP), and his SFLCs were normal. He was referred to the NAC for exclusion of systemic disease and underlying plasma cell dyscrasia; a diagnosis of localised AL amyloidosis was confirmed. The patient was discharged from haematology later that year, and his oral white patches continue to be monitored in OS.

3.2. Case 2

A 56-year-old female was referred to the OS dysplasia clinic in 2015 regarding biopsy-proven low-grade dysplasia affecting the buccal gingivae adjacent to the lower left canine (Figure 4). Her medical history was clear, she had never smoked and consumed approximately 10 units of alcohol per week. Management involved excision and review. At 1 year, a follow-up biopsy of the site (which appeared clinically normal) was undertaken to check for recurrence and was found to contain amyloid, with no evidence of residual OED or malignancy (Figures 5 and 6). The patient was referred to haematology, where she underwent the following investigations: FBC, renal function, LFTs, C-reactive protein (CRP), bone profile, protein electrophoresis and an ECG—all results were normal. There was a normal SFLC ratio, no
monoclonal light chain band on serum immunofixation, no BJPs and bone marrow biopsy was unremarkable. The patient had no cardiovascular, gastrointestinal or neurological symptoms. The NAC confirmed the diagnosis to be localised AL amyloid deposits within an area of scar tissue (secondary to inflammation), with no evidence of systemic disease. She was discharged from haematology in 2016 with a request to her GP for annual testing of the above bloods, protein electrophoresis and urine BJPs. She was subsequently discharged from the OS dysplasia clinic in 2018 as her oral cavity remained asymptomatic and showed no signs of recurrence.

4. DISCUSSION

Two cases of localised AL amyloidosis in the context of OED have been presented; whilst one case presented with a white patch and the other appeared clinically normal, both were detected in sites from which dysplasia had previously been diagnosed. Interestingly, when other mucosal biopsies from the maxilla were reviewed in case 1, they also contained small deposits of amyloid. Both patients underwent thorough investigations to exclude systemic amyloidosis and to confirm amyloid fibril type, as this forms the basis for treatment of such cases. Interestingly, haematology recommended annual investigations to screen for a plasma cell dyscrasia in case 2 but not for case 1.

4.1. Clinical presentation and diagnosis

In the majority of cases, oral amyloidosis is a manifestation of systemic amyloidosis; less than 9% of reported oral amyloidosis cases are localised. Oral amyloidosis most commonly affects the tongue and patients with substantial tongue deposits can present with macroglossia and a fissured nodular appearance, thus reducing tongue mobility. Macroglossia is a classical sign of systemic AL amyloidosis, occurring in up to 40% of cases. However, systemic amyloidosis affecting the oral cavity has a heterogeneous presentation with reports of purple bullae, ulceration and bullous formation. Other structures in the head and neck region may be affected and patients may present with enlargement of major salivary glands and submandibular soft tissues. Furthermore, amyloid deposits have been found in other head and neck pathologies, for example, salivary gland tumour.

Localised oral amyloidosis has been reported to present as nodules or swellings affecting the tongue, hard palate, gingivae and buccal mucosa. There is also a report of localised oral amyloidosis presenting as a purple patch affecting the hard palate.

However, these cases highlight that amyloidosis can present clinically in a much more non-specific fashion and therefore arguably should be considered more often as a differential diagnosis. As well as considering amyloidosis clinically, histopathologists should have a high index of suspicion when viewing oral mucosa with eosinophilic strands in the submucosa; promoting special staining with Congo Red. In case 1, the amyloid present in previous biopsies was detected on retrospective review. This had no serious consequences but in a case of systemic amyloidosis the consequence of a delayed diagnosis could be significant. An awareness that amyloidosis can affect all sites of the oral cavity is key to picking up these rare histological subtleties that can have important clinical consequences.

4.2. Localised oral amyloidosis in the context of OED

Localised oral amyloidosis is rare, but it has been reported in the context of OED and oral squamous cell carcinoma before. However, in contrast to the cases presented in this paper, this amyloid was found to be derived from cytokeratins (CKs) (i.e., not the AL type). Ueno et al., stained 266 specimens of oral, pharyngeal and laryngeal squamous cell carcinoma (SCC) and dysplasia with Congo Red. Amyloid was most common in laryngeal specimens and found in 11% of the oral SCCs (8/73) and 14.3% of the OEDs (1/7). Anticytokeratin antibodies were used to investigate the precursor to the amyloid in 19 of these squamous dysplasias/SCCs and reacted with both the extracellular amyloid deposits and the squamous cells cytoplasm. This suggests that CKs can be an amyloid precursor in certain types of localised amyloidosis, in the context of SCCs and squamous dysplasias, although the mechanism of how the CK exits the cells and forms amyloid fibrils is not fully understood.

The amyloid precursor in the presented cases was found to be immunoglobulin light chains (AL amyloidosis). Localised AL amyloidosis is caused by clonal expansion of a B cell or plasma cell in the affected tissue and is now largely recognised as a true neoplasm of plasma cell clones. The pathophysiology is not fully understood but it is thought that the IgG light chains produced by the clone of plasma cell are modified by giant cells, situated in the surrounding vicinity, to form amyloid deposits. Giant cells are not present in systemic AL amyloidosis and their role in localised amyloidosis has been a subject of debate. Localised AL amyloidosis typically occurs in mucous membranes in contact with the external environment. Therefore, it has been hypothesised that an antigen may induce the plasma cell clonal expansion. Interestingly, there have also been reports of AL amyloidosis occurring in the context of chronic inflammation (e.g., Sjogren’s syndrome and rheumatoid arthritis).

To our knowledge localised oral AL amyloidosis in association with OED has not been previously reported. Whilst it may be coincidental, it is possible that inflammation is a common factor in these two disease processes. It is well documented that inflammatory mediators play a role in the drive of OED and progression to malignancy. For example, overexpression of the inflammatory cytokine tumour necrosis factor (TNF-β) is associated with malignant
transformation of OED and an increase in mast cell production in dysplastic lesions is thought to be associated with angiogenesis. Could the chronic inflammation involve in OED act as a trigger for the clonal expansion of plasma cells and lead to a localised amyloid deposit? Alternatively, it could be hypothesised that OED and amyloidosis share a common external environmental trigger. However, in both cases, the patients were non-smokers, excluding this as a potential contributing factor.

5. CONCLUSION

Whilst oral amyloidosis is rare and usually detected in tongue tissue, clinicians and pathologists should consider this as a differential diagnosis of mucosal abnormalities and also be aware of its potential as an accidental finding in the context of oral biopsies from any site. Whilst the cases we present are those of localised oral amyloidosis, the consequences of a delay in the diagnosis of systemic amyloidosis could be significant. All cases of amyloidosis should be referred to haematology for investigation and management in conjunction with the NHS NAC.

ETHICS STATEMENT

Written patient consent was gained for the cases in this submission using the standard Wiley patient consent form.

CONFLICT OF INTEREST

No potential conflict of interest is reported by the authors.

AUTHOR CONTRIBUTIONS

M. L. Dobson and A. L. Wright conducted literature search on the topic and drafted and revised the paper. S. J. White led histopathology interpretation of case and revised the paper. M. Macluskey supervised work, conceived the present idea and revised the paper.

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