

Oral amyloidosis: A case report and diagnostic algorithm

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Abstract

Background: Amyloidosis is a distressing and infrequent condition caused by accumulation of abnormally folded proteins as aggregates in the extracellular tissue spaces of the body, leading to destruction of organ structure and function. Presentation of Oral Amyloidosis is generally a rare phenomenon, tongue being the most common site to manifest the disease process. Accurate recognition of the amyloid protein and its sub typing is absolutely critical for clinical management and to assess prognosis such as to avoid misdiagnosis and unwanted, potentially harmful treatment.

Case Report: We report a case of 84 year old male patient with an enlarged tongue, who presented with burning sensation and a facial violaceous papules with no other known systemic findings. Incisional biopsy revealed amorphous deposits confirmed for amyloid by congo red stain and Immunohistochemistry.

Conclusion: The suspicion of Amyloidosis should always be kept in mind whenever a solitary enlargement of the tongue is noticed. Close follow-up and an entire panel of investigations is mandatory, both to manage recurrences and to monitor the possible advancement of the disease into a full blown systemic form.

Keywords: Amyloidosis, Congo red stain and Immunohistochemistry, tongue

Key Messages:

Accurate and early diagnoses of diseases like Amyloidosis are key to successful management of patients suffering with these rare types of disorders. Clinicians and pathologists should be well versed with varied symptoms that these lesions present with and the exhaustive panel of diagnostic tests which must be advised to arrive at a definite diagnosis.

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INTRODUCTION

Most of the clinicians and pathologists would invariably agree to the fact that amyloidosis is a mystifying disease, often only considered following an unexpected pathology report. Essentially, amyloidosis is a complex disease characterized by tissue deposition of a protein forming

an insoluble beta-pleated sheet structure which can eventually obstruct the normal functioning of any organ.^[1] Amyloidosis is known to occur more frequently in men than in women.^[2]

Amyloidosis can be classified as primary, secondary and familial. The subtypes are currently named according to

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the specific protein that is deposited, using the prefix A for amyloid, followed by letters that indicate the protein (AL: primary or AA: secondary) and the distribution of amyloid deposition (localized or systemic). Amyloid light-chain amyloidosis is commonly associated with plasma cell disorders and multiple myeloma mostly affects the kidneys, liver, heart and nerves. Amyloid A or secondary systemic amyloidosis is usually associated with chronic infections or inflammatory diseases, such as osteomyelitis, tuberculosis, rheumatoid arthritis and Crohn's disease.^[3,4]

Amyloidosis of the oral cavity, a form of localized disease, usually affects the tongue less commonly the gingiva. When the tongue is affected, it can result in macroglossia furthering which systemic manifestation should be evaluated.^[5] We report a case of amyloidosis of the tongue that was diagnosed as one of the first manifestations of the disease, restressing on the fact that our oral cavity is the mirror of our general health.^[6]

CASE REPORT

An 83-year-old male patient, a former smoker, presented to the outpatient department with burning sensation in

the mouth for the past 3–4 months with difficulty to raise or protrude the tongue for the past 1 year. The patient described gradual deterioration of his general health over the past few months with generalized fatigue.

On extraoral examination, raised hyperpigmented violaceous plaques were noticed on both sides of the face and back. No significant hindrance to the daily routine activity of the individual because of the plaques was reported [Figure 1a and b].

On intraoral examination, a blanched white appearance of the tongue with hard and fibrous consistency was noticed. The lower labial mucosa also gave a blanched appearance. However, no palpable fibrous bands were noticed intraorally in any of the sites. There was the indentation of the teeth on the lateral border of the tongue on each side along with obvious restricted movement [Figure 2a and b]. Incisional biopsy was performed from both sides of the tongue; however, during the procedure, the surgeon hardly observed any bleeding from the biopsy/surgical site.

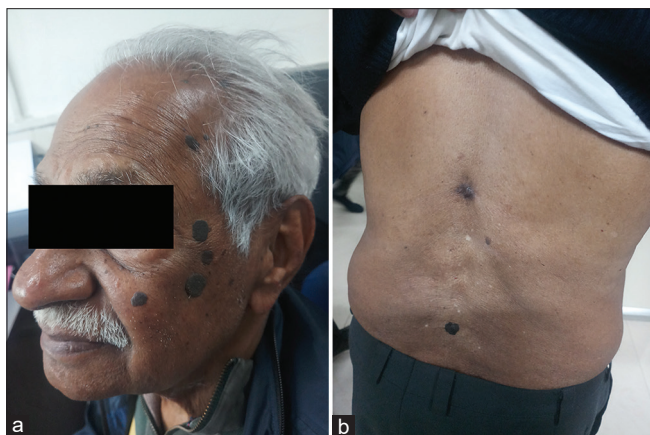


Figure 1: (a) Multiple hyperpigmented violaceous plaques on either sides of the face. (b) Hyperpigmented violaceous plaques on the back



Figure 2: (a): Restricted movement of the tongue. (b) Lateral indentation of the teeth on the tongue

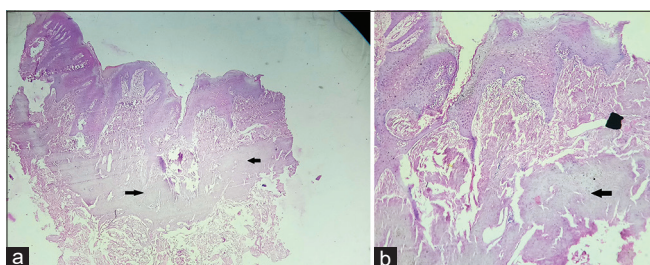


Figure 3: (a) Photomicrograph showing surface stratified squamous epithelium with submucosa showing a dense collection of amorphous material. (black arrows) (H&E, x4). (b) Photomicrograph showing amorphous material to be acellular and eosinophilic in nature. (Black arrows) (H&E, x10)

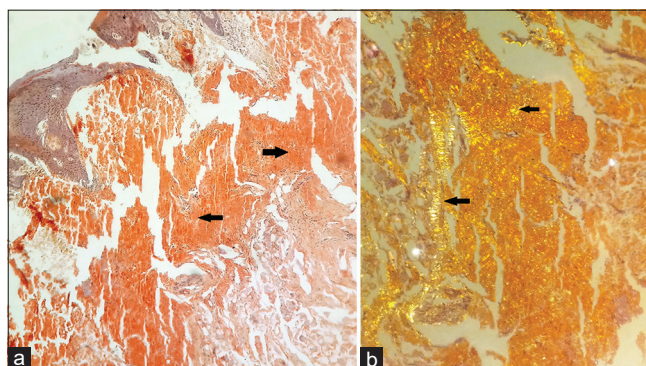


Figure 4: (a) Sections stained were positive for Congo red as the amorphous material was congophilic. (Black arrows) (x10). (b) Under polarizing microscopy, sections showed characteristic apple-green/orangish birefringence. (Black arrows)

Biopsy of the tongue on H and E sections showed a fragment of mucosa with surface stratified squamous epithelium and adjacent connective tissue with mild inflammatory infiltrate. The submucosa showed amorphous, acellular and eosinophilic material probably suggestive of Amyloid which was diffusely present intermixed with loosely arranged collagen fibers [Figure 3a and b].

On special stain with Congo Red, the eosinophilic material stained in a pale red orangish color confirming the presence of amyloid [Figure 4a]. Under polarizing microscopy, apple-green/yellow birefringence was noted which was diagnostic of amyloidosis [Figure 4b].

On histopathological confirmation, the patient was referred to the hematology department for systemic evaluation and further management. On primary investigation, blood picture was within normal limits. His hemoglobin was 14.4 g/dl, white blood cell: $1205 \times 10^9/l$ and platelet: $3.63 \times 10^9/l$;

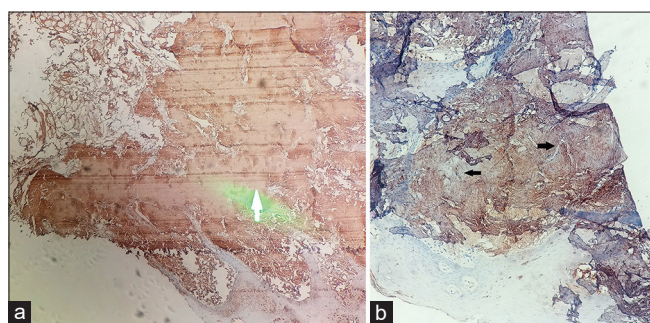


Figure 5: (a) Subtyping of amyloid through immunohistochemistry showed kappa light-chain restriction (3+) prominent. positivity (fluorescent arrow) ($\times 10$). (b) Subtyping of amyloid through immunohistochemistry showed lambda (1+) less prominent compared to kappa (black arrows) ($\times 4$)

peripheral blood smear was normal. His serum electrolytes, renal and liver function tests were well within normal limits. Serum electrophoresis was positive for M-band. An entire panel of investigations was advised by the hematologist, findings of which are enumerated in Table 1.

Immunohistochemistry for subtyping on PEFE- Paraffin Embedded Formalin Fixed block was carried out which showed kappa light chain restriction (3+) positivity compared to lambda (1+). SAA evaluation was negative [Figure 5a and b].

Her bone marrow biopsy showed mild plasmacytosis. Two-dimensional echocardiography showed decreased left ventricular (LV) ejection fraction (around 45%) highlighting a definite underlying cardiac disease. Correlating with all the investigation reports, a diagnosis of Light Chain Deposition Disease(k-kappa light chain) was rendered.

The patient has now been put on injection bortezomib 2 mg SC and tablet dexamethasone 10 mg both for weekly administration for an initial period of 7 weeks. He has also been supplemented with tablet doxycycline, tablet acyclovir, tablet Shelcal and tablet Vitamin D3.

After about 2 months of therapy, the results were encouraging as there has been a significant reduction in his burning sensation complaint from the oral cavity with partial relief in his restricted tongue movements. Overall, the treatment response was more than satisfactory in a limited time period of 2 months.

DISCUSSION

Amyloidosis is basically caused by extracellular accumulation

Table 1: The entire panel of investigations, present readings and its relevance

Investigation	Relavnt findings
CBC, blood sugar profile, HbA1C	Increase RDW, TLC, neutrophils, 6.8 (HbA1c)
Lipid profile, LFT, KFT	Within normal limits
Ultrasound, serum electrolytes	Kidney and gall blader show tiny echogenic foci. Rest within normal limits
Anti-ds DNA Ab serum	Within normal limits
p-ANCA, MPO antibody serum, c-ANCA serine proteinase	Within normal limits
Serum immunoglobulin profile	Decreased IgM level
SPEP, 24 h urine protein electrophoresis	Serum 'M' spike seen in gamma globulin region, no M spike seen in urine
NT PRO BNP	1841 pg/MI showing cardiac function getting effected
Doppler echocardiography	Underlying cardiac disease, LVEF 45%, old MI
Whole body PET scan	No metabolically active lesion in tongue or rest of body
FISH cytogenetics	No deletion/translocation of 13q14.3,17p13
Serum immunofixation/immunotyping	M spike seen as IgG, Kappa
SFLC assay	Kappa free light chain increased, altered kappa/lambda ratio of 18.68 suggestive of monoclonal gammopathy with renal impairment
Bone marrow aspiration/biopsy	12% mature large pleomorphic plasma cells were seen suggestive of mild plasmacytosis

CBC: Complete blood count, HbA1C: Hemoglobin A1c, RDW: Red blood cell distribution width, TLC: Total leucocyte count, LFT: Liver function tests, KFT: Kidney function test, Anti-ds DNA: Anti-double stranded DNA, ANCA: Antineutrophil cytoplasmic antibodies, p-ANCA: Perinuclear-ANCA, MPO: Myeloperoxidase, c-ANCA: Cytoplasmic-antineutrophil cytoplasmic antibodies, IgM: Immunoglobulin M, SPEP: Serum protein electrophoresis, NT PRO BNP: N-terminal pro-b-type natriuretic peptide, LVEF: Left ventricular ejection fraction, MI: Myocardial infarction, PET: Positron emission tomography, FISH: Fluorescence *in situ* hybridization, SFLC: Serum free light chain, M: Monoclonal

of misfolded proteins which are stained with Congo red dye as initial confirmation and produces a characteristic and pathognomic apple-green birefringence under polarized light microscopy more commonly occurring in males older than 60 years of age, similar to the case presented by us.^[7] The oral manifestations of amyloidosis are usually represented in the form of nodules, papules, plaques and macroglossia of the tongue and the color of the mucosa may range from yellow, orange, red, blue and purple.^[8] However, macroglossia, which is a generalized enlargement of the tongue, can be seen in other systemic conditions also namely myxedema, acromegaly and lymphangioma apart from our reported case of amyloidosis. In the oral cavity, amyloid deposits are rare, but when it occurs, the tongue is usually the most involved anatomic site followed by the lip, gingiva and palate.^[4]

Normal proteins, facing some systemic conditions such as cell changes and chronic inflammatory disorders, might form insoluble fibrils as part of systemic amyloidosis which can result in organ damage and dysfunction.^[9] Once a patient develops systemic disease, heart and multiorgan failure, amyloidosis should be on the differential diagnosis. The earlier the diagnosis is made, the faster the therapies can begin, delaying or averting the development of irreversible conditions such as cardiomyopathy.^[10]

After a tissue biopsy has been recognized, confirmation of AL disease requires bone marrow aspirate and biopsy showing predominance of normal or abnormal plasmacytosis or presence of amyloid as was seen in our present case. Serum protein electrophoresis (SPE) is used to identify patients with monoclonal gammopathies such as multiple myeloma, Waldenstrom macroglobulinemia and AL amyloidosis. SPE has good sensitivity in detecting intact monoclonal protein but has limited sensitivity in detecting monoclonal free light chains (FLCs).

Immunofixation electrophoresis (IFE) is used for immunotyping of monoclonal proteins which identifies the monoclonal immunoglobulin heavy chain (gamma, alpha and mu) and/or light chain type (kappa or lambda). IFE along with SPE is a test recommended as an initial screening panel and also for confirmation of complete response to therapy. The serum FLC assay is quantitative and its utility is not only in making the diagnosis but also in assessing progression and response to treatment.^[11,12] Combination of FLC with SPE and IFE improves the sensitivity in diagnosing by 99%.

The patient was also evaluated for perinuclear-antineutrophil cytoplasmic antibodies (ANCA), cytoplasmic-ANCA and

anti-double stranded DNA antibodies to rule out systemic vasculitis, Wegener's granulomatosis and systemic lupus erythematosus; however, in our case, both the tests were noncontributory negating the possibility of any of the above disease process, contrary to the findings in the case reported by Liakou *et al.*^[13]

Lehrke *et al.* conducted prognostic value evaluation of N-terminal pro-b-type natriuretic peptide (NT-pro BNP) in patients with AL and Transthyretin(TTR) amyloidosis and postulated that it can serve as a healthy correlation factor for myocardial amyloid burden such as LV-mass and Late Gadolinium enhancement (LGE), supporting the concept of NT-proBNP as a biomarker reflecting the severity of cardiac amyloid infiltration.^[14] Our present case showed levels of 1841 pg/ML which was well above the permissible range signifying the relevance of NTProBNP as a potential novel biomarker for assessing cardiac function and status in patients affected with amyloidosis.

An initial diagnosis of AL amyloidosis can be suspected by a clinician in a patient with nephrotic range proteinuria, heart failure with preserved ejection fraction,^[15] nondiabetic peripheral neuropathy,^[16] unexplained hepatomegaly^[17] or diarrhea.^[18]

Correct classification of the type of amyloid through IHC and its biochemical nature is important for treatment consequences.^[19] However, though expensive and less frequently available, the gold standard for subtyping of the nature of amyloid protein subunit will only be laser capture mass spectroscopic proteome analysis.^[20]

The aim of AL amyloidosis therapy should be to swiftly decrease the amyloidogenic monoclonal light chain load, by controlling the underlying plasma cell dyscrasia, if any.^[21]

A therapeutic strategy can also involve dissolving amyloid deposits or at least preventing their fresh accumulation. Patients with localized amyloidosis generally do not require systemic therapy, and management can be supportive or localized, chemotherapy or surgical excision.^[22] The treatment options for systemic amyloidosis include chemotherapy with or without autologous stem cell transplant.

Clinical relevance

This case brings out the clinicopathological profile of patients with amyloidosis and the entire panel of investigations both primary and secondary that needs to

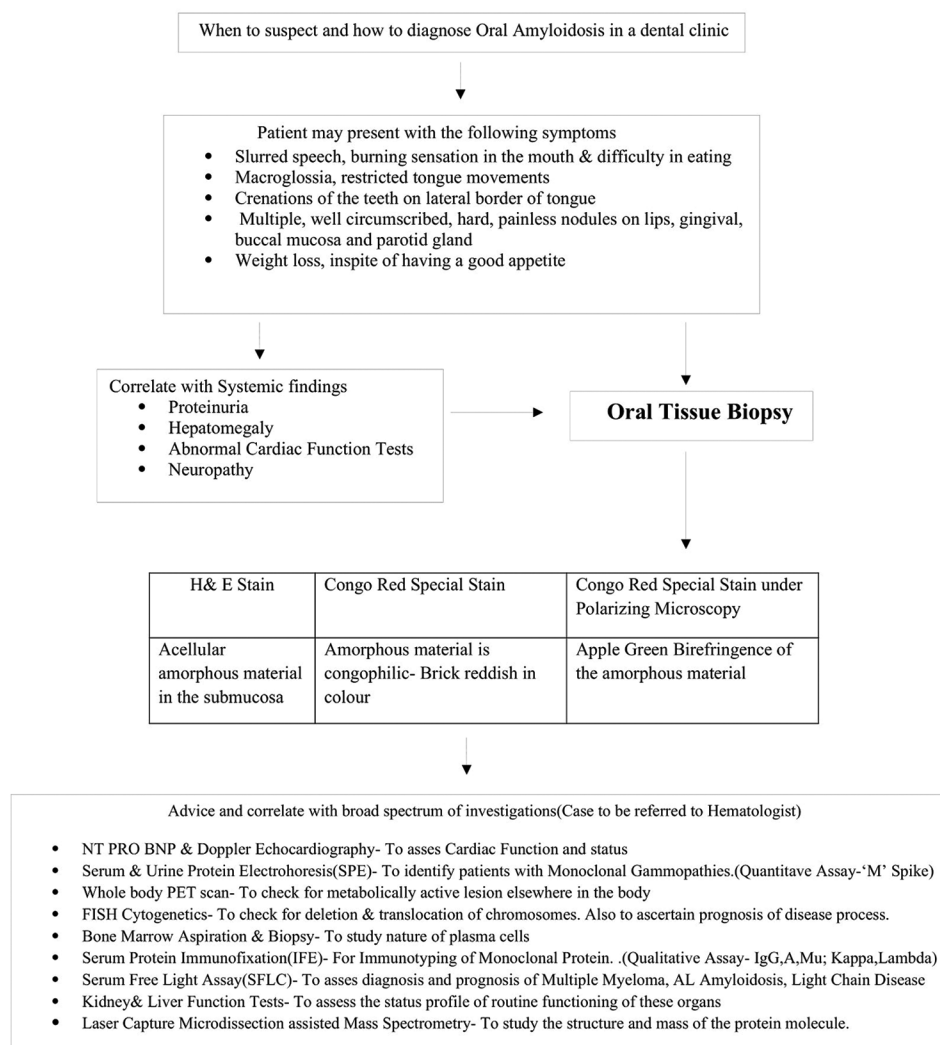


Figure 6: Diagnostic algorithm for cases with suspected amyloidosis

be carried out before finalizing a treatment modality in a patient [Figure 6]. Close monitoring and regular follow-up is critical for successful management of patients.^[19]

CONCLUSION

Amyloidosis is difficult to be recognized early due to its varied symptoms, broad array of manifestations and rarity. Early diagnosis will guarantee early therapeutics which will ensure maximum benefit to the patient.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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