International Journal of Health Sciences and Research
Vol.13; Issue: 7; July 2023
Website: www.ijhsr.org
Case Report *ISSN: 2249-9571*

Unraveling the Amyloid and Acromegaly Dilemma: A Challenging Case Report

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DOI: https://doi.org/10.52403/ijhsr.20230723

ABSTRACT

Systemic amyloidosis encompasses a range of conditions caused by various factors, characterized by the production and abnormal accumulation of misfolded proteins outside cells in different organs, leading to tissue damage. Due to the varied and non-specific symptoms associated with the disease, diagnosing this condition is often delayed. The predominant types of this condition include light chain (AL) amyloidosis, Amyloid A (AA), and transthyretin-related ATTR amyloidosis. We present a case report of a 61-year-old gentleman who presented with progressive enlargement of the tongue and prognathism mimicking acromegaly.

Keywords: Amyloidosis, Acromegaly, Prognathism, Plasma Cell Disorders

INTRODUCTION

Amyloidosis is a collective term for a group of diseases with a shared characteristic: the deposition of abnormal insoluble fibrillar proteins outside cells in organs and tissues. In the mid-19th century, Virchow adopted the term "amyloid," initially used in botany to refer to starch or cellulose, to describe abnormal extracellular material observed in the liver during autopsies. Later, it was discovered that amyloid could be stained with Congo red, appearing red under normal light but exhibiting an apple-green color when observed under polarized light. Almost a century after Virchow's initial observations, the fibrillar nature of amyloid was elucidated through electron microscopy, and the characteristic beta-pleated-sheet structure, now understood to be responsible for the distinctive staining properties, was identified. (1)

The clinical presentations of amyloidosis exhibit significant heterogeneity, influenced by the specific subtype and the extent and severity of organ involvement. Due to their nonspecific nature, prodromal symptoms are often misinterpreted, commonly resembling those of more common diseases. As a consequence, diagnosis is frequently delayed. (2)

CASE REPORT

A 61-year-old gentleman with a known history of hypothyroidism complained of progressive tongue enlargement, snoring, and generalized fatigue over the past 6 months. His vital signs were stable, with a pulse rate of 74/minute and blood pressure of 122/70 mmHg. The clinical examination revealed the presence of macroglossia, thickened forehead skin, finger thickening, and macrognathia (Fig. 1).

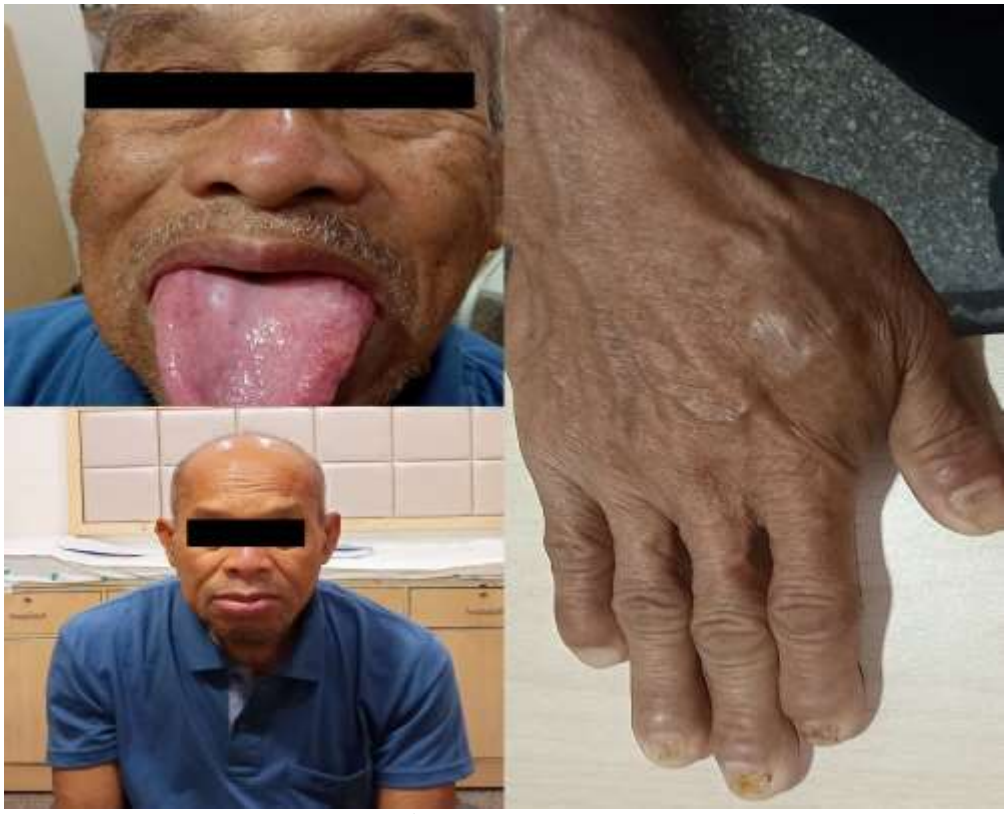

Figure 1: Macroglossia, Thickened forehead skin, and subungual tissue (Counter clockwise)

Given the clinical presentation, the differentials considered were amyloidosis and acromegaly. His basic investigations are given in Table 1.

Table 1: Basic investigations of the patient at presentation.

Test Parameters	Patient's data	Normal Range
Complete blood count:		
Haemoglobin	8.2 (g/dL)	11.5-16.5 (g/dL)
Total White blood cell count	6* 10^3 /mm^3	4-11 10^3 /mm^3
Neutrophils	61%	40-80%
Lymphocytes	28%	20-40%
Monocytes	8%	02-10%
Platelet count	150*10^3 /mm^3	150-450 10^3 /mm^3
ESR	18	0-20 mm/hr
Liver Function tests:		
Total Bilirubin	1.2 mg/dL	0.0-1.3 mg/dL
Direct bilirubin	0.4 mg/dL	0.0-0.5 mg/dL
Indirect Bilirubin	0.8 mg/dL	0.0-1.2 mg/dL
SGOT/ AST	90 U/L	<31 U/L
SGPT/ ALT	70 U/L	<34 U/L
Alkaline Phosphatase	304 U/L	<98
Gamma Glutamyl Transpeptidase (GGTP)	272 U/L	<140 U/L
Serum Albumin	4.1 g/dl	3.2 - 4.6 g/dl
Serum Globulin	2.5 g/dl	2.0 - 3.5 g/dl
Renal Function Tests:		
Urea	30 mg/dl	13-43 mg/dl
Creatinine	0.9 mg/dl	0.6 - 1.1 mg/dl
Special Tests:		
Growth Hormone	4.8 ng/ml	> 1YEAR: < 5 ng/ml
IGF-1		
Serum Calcium	9.1 mg/dl	8.6-10.2 mg/dl
LDH	310	>12 Years: 125 - 220

MRI brain showed no significant abnormalities, ruling out intracranial pathology. Also, serum IGF-1 and growth hormone levels were within normal limits, suggesting that acromegaly was unlikely. His 2D ECHO showed no regional wall motion abnormalities with an EF of 61%. Urine routine examination was notable for no proteinuria.

To establish a definitive diagnosis, a biopsy was performed on the tongue. Histopathological examination revealed fragments of mucosa lined by stratified squamous epithelium with acanthosis, hyperplasia, and subepithelial connective tissue showing interstitial and perivascular pale eosinophilic glassy material. Interspersed stromal cells were observed, extending into the underlying skeletal muscle bundles. Superficial vascular proliferation and scattered chronic inflammation were also noted. Mild spongiosis was observed. Congo red staining demonstrated congophilia with apple green birefringence on plane-polarized light, which was lost after $KMnO_4$ treatment. These findings were consistent with amyloidosis (Fig. 2).

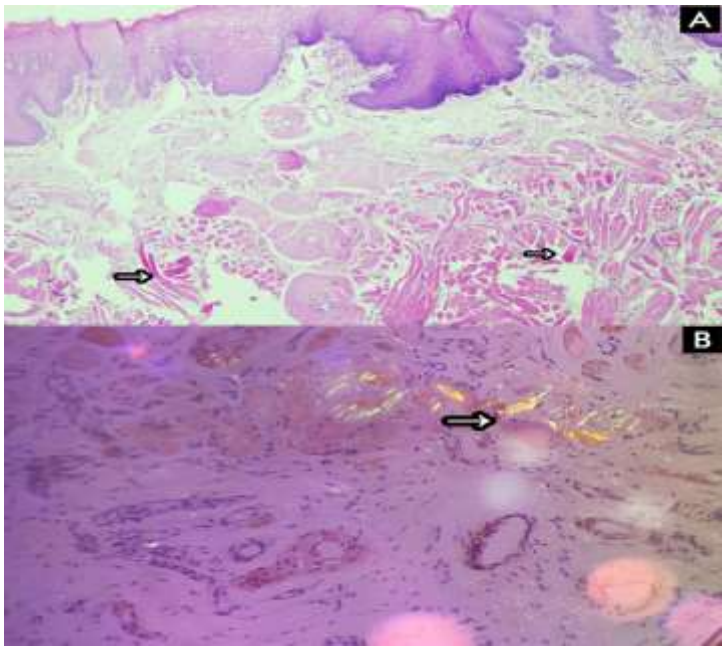

Figure 2: Tongue biopsy photomicrographs: (A): Subepithelial connective tissue showing interstitial and perivascular pale eosinophilic glassy material. (B): Congo red staining shows congophilia with apple green birefringence.

The patient received appropriate counseling and was being prepared for further investigations like free light chain assay, Serum Protein electrophoresis, Urinary Bence Jones protein assay, and treatment. Unfortunately, the patient was lost to follow-up.

DISCUSSION

Unexplained weight loss, persistent fatigue, and diuretic-resistant edema are common clinical manifestations in amyloidosis cases. [3] In amyloidosis, aggregates primarily accumulate outside the cells, where the misfolded protein subunits adopt a shared structural conformation characterized by antiparallel β-pleated sheets. This conformation leads to the formation of higher-order oligomers and subsequent fibrils, displaying distinct staining properties. [4]

Classification of amyloid is based on factors such as systemic or localized involvement, acquired or inherited nature, and clinical patterns. The standard nomenclature employs the format AX, where A represents amyloidosis, and X denotes the specific protein found within the fibril. This article primarily focuses on the systemic forms of amyloidosis. The AL subtype pertains to amyloid composed of immunoglobulin light chains (LCs). It is associated with a clonal B-cell or plasma cell disorder, often seen in conjunction with myeloma or lymphoma. ATTR, the most prevalent form of familial amyloidosis, involves amyloid derived from either wild-type or mutated transthyretin (TTR), a protein involved in thyroid

hormone and retinol-binding. AA amyloid comprises serum amyloid A (SAA), an acute-phase reactant protein. It arises in chronic inflammatory or infectious diseases, previously called secondary amyloidosis. Aβ2M amyloid results from misfolded β2-microglobulin and typically occurs in individuals with long-standing renal disease who have undergone dialysis for an extended period. Aβ, the most commonly observed form of localized amyloidosis, is found in the brains of Alzheimer's disease patients and is associated with abnormal proteolytic processing and aggregation of polypeptides derived from the amyloid precursor protein. [1,4]

A study on 11,006 patients diagnosed with amyloidosis between 1987 and October 2019 revealed a significant increase in cases. Specifically, there was a 670% rise from 1987-1999 to 2010-2019. Among all the cases, systemic light-chain (AL) amyloidosis remained the predominant type, representing 55% of the total cases. [5]

Distinguishing amyloidosis from other conditions like hypertrophic cardiomyopathy (HCM), membranous glomerulopathy, neuropathy associated with monoclonal gammopathy of undetermined significance (MGUS), and acromegaly is crucial.[3] Upon literature search, we could find two case reports by Jiang M et al, and Abdelsalam et al, where amyloidosis was considered in the differentials of evaluation of acromegaly.[6,7] Employing definitive diagnostic methods to exclude these common conditions is essential for precise patient management and treatment. [3,6]

The diagnosis and treatment of amyloidosis rely on the histopathologic identification of amyloid deposits and immunohistochemical, biochemical, or genetic methods to determine the specific type of amyloid. In systemic amyloidosis, a biopsy of clinically affected organs is commonly performed, although amyloid deposits can be found in any tissue throughout the body. Traditionally, blood vessels in the gingiva or rectal mucosa have been examined. [4,8]

Pathologically, hematoxylin and eosin stains under the light microscope show that amyloid is an amorphous, eosinophilic, hyaline extracellular material. Several histochemical stains are used to distinguish amyloid from other hyaline materials (such as collagen and fibrin). The Congo red stain is the most popular and gives tissue deposits a pink or red color under standard lighting. Still, polarizing microscopy makes the green birefringence of the stained amyloid much more noticeable and distinct. The crossed-pleated sheet shape of amyloid fibrils contributes to this staining reaction, which is present in all forms of amyloid. Electron microscopy exhibits amorphous nonoriented thin fibrils and can be used as confirmation. [9]

Comprehensive investigations typically include immunofixation of serum and urine, measurement of free light chains (FLC), bone marrow plasma cell (BMPC) FISH analysis, skeletal survey, NT-proBNP (or BNP) measurement, cardiac troponin levels, electrocardiography (ECG), Holter monitoring, echocardiography, cardiac MRI, 24-hour proteinuria assessment, creatinine measurement (with estimated glomerular filtration rate calculation), and liver function testing. [4,8]

The treatment strategy in amyloidosis aims to target the underlying clone. It should be adapted to the patient's risk profile, focusing on promptly administering the most effective therapy that can be safely tolerated. Autologous stem cell transplantation may be considered an upfront or post-bortezomib-based conditioning approach in approximately 20% of patients. Bortezomib plays a crucial role in improving response depth following transplantation and serves as a foundational treatment for patients who are not eligible for transplantation. An emerging novel standard of care in AL amyloidosis is the combination of daratumumab and bortezomib. Treatment objectives should prioritize achieving early and substantial hematologic and organ response over the long term. [8]

CONCLUSION

This case report underscores the importance of heightening awareness regarding amyloidosis as a potential differential diagnosis in patients with non-specific features. It also highlights the significance of comprehensive investigations, including the utilization of tissue biopsy, to establish a definitive diagnosis.

Declaration by Authors

Ethical Approval: Not applicable

Acknowledgment: We thank Dr. Suganthi, Department of Pathology, for helping with the photomicrographs of the slides.

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Jagadeesh Chandrasekaran, Manjunatha Gajanana Hegde, Boochandran TS et.al. Unraveling the amyloid and acromegaly dilemma: a challenging case report. *Int J Health Sci Res.* 2023; 13(7):162-166.
DOI: *https://doi.org/10.52403/ijhsr.20230723*

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