folia medica

Folia Medica 67(6)
DOI: 10.3897/folmed.67.e145063

Case Report

Echoes of a hidden killer: a case of oral and cardiac amyloidosis

Areti Kalfoutzou[1], Adam Mylonakis[2], Margaritis Tsantopoulos[3], Nikolaos Chaleplidis[3], Christos Piperis[4], Maria Dimitrakoudi[5], Konstantinos Kounouklas[6], Eleftheria Bagiokou[1], Eleni Mostratou[6]

1 *Department of Medical Oncology, 251 Air Force General Hospital, Athens, Greece*
2 *First Department of Surgery, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece*
3 *Department of Pathology, 251 Air Force General Hospital, Athens, Greece*
4 *Department of Cardiology, Georgios Gennimatas Peripheral General Hospital, Athens, Greece*
5 *Department of Hematology, National and Kapodistrian University of Athens, Laikon General Hospital, Athens, Greece*
6 *Second Department of Internal Medicine, 251 Air Force General Hospital, Athens, Greece*

Corresponding author: Areti Kalfoutzou, Department of Medical Oncology, 251 Air Force General Hospital, Athens, Greece; Email: aretik92@gmail.com

Received: 21 December 2024 ♦ **Accepted:** 6 February 2025 ♦ **Published:** 18 December 2025

Citation: Kalfoutzou A, Mylonakis A, Tsantopoulos M, Chaleplidis N, Piperis C, Dimitrakoudi M, Kounouklas K, Bagiokou E, Mostratou E. Echoes of a hidden killer: a case of oral and cardiac amyloidosis. Folia Med (Plovdiv) 2025;67(6):e145063. doi: 10.3897/folmed.67.e145063.

Abstract

Light chain amyloidosis (AL) is a rare systemic disorder caused by the accumulation of immunoglobulin light chains in various organs, most notably the heart. Its clinical presentation is often nonspecific, leading to delayed diagnosis and poor prognosis. We report the case of a 71-year-old woman who presented with macroglossia and periorbital ecchymosis, symptoms that persisted for six years before diagnosis, along with dyspnea on exertion for the past year. Comprehensive evaluation revealed AL amyloidosis with significant cardiac involvement, evidenced by echocardiographic findings of concentric ventricular wall thickening and diastolic dysfunction consistent with restrictive cardiomyopathy. Laboratory workup confirmed elevated serum free light chains (FLC), and histopathology demonstrated the presence of amyloid deposits confirming the diagnosis. This case acknowledges cardiac AL amyloidosis as a rare cause of cardiac failure with preserved ejection fraction, often accompanied by systemic manifestations of the disease such as macroglossia and periorbital ecchymosis, and highlights the critical need for high clinical suspicion and early recognition of cardiac involvement in AL patients.

Keywords

amyloidosis, amyloid, cardiac failure, case report

Introduction

Light chain amyloidosis is a rare and often fatal systemic disorder characterized by extracellular deposition of misfolded monoclonal light chains in organs, mainly the heart, kidneys, liver, skin, and peripheral nervous system.[1] Cardiac involvement occurs in up to 90% of AL amyloidosis cases and is particularly concerning due to its impact on patient mortality.[2] The deposition of amyloid fibrils in the myocardium typically causes restrictive cardiomyopathy, heart failure with preserved ejection fraction, or various conduction abnormalities.[2] This case report presents a 71-year-old woman who was diagnosed with cardiac AL (CA-AL) 6 years after initial symptoms of oral involvement, highlighting the challenges of recognizing this rare disease and the importance of a multidisciplinary approach to patient management.

Case report

A 71-year-old woman reported worsening dyspnea on exertion over the past year. Her past medical history included arterial hypertension and hyperlipidemia. She reported no

Copyright by authors. This is an open access article distributed under the terms of the Creative Commons Attribution License (CC-BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

PENSOFT.

history of smoking, alcohol abuse, or illicit drug use. Clinical examination revealed significant macroglossia with perioral purpura ***(Fig. 1)****, periorbital ecchymosis, and enlarged bilateral submandibular lymph nodes. Upon auscultation, breath sounds were diminished at the bilateral lung bases.*

Laboratory examinations indicated leukocytosis (white blood cell: 10.6, normal range: 4–10 K/μL) with a polymorphonuclear predominance (76%), an elevated creatinine level (1.6, normal range: 0.5–1.2 mg/dL), N-terminal pro-natriuretic peptide type-B (NT-proBNP: 2123, normal range: 0–125 pg/mL), and troponin-T (56, normal range: 10–40 ng/L). Additionally, the patients had an elevated erythrocyte sedimentation rate (ESR) of 23 mm/h (normal range: 0–20 mm/h). Immunological assays demonstrated elevated β2-microglobulin levels (3.14, normal range: 1–2.7 mg/L). Urine/serum protein electrophoresis with immunofixation (SPEP/UPEP with IFE) showed elevated free λ chains, with serum levels at 284 mg/L (normal range: 5.7–26.3 mg/L), consistent with monoclonal protein overproduction. The kappa/lambda ratio was calculated at 0.04 (normal range: 0.26–1.65).

A chest X-ray revealed bilateral pleural effusions necessitating pleurocentesis ***(Fig. 2)****. Electrocardiography (ECG) indicated diffuse low QRS voltages in all leads* ***(Fig. 3)****. Echocardiogram was suggestive of restrictive cardiomyopathy, consisting of a preserved ejection fraction (EF: 60%, normal range: >55%), low end-diastolic diameter of the left ventricle (42, normal range: 45-56 mm), biatrial enlargement, and increased ventricular wall thickness (13, normal range: 6-11 mm) along with a "granular sparkling" appearance of the ventricular wall. Computed tomography (CT) scans of*

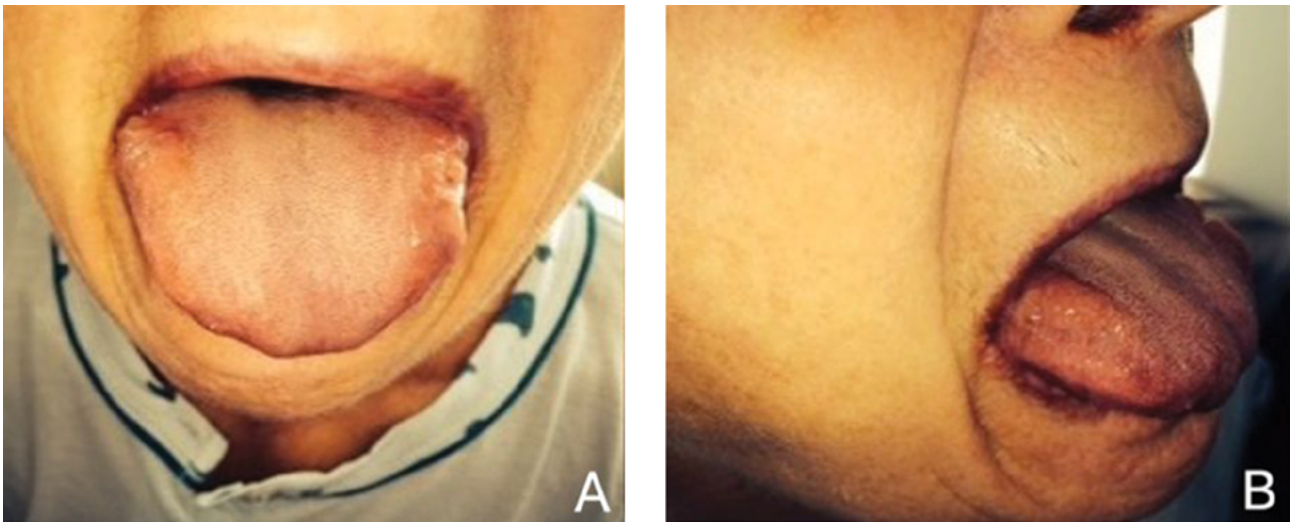

Figure 1. The figure captures our patient presenting with significant macroglossia, tongue surface ulcerations (left side of tongue), and purplish lip lesions, consistent with oral AL amyloidosis.

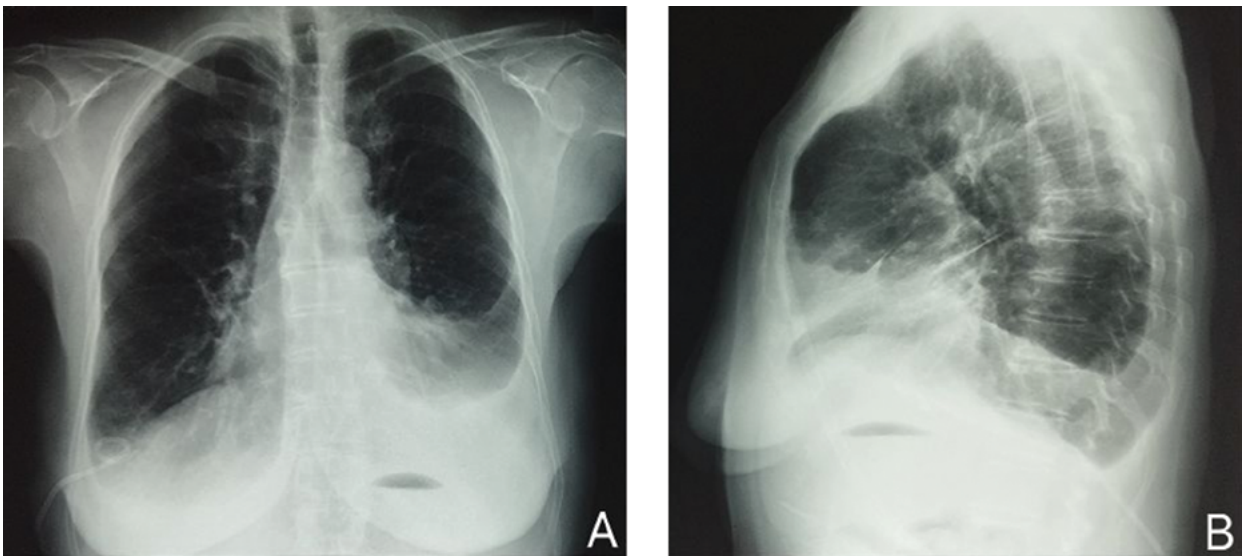

Figure 2. Chest X-ray in frontal (**A**) and lateral (**B**) views showing atelectasis in the left lower lobe and significant bilateral pleural effusions with a pleural catheter in place on the right side.

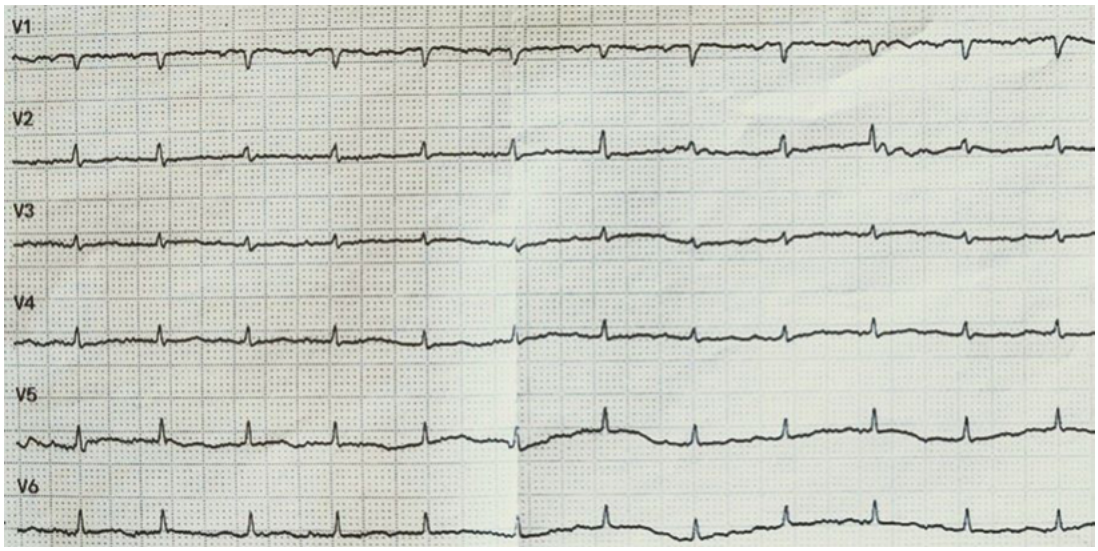

Figure 3. ECG of the patient showing diffuse low QRS voltages in all leads.

the chest and abdomen revealed bilateral pleural effusions, thickening of the intralobular septa, bilateral axillary and external iliac lymphadenopathy.

Due to cardiac, lung, and renal manifestations, along with the clinical features of macroglossia and lymphadenopathy, a systemic disorder was strongly suspected. Therefore, biopsies of abdominal fat, tongue, and bone marrow were performed. Histopathology revealed the presence of amyloid deposits, which stained positive with Congo red ***(Fig. 4A)*** *and showed apple-green birefringence under a polarized-light microscope* ***(Fig. 4B)****, leading to the diagnosis of AL amyloidosis. The bone marrow biopsy revealed a clonal population of slightly atypical plasma cells comprising less than 10% of the marrow cellularity, consistent with monoclonal gammopathy of undetermined significance (MGUS).*

*Based on the Mayo 2012 staging system for cardiac AL amyloidosis[3], the patient was classified as Stage III, given her troponin-T, her BNP level of 2123 pg/ml, and a serum free light chain difference exceeding 180 (272.64 mg/L)***.** *During her hospital stay, the patient experienced a slight elevation in liver function tests (LFTs), which subsequently reversed. She was discharged on a combination of irbesartan and furosemide and was referred to the Hematology Department to initiate systemic treatment with bortezomib, cyclophosphamide, and dexamethasone. A subsequent amyloid typing with mass spectrometry identified λ light chains as*

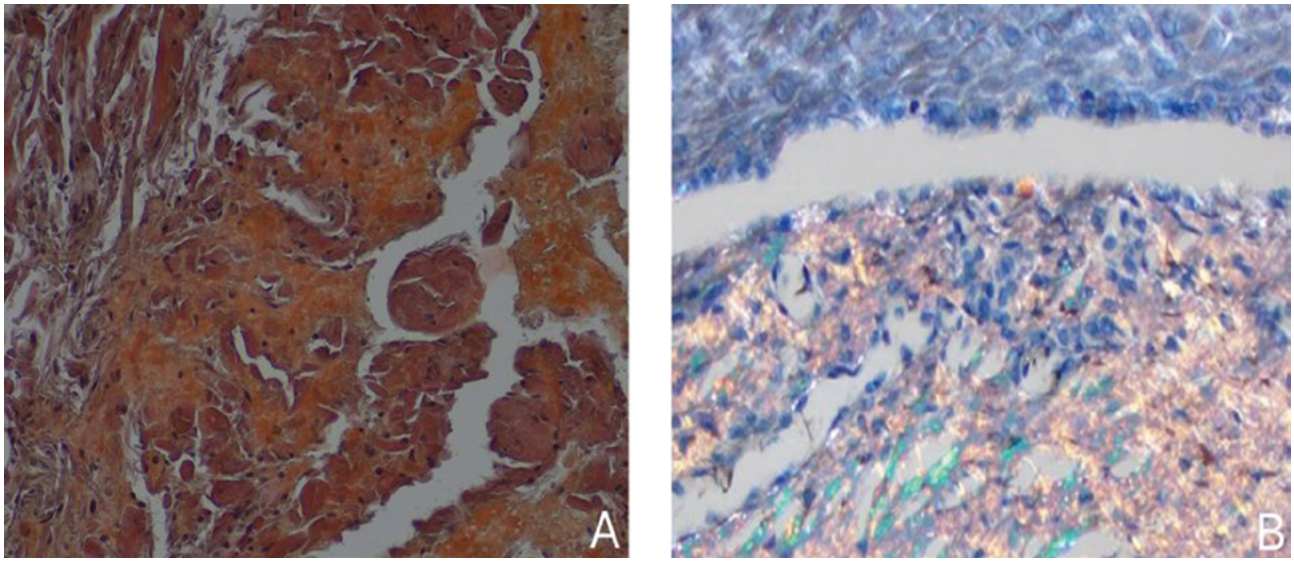

Figure 4. Histopathological examination of a skin biopsy specimen showed positive Congo red staining, indicating the presence of amyloid deposits (**A** – magnification 20×). Under polarized light, the amyloid deposits exhibited yellow-green birefringence (**B** – magnification 20×).

Folia Medica

the amyloidogenic protein. Sadly, she succumbed to cardiac failure 7 months after treatment initiation. Written informed consent for publication of this case report and any accompanying images was obtained from the patient's next of kin.

Discussion

Amyloidosis encompasses a broad spectrum of diseases characterized by the extracellular accumulation of amyloid fibrils, a proteinaceous substance, on organs and tissues.[1] Nearly 36 protein precursors have been found to result in systemic amyloidosis, 9 of which are known to infiltrate the heart, causing cardiac amyloidosis (CA).[3,4] Among these, the most prevalent forms are transthyretin cardiac amyloidosis (ATTR-CA), and light chain cardiac amyloidosis (AL-CA).[4] AL-CA is caused by the overproduction of immunoglobulin light chain proteins.[5] It has an estimated incidence of 8-12 cases per million individuals and exhibits a 3:2 male predominance.[5]

Clinical presentation of systemic AL amyloidosis is atypical and results from the protein deposition on various organs. The main organs involved include the kidneys, lungs, liver, peripheral nervous system, and skin.[6] Patients may exhibit sensorimotor peripheral neuropathy, postural hypertension, hepatomegaly with altered liver function tests, or nephrotic syndrome that progressively evolves into renal failure.[7] Macroglossia is a distinct feature highly specific for AL amyloidosis, sometimes accompanied by perioral or periorbital purpura.[7,8] Systemic symptoms such as lymphadenopathy, fatigue, or weight loss may also be present, further complicating the diagnostic process.[7] Cardiac involvement manifests with a wide spectrum of symptoms, including cardiac failure and conduction abnormalities such as atrial fibrillation, syncope, or sudden death.[9] Our case exhibited macroglossia with perioral purpura and lymphadenopathy, as well as dyspnea and pleural effusion attributed to cardiac failure.

Cardiac damage in AL amyloidosis is induced by multiple mechanisms. The deposition of amyloid fibrils within the myocardial tissue causes stiffness and diastolic dysfunction, ultimately leading to cardiomyopathy and conduction disturbances.[6,9] Myocardial damage is additionally exacerbated by the generation of reactive oxygen species (ROS) in high levels by the amyloidogenic light chains, leading to mitochondrial damage and cardiotoxicity.[10] Furthermore, the accumulation of amyloid fibrils is associated with the activation of pathways that lead to cell death and fibrosis, further compromising cardiac function.[10]

The diagnostic approach for AL amyloidosis should include a combination of blood differential, biochemical tests, and testing for monoclonal protein, such as serum free light assay, along with SPEP/UPEP with IFE.[6] Modern diagnostic techniques, including light microscopy, immunohistochemistry, immunoelectron microscopy, and mass spectrometry-based proteomics, aid in classifying the protein subunit.[8] Imaging studies, such as CT or magnetic resonance imaging (MRI) scans, might aid in identifying specific organ involvement. However, definitive diagnosis of AL amyloidosis relies on histopathological confirmation of amyloid deposits in tissue, indicated by positive Congo red staining and apple-green birefringence under a polarized-light microscope.[11] The abdominal fat pad serves as the most accessible and least invasive biopsy location.[12] In strong suspicion of systemic amyloidosis where the fat aspirate is negative, additional biopsy sites include the minor salivary gland, liver, endomyocardial region, or exploration via gastrointestinal endoscopy.[12,13] Additionally, a bone marrow biopsy is strongly recommended due to the frequent association of AL amyloidosis with multiple myeloma.[7,8] In our case, an endomyocardial biopsy was not deemed necessary because the diagnosis was established through the presence of amyloid deposits in abdominal fat and tongue specimens.

Standard methods such as ECG and echocardiography are usually helpful in identifying the extent of cardiac involvement. On ECG, AL-CA may exhibit diffuse low QRS voltages, a "pseudoinfarction pattern," or conduction abnormalities, such as atrial fibrillation, attributed to widespread atrial amyloid deposition on the myocytes and diastolic dysfunction.[2,8] Echocardiography typically reveals a restrictive cardiomyopathy pattern, characterized by a preserved ejection fraction (EF), increased ventricular wall thickness, and a "granular sparkling" appearance of the ventricular wall.[14] Diastolic dysfunction is one of the earliest pathophysiological impairments, worsening as myocardial infiltration progresses, whereas systolic function usually decreases in end-stage disease.[9] Ischemic change due to amyloid deposition on coronary arteries is a rare finding.[9] Additionally, cardiac magnetic resonance imaging is sensitive in detecting amyloid deposits and shows characteristic late gadolinium enhancement of the myocardial walls.[2,7] Our case manifested with diffuse low QRS voltages on ECG, as well as cardiac failure with preserved EF indicative of restrictive cardiomyopathy, and a "granular sparkling" appearance of the ventricular walls on echocardiogram.

Treatment of systemic AL amyloidosis focuses on reducing light chain production and managing the underlying plasma cell dyscrasia.[13] Recent advances include several treatment options, including dexamethasone, alkylating agents, proteasome inhibitors, and immunomodulatory drugs.[3] Combination regimens such as cyclophosphamide, bortezomib, and dexamethasone (CyBorD), along with monoclonal antibodies such as daratumumab, have been shown to reduce light chain deposition and improve organ function.[16]

Standard cardiac failure treatments (beta blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors) are often associated with adverse outcomes in cardiac AL amyloidosis.[5] Anticoagulation is the key to preventing thromboembolism in cases of atrial fibrillation.[2] The use of pacemakers or defibrillators remains challenging, while heart transplantation has shown limited efficacy in AL amyloidosis cases.[2] The role of autologous

stem cell transplantation in cases of AL amyloidosis with cardiac involvement remains under debate.[4]

Cardiac involvement is a strong predictor of survival and the most common cause of death in AL-CA.[15] Its prognosis remains poor, with a median survival of 4-6 months in advanced cardiac failure stages, compared to several years in AL amyloidosis patients without cardiac involvement.[7] Myocardial enzymes such as highly sensitive troponin T and NT-proBNP are considered prognostic markers of myocardial damage.[4] Furthermore, a 30% reduction in NT-proBNP has been proposed as a direct surrogate of cardiac response to therapy.[2] The Mayo 2012 staging system for cardiac AL amyloidosis stratifies patients into four stages (0–III) with worsening outcomes based on thresholds for troponin T, NT-proBNP, and the difference between involved and uninvolved serum-free light chains (dFLC).[3] Based on this staging system, our patient was stratified as stage III, with an expected median survival of 6.7 months.

Our case highlights a delayed diagnosis of cardiac AL amyloidosis. The classic phenotypic signs of the systemic disease were present for several years before the definitive diagnosis. Cardiac failure, as evidenced by the characteristic clinical, ECG, and echocardiogram features, had also probably existed for many years but had remained undetected. This case underscores the need for early recognition of cardiac AL amyloidosis in order to achieve life-saving outcomes and enhance patients' quality of life.

Conclusion

This case report highlights the critical importance of considering cardiac AL amyloidosis in all patients with unexplained cardiac failure with preserved EF. The delayed diagnosis and poor outcome in this case underscore the necessity for heightened clinical suspicion among all clinicians and the pursuit of appropriate diagnostic examinations, including tissue biopsy, to achieve an early diagnosis, which could prove life-saving, particularly in patients with cardiac involvement. Additionally, this case emphasizes the critical role of amyloid typing via mass spectrometry in confirming the diagnosis of AL amyloidosis and distinguishing it from other forms of systemic amyloidosis, particularly transthyretin amyloidosis (ATTR). This is especially relevant in clinical settings where amyloid typing may not be routinely available, yet remains essential for guiding targeted therapy and improving patient outcomes.

Author contributions

A.K. and A.M. conceptualized and designed the case report; A.K. and K.K. drafted the initial manuscript; N.C., M.T., and M.D. gathered and analyzed the clinical and pathological data; C.P. and E.M. supervised the study and provided critical revisions. All authors reviewed and approved the final manuscript.

Funding

The authors have no funding to report.

Competing interests

The authors have declared that no competing interests exist.

Acknowledgements

The authors have no support to report.

References

1. Palladini G, Merlini G. What is new in diagnosis and management of light chain amyloidosis? Blood 2016; 128(2):159–68.
2. Mankad AK, Sesay I, Shah KB. Light-chain cardiac amyloidosis. Curr Probl Cancer 2017; 41(2):144–56.
3. Taylor MS, Sidiqi H, Hare J, et al. Current approaches to the diagnosis and management of amyloidosis. Intern Med J 2022; 52(12):2046–67.
4. Adam RD, Coriu D, Jercan A, et al. Progress and challenges in the treatment of cardiac amyloidosis: a review of the literature. ESC Heart Fail 2021; 8(4):2380–96.
5. Barge-Caballero G, Barge-Caballero E, López-Pérez M, et al. Cardiac amyloidosis: Description of a series of 143 cases. Med Clínica Engl Ed 2022; 159(5):207–13.
6. Maurer MS, Elliott P, Comenzo R, et al. Addressing common questions encountered in the diagnosis and management of cardiac amyloidosis. Circulation 2017; 135(14):1357–77.
7. Rubin J, Maurer MS. Cardiac amyloidosis: overlooked, underappreciated, and treatable. Annu Rev Med 2020; 71(1):203–19.
8. Milani P, Merlini G, Palladini G. Light chain amyloidosis. Mediterr J Hematol Infect Dis 2018; 10(1):e2018022.
9. Gertz MA, Dispenzieri A, Sher T. Pathophysiology and treatment of cardiac amyloidosis. Nat Rev Cardiol 2015; 12(2):91–102.
10. Mugnai G, Cicoira M, Rossi A, et al. Syncope in cardiac amyloidosis and chronic ischemic heart disease: A case report. Exp Clin Cardiol 2011;16(2):51.
11. Diomede L, Romeo M, Rognoni P, et al. Cardiac light chain amyloidosis: the role of metal ions in oxidative stress and mitochondrial damage. Antioxid Redox Signal 2017; 27(9):567–82.
12. Lv P, Li Y, Wu L, et al. Case report: systemic amyloidosis involving the heart and skeletal muscle. Front Cardiovasc Med 2022; 9:816236.
13. John S, Subba P, Aramugam A, et al. A serious warning: A case report on localized amyloidosis of the oral cavity. Indian J Pathol Microbiol 2025; 68(1):212–5. Available from: https://journals.lww.com/10.4103/ijpm.ijpm_720_23
14. Indu S, Roy I, Tewari R, et al. Oral amyloidosis: A case report and diagnostic algorithm. J Oral Maxillofac Pathol 2021; 25(3):559.
15. Tsai SB, Seldin DC, Wu H, et al. Myocardial infarction with "clean coronaries" caused by amyloid light-chain AL amyloidosis: a case report and literature review. Amyloid 2011; 18(3):160–4.
16. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med 2021; 385(1):46–58.