International Journal of Research in Medical Sciences
Sarwala SP et al. Int J Res Med Sci. 2025 Jun;13(6):2637-2639
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20251660

Case Report

Unravelling the cardiac conundrum of amyloidosis: an experience from a tertiary care centre

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Received: 08 April 2025
Revised: 10 May 2025
Accepted: 20 May 2025

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ABSTRACT

Amyloidosis encompasses a spectrum of diseases caused due to extracellular deposition of misfolded proteins in body. The most common subtypes that infiltrate cardiac tissue are AL, ATTRwt (wild type), ATTRv (mutated) and Isolated atrial amyloidosis. Here, we elaborate such an interesting case of cardiac AL amyloidosis. A 69-year-old male presented with shortness of breath and restrictive cardiomyopathy. Further endomyocardial biopsy showed acellular, light eosinophilic deposit. Direct immunofluorescence showed lambda light chain restriction, concordant with elevated serum free λ light chain level. Finally, positive Congo red stain with apple green birefringence under polarised light clinched the diagnosis of Cardiac AL Amyloidosis. Endomyocardial biopsy with congo red stain and immunofluorescence is indispensable for diagnosis and subtyping of AL amyloidosis. This sets apart other amyloid subtypes and cardiac light chain deposition disease. Early diagnosis of cardiac amyloidosis subtype is imperative to guide the therapy and evaluate the prognosis of the patient.

Keywords: Cardiac amyloidosis, Endomyocardial biopsy, Congo red, Lambda light chain restriction

INTRODUCTION

Amyloidosis encompasses various inherited and inflammatory disorders where fibrillary proteins form extracellular deposits leading to tissue damage and functional compromise.[1] According to International Society of amyloidosis, 42 protein types are amyloidogenic in humans.[2,3] At least 12 of them are known to involve the heart or great vessels.[4]

Most common subtypes that infiltrate cardiac tissue are AL (immunoglobulin light chain amyloidosis), ATTRwt (senile systemic amyloidosis), ATTRv (familial amyloidotic neuropathy) and Isolated atrial amyloidosis (IA), resulting in a restrictive cardiomyopathy.[5] Similar clinical and histopathological presentation is also noted in cardiac light chain deposition disease (LCDD). Here, we present such a tricky case which presented a diagnostic dilemma.

CASE REPORT

A 69-year-old male presented with shortness of breath since the last 5 months. He also experienced abdominal discomfort, pedal swelling and altered olfactory sensation. On physical examination, patient had pitting oedema with elevated jugular venous pressure (JVP). Detailed laboratory workup showed mildly elevated serum urea 33 mg/dl and consistently elevated troponin I (TnI) (0.14-0.23 ng/ml).

Remaining liver function tests, thyroid function tests and serum electrolytes were unremarkable. Electrocardiography (ECG) showed poor R wave progression. Consecutive Echocardiography with Doppler study revealed restrictive cardiomyopathy (RCMP) with reduced ejection fraction (35%), moderate mitral regurgitation, moderate to severe tricuspid regurgitation and grade III left ventricular diastolic dysfunction

(LVDD). Subsequently done cardiac MRI revealed: mild asymmetric wall thickening of interventricular septum with diffuse global hypokinesia of cardiac chambers. Coronary angiography (CAG) was unremarkable.

To investigate further, endomyocardial biopsy was done, which showed myocardial fibres and intervening fibroconnective tissue stroma.

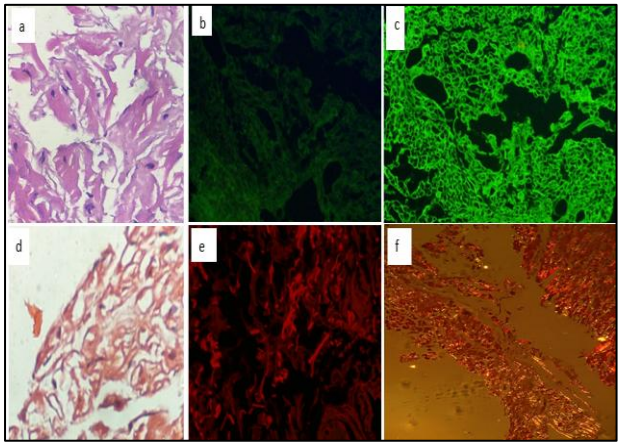

Figure 1: λ restricted cardiac amyloidosis (a) H&E 400X: Deposits of acellular light eosinophilic material in between myocardial fibres. (b) DIF: κ: negative. (c) DIF: λ: 3+ pericellular positivity around myocardiocytes. (d) 400X pale rose pink congophilic deposit in Congo red stain in light microscope. (e) amyloid appears red with Congo red stain under DIF microscope. (f) Congo red positive amyloid deposits show apple green birefringence under polarizing microscope.

Interstitial pericellular deposits of acellular light eosinophilic material in between myocardial fibres was noted. Occasional arteriole sized blood vessels were uninvolved (Figure1a). Direct immunofluorescent (DIF) findings: kappa: negative (Figure 1b); lambda: 3+ pericellular positivity around myocardiocytes (Figure 1c).

To corroborate with DIF findings, results of free light chain (FLC) analysis showed a marked elevation in serum free λ light chain level (673 mg/l) with an abnormal κ/ λ ratio of 0.0772. Follow up bone marrow biopsy to rule out plasma cell dyscrasia, revealed normal plasma cell percentage. Considering the lambda light chain restriction in DIF, diagnostic possibilities were AL-amyloidosis, light chain deposition disease (LCDD). For clinching the diagnosis, Congo red stain in tissue showed congophilic deposit within the stroma (Figure 1d, 1e), which had apple green birefringence under polarised light (Figure 1f).

Final diagnosis was cardiac amyloidosis, AL type (lambda light chain restricted). Following which, the patient received 2 cycles of chemotherapy (CyBorD-Cyclophosphamide, bortezomib and dexamethasone). Unfortunately, a month later, patient returned to the emergency department with chest pain, suffered from pulseless electrical activity arrest and expired.

DISCUSSION

Cardiac amyloidosis, may be a sequela of focal amyloid deposition in subendocardial tissue (hampering the conduction, reflected in ECG) and within the myocardium between the muscle fibres (causing pressure atrophy of myocardial fibres, RCMP).[1] It has been historically difficult to diagnose due to non-specific presentation. This case presented with dyspnoea, pitting oedema, elevated JVP and TnI. Similar studies by Edwards et al, Taiwo et al, Flodrova et al showed non-specific signs and symptoms including fatigue, exertional dyspnoea, macroglossia, rales, pitting oedema, abdominal distension, elevated JVP, and a third heart sound.[5-7] Prior studies showed that cardiac markers: troponin T, troponin I, N terminal pro-brain natriuretic peptide reflect the magnitude of myocardial involvement.[6,7] Similarly, we found consistently elevated TnI in our case. ECG showed poor R wave progression. Discrepant studies have divulged low voltage of the QRS complex, a pseudo infarction pattern consistent with cardiac amyloidosis AL type.[5-7] In our case, echocardiograph revealed reduced ejection fraction (35%), grade III LVDD, RCMP. MRI showed mild asymmetric wall thickening of interventricular septum, diffuse global hypokinesia of cardiac chambers. Concordant studies found the hallmark findings to be concentric hypertrophy, a thickened interventricular septum, and diastolic dysfunction.[5,7]

Biopsy showed interstitial pericellular deposits of acellular light eosinophilic material in between myocardial fibres (Figure1a). Osanami et al found amyloid deposits around cardiomyocytes; along and inside the endocardial layer of the myocardium and rarely around small blood vessles.[9] Flodrova et al states that the two main types of interstitial involvement in myocardium are pericellular and nodular, with a continuous spectrum between the two.[7] Lambda light chain restriction in DIF (Figure 1b, c) and altered serum FLC ratio led to a diagnostic dilemma between cardiac AL amyloidosis and LCDD. According to Osanami et al, these 2 are branches of the same tree with identical clinical, histopathological and DIF presentation.[9] Congo red stain and electron microscope differentiates the two.

Amyloid deposits have 3 characteristic properties: affinity for Congo red stain (gold standard) with birefringence under polarised light (Figure 1d, 1f), organised ultrastructure with rigid non-branching fibrils (8-12 nm diameter) and distinct X-ray crystallographic diffraction patterns. The polarising shadow may be circumvented by use of Thioflavin T stain or fluorescence microscopy (Figure 1e). Apart from the target organ (cardiac tissue), abdominal fat, rectal and bone marrow biopsies may be used.[8] Amyloid typing is done by frozen section immunofluorescence (FSIF), paraffin section immunofluorescence (PSIF), paraffin section

immunohistochemistry (PSIHC), immunogold labelling in electron microscope.[8] In this case, we used FSIF. Immunofluorescence has higher sensitivity and specificity for diagnosing AL than AHL and AH.[2] Also, FSIF is superior to immunoperoxidase based PSIHC for subtyping of amyloid.[4] Determination of subtype is absolutely vital as treatment and prognosis is individualised. AL amyloidosis has the worst prognosis and its treatment is plasma cell clone directed chemotherapy followed by autologous hematopoietic stem cell transplant. Familial amyloidotic neuropathy, known as ATTRm (mutated)/ATTRv (variant), is treated by liver transplantation. Whereas senile systemic amyloidosis, ATTRwt is treated symptomatically.[1,2,5-7]

CONCLUSION

Cardiac amyloidosis should be suspected in any patient that presents with restrictive cardiomyopathy. Cardiac biomarkers and advanced imaging techniques may be supportive, but endomyocardial biopsy for amyloid deposition is the ultimate benchmark for confirmation. Congo red stain with birefringence under polarising light is indispensable for diagnosis. Subtyping is done by convenient and effective methods like FSIF. Close differential diagnosis of cardiac AL (λ restricted) amyloidosis is cardiac LCDD and other subtypes of amyloidosis (ATTRv/ATTRwt). Early diagnosis and subtyping of amyloidosis is absolutely imperative for effective treatment and better prognosis of patient.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Sarwala SP, Karmakar S, Basu K. Unravelling the cardiac conundrum of amyloidosis: an experience from a tertiary care centre. Int J Res Med Sci 2025;13:2637-9.