ESC European Society of Cardiology

European Heart Journal - Case Reports (2019) **3**, 1–7
doi:10.1093/ehjcr/ytz162

CASE REPORT
Heart failure

A case report of cardiac amyloidosis presenting with chronic pericardial effusion and conduction block

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Received 7 April 2019; first decision 17 May 2019; accepted 3 September 2019; online publish-ahead-of-print 24 September 2019

Background Amyloidosis is caused by the deposition of abnormal proteins in the extracellular space of various organs. The clinical features of amyloidosis depend on the type of amyloid protein and the organ system involved.

Case summary A 51-year-old woman developed complete heart block which warranted a permanent pacemaker insertion. She was referred for evaluation of chronic pericardial effusion. The patient had stable vital signs and muffled heart sounds on examination of the cardiovascular system. Her chest X-ray film showed a permanent pacemaker *in situ*, and echocardiogram showed a chronic pericardial effusion without features of tamponade. On further evaluation, she was found to have an M band on serum electrophoresis, elevated free light chain ratio and amyloid deposits in bone marrow biopsy. Technetium pyrophosphate (Tc-PYP) scintigraphy was consistent with cardiac amyloidosis.

Discussion Cardiac amyloidosis can have diverse clinical presentations. Chronic pericardial effusion and conduction block can be a rare presentation of cardiac amyloidosis and needs to be considered while evaluating the same. Cardiac magnetic resonance imaging and Tc-PYP imaging can be used in establishing the diagnosis of cardiac amyloidosis, if endomyocardial biopsy is not feasible.

Keywords Cardiac amyloidosis • Pericardial effusion • Complete heart block • Case report

Learning points

- Cardiac amyloidosis is seen in 20% of patients with systemic amyloidosis and can have diverse clinical presentations.
- Cardiac amyloidosis can present with chronic non-resolving pericardial effusion or conduction abnormality like complete heart block due to infiltration of amyloid into the conduction system.
- Cardiac magnetic resonance imaging and technetium pyrophosphate imaging can be used in establishing the diagnosis of cardiac amyloidosis, if endomyocardial biopsy is not feasible.

Introduction

Amyloidosis is caused by dysfunctional protein folding leading to deposition of amyloid fibrils in the extracellular space leading to protean clinical manifestations.[1] Involvement of various organs like the kidney, heart, liver and bone marrow, causes organ dysfunction leading to morbidity and mortality. Cardiac involvement is seen in about 20% of patients with systemic amyloidosis.[2] Patients with cardiac involvement can present with cardiomyopathy, heart failure, or arrhythmias. Here we describe a rare presentation of cardiac amyloidosis in a patient who presented to us with complete heart block and pericardial effusion.

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Handling Editor: Tom de Potter

Peer-reviewers: Riccardo Liga and Joseph Moutiris

Compliance Editor: Mark Philip Cassar

Supplementary Material Editor: Peregrine Green

Timeline

Initial presentation	Left-sided non-pleuritic chest pain and dyspnoea
2 months later	Two episodes of syncope, evaluated and diagnosed with complete heart block, permanent pacemaker implanted
	Found to have pericardial effusion which was treated with an empiric course of anti-tuberculosis therapy
10 months later	Pericardial effusion did not resolve. Hence, admitted for re-evaluation
	Chest X-ray film showed cardiomegaly and the presence of a pacemaker *in situ*
	Echocardiogram showed large pericardial effusion and global left ventricular systolic dysfunction
	Serum protein electrophoresis M band positive, Serum free light chain ratio elevated (κ/λ) 5.3
	Computed tomography scan of the thorax confirmed cardiomegaly and pericardial effusion
	The bone marrow biopsy showed pale eosinophilic deposits in the vessel wall and Congo red stain revealed reddish-orange deposits which showed green birefringence under polarizing microscope thus confirming the presence of amyloid
	Technetium pyrophosphate scintigraphy showed moderate uptake of tracer equal to bone activity (Grade 2) in the region of the heart consistent with cardiac amyloidosis
	Symptomatic improvement with fluid restriction, diuretics, and angiotensin-converting enzyme-inhibitors
	Though further evaluation and treatment was planned patient got discharged to continue further treatment in a hospital near her hometown. No further follow-up

Case presentation

A 51-year-old woman, without any previous comorbidities, illnesses, allergies or addictions, presented with a history of persistent, left-sided, non-radiating, non-pleuritic, chest pain, and insidious onset, gradually progressive dyspnoea of 1-year duration. She had two episodes of syncope, 8 months before. She did not give any history of constitutional symptoms including fever or loss of weight.

Upon initial evaluation in another hospital, she was diagnosed with complete heart block which required a permanent pacemaker insertion. She was also found to have pericardial effusion which was treated with an empiric course of anti-tuberculosis therapy (ATT). Despite taking ATT for 8 months, she did not have resolution of the pericardial effusion and was referred to our hospital for further evaluation.

On examination, she was found to be afebrile, with a blood pressure of 100/70 mmHg in both upper limbs without any evidence of pulsus paradoxus. Her heart rate was 78 beats/min, respiratory rate was 18 breaths/min, and arterial oxygen saturation on room air was 98%.

Examination of the cardiovascular system showed muffled heart sounds and an absence of murmurs, rubs, or gallops. Examination of other systems was normal.

A provisional diagnosis of chronic symptomatic pericardial effusion was made, and she was evaluated further. Chest X-ray film showed cardiomegaly and the presence of a pacemaker *in situ* (*Figure 1*). Echocardiogram showed large pericardial effusion with a maximum extent of 27 mm posteriorly. It also showed evidence of global left ventricular systolic dysfunction with an ejection fraction of 41.3%, tricuspid annular plane systolic excursion of 19 mm, and *E/A* ratio of 1.9. There was global hypokinesia, mild mitral regurgitation, and myocardial 'sparkling' was noted in the septum (*Figure 2*). Details of laboratory investigations are shown below (*Table 1*).

Computed tomography scan of the thorax and abdomen did not give any significant findings other than cardiomegaly and pericardial effusion. Autoimmune workup and serum angiotensin-converting enzyme (ACE) levels were normal.

In view of the presence of chronic pericardial effusion, the differentials that were considered included infections (tuberculosis, post-viral), connective tissue disorders (systemic lupus erythematosus, rheumatoid arthritis, scleroderma), infiltrative disorders (amyloidosis, sarcoidosis, histiocytic disorders), malignancy (lymphoma or secondary pericardial effusion from lung, oesophageal, or breast malignancy), and IgG4-related disease.[3]

Relevant investigations for all but one of the differentials considered were negative. Serum protein electrophoresis showed an M band. The bone marrow biopsy showed pale eosinophilic deposits in the vessel wall and Congo red stain revealed reddish-orange deposits which showed green birefringence under polarizing microscope thus confirming the presence of amyloid (*Figure 3*). Serum free light chain (sFLC) ratio was elevated. A cardiac magnetic resonance imaging (MRI) scan could not be done as the patient's pacemaker was not MRI compatible. Technetium pyrophosphate (Tc-PYP) scintigraphy showed moderate uptake of tracer equal to bone activity (Grade 2) in the region of the heart consistent with cardiac amyloidosis (*Figure 4*). The patient did not give consent for a pericardial or myocardial biopsy. A final diagnosis of systemic amyloidosis with cardiac involvement causing systolic dysfunction, chronic pericardial effusion, and complete heart block was made.

She had good clinical improvement with medical management. Though further evaluation and specific treatment for systemic amyloidosis were planned, she wished to continue further treatment in a hospital near her hometown, and hence was referred there. Details of further follow-up were not available.

Discussion

Amyloidosis is a disease where deposition of beta-pleated fibrils of the various proteins, in the extracellular space of organs like the kidney, heart, liver, etc. causes organ dysfunction leading to morbidity

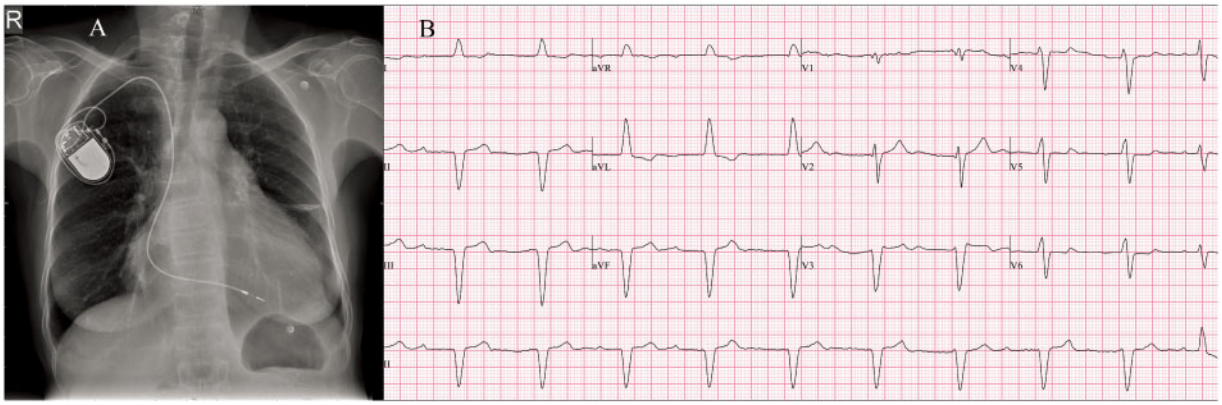

Figure 1 (*A*) Chest X-ray film showing cardiomegaly and permanent pacemaker *in situ*. (*B*) Electrocardiogram showing broad QRS complexes.

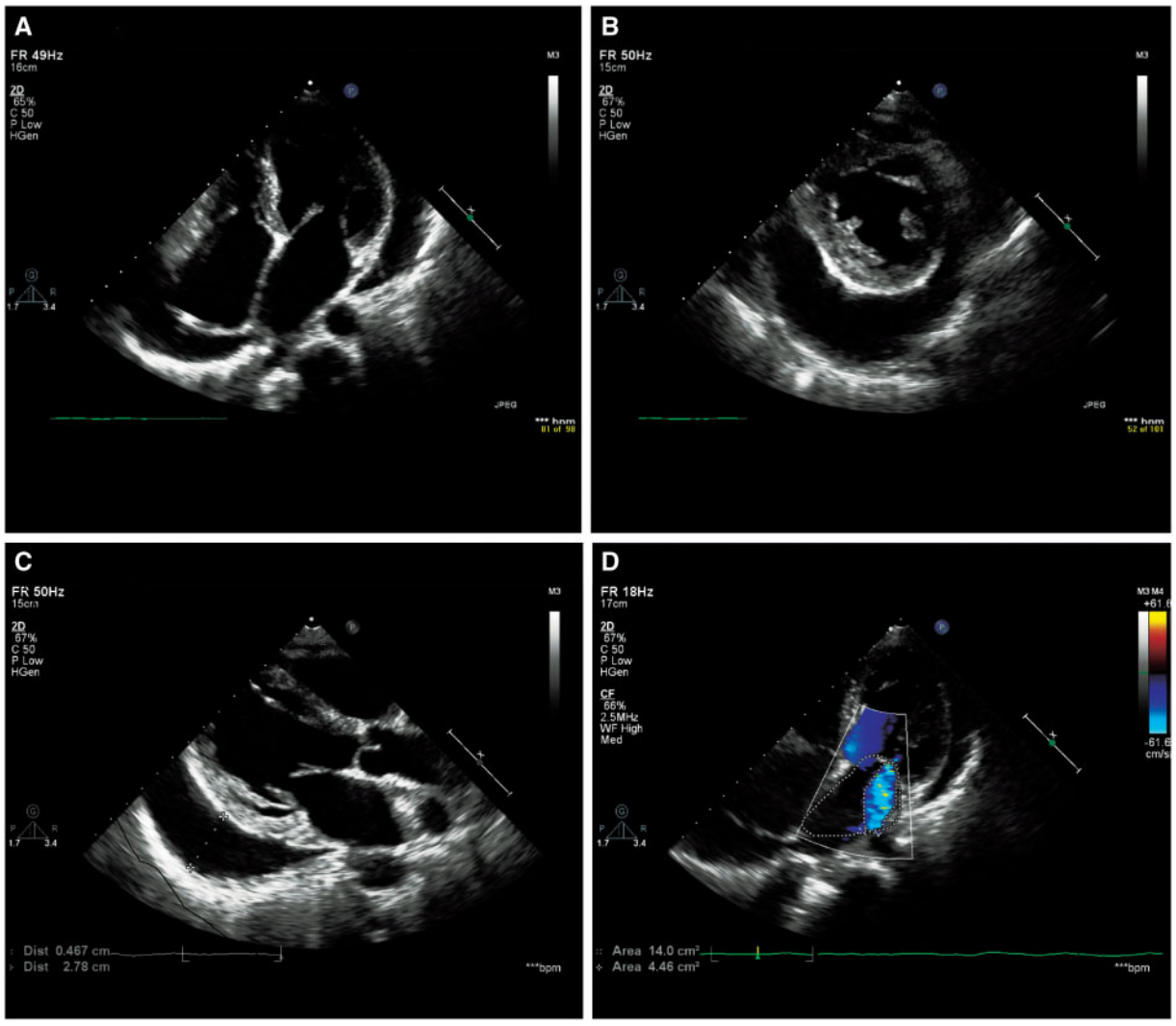

Figure 2 Echocardiogram showing left ventricular hypertrophy and pericardial effusion. (*A*) Apical four-chamber view. (*B*) Short-axis view. (*C*) Parasternal long-axis view. (*D*) Mitral regurgitation.

Table 1 Laboratory investigations

Investigations	Results[a]
Haemoglobin (g/dL)	14.6 (11–15)
Total count (/cu mm)	5600 (400012 000)
Differential count (%)	N 40, L 47, M 8, E5, B 0
Platelet count (/cu mm)	1 82 000 (1 50 000–4 50000)
HIV, HBV, HCV serology	Negative
Thyroid stimulating hormone (TSH) (μIU/mL)	4.6 (0.3–4.5)
Serum cortisol (μg%)	9.1 (7–25)
Serum sodium (mmol/L)	136 (135–145)
Serum potassium (mmol/L)	4.1 (3.5–5)
Serum creatinine (mg%)	0.61 (0.5–1.1)
Erythrocyte sedimentation rate (ESR) (mm/h)	10 (5–20)
C-reactive protein (CRP) (mg/L)	<3.16 (<3.16)
Anti-nuclear antibody (ANA)	Negative
Rheumatoid factor (RF) (IU/mL)	<9.69 (<9.69)
Serum angiotensin-converting enzyme (ACE) (U/L)	7 (8–52)
Serum M band (g%)	0.4
Serum free light chains (sFLC) κ and λ (mg/L)	κ = 160, λ = 30 (κ: 3.3–19.4, λ: 5.7–26.3)
sFLC ratio (κ/λ)	5.3 (0.26–1.65)
Pericardial fluid total white cell count (/cu mm)	310 (N 8%, L 92%)
Pericardial fluid total red cell count (/cu mm)	30 (none)
Pericardial fluid glucose (mg/dL)	88 (70–14)
Pericardial fluid protein (g/dL)	4.9 (0–3)
Pericardial fluid adenosine deaminase (ADA) (U/L)	5 (0–30)
Pericardial fluid cytology	No malignant cells

[a]Normal ranges for test results given in parentheses.

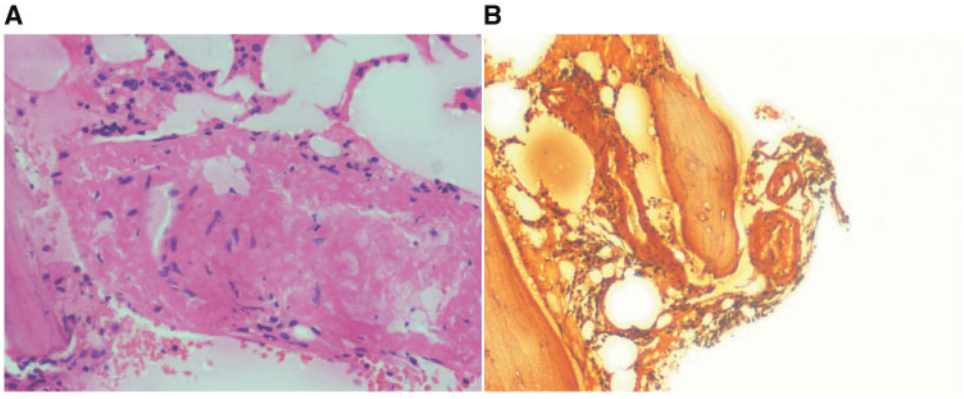

Figure 3 Photomicrograph of bone marrow biopsy (*A*) showing pale eosinophilic material around blood vessels (Haematoxylin and Eosin stain, 40×). (*B*) Congo red stain showing reddish-orange amyloid deposition in the vessel wall (100×).

and mortality. The three most common types of amyloidosis affecting the heart are light chain (AL), familial or senile (ATTR), and secondary (AA) amyloidosis. The amyloid protein in these three types of amyloidosis are monoclonal light chains secondary to a plasma cell dyscrasia, the wild-type (non-mutant) or mutated transthyretin, and fragments of serum amyloid A protein (an acute phase reactant), respectively.

Cardiac amyloidosis can present with heart failure, involvement of the conduction system, pericardial disease, thromboembolism, stroke, syncope, or sudden cardiac death. A progressive disease of

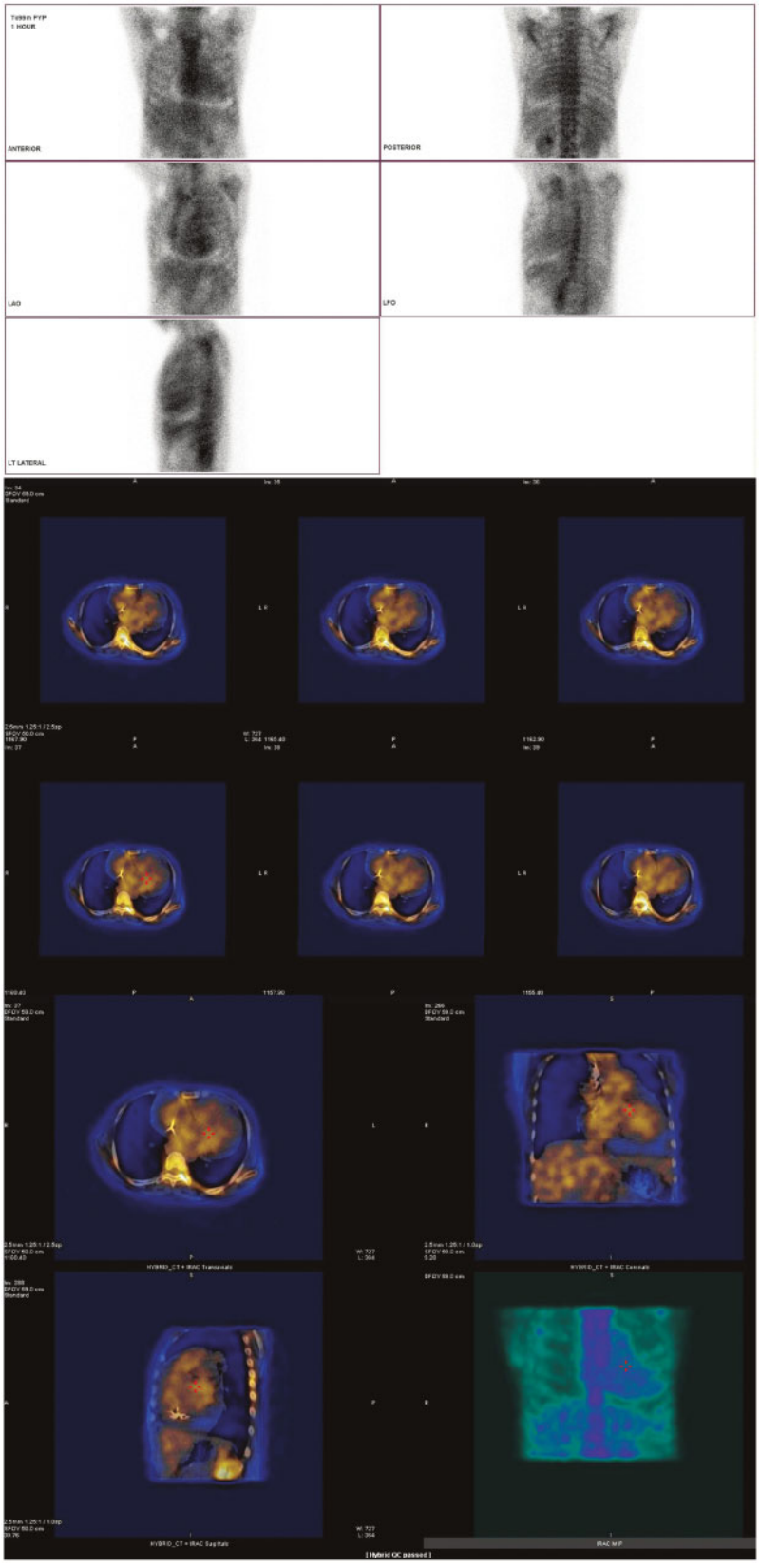

Figure 4 Nuclear imaging with technetium pyrophosphate showing moderate uptake of tracer equal to bone activity in the region of the heart consistent with ATTR cardiac amyloidosis.

the conduction system is more common with ATTR amyloidosis when compared to AL amyloidosis. High-degree atrioventricular block requiring permanent pacemaker implantation is uncommon but described and was seen in our patient.[4] Pericardial effusion and rarely cardiac tamponade can be caused due to amyloid deposition in the pericardium.

Electrocardiogram changes in patients with cardiac amyloidosis include low-voltage in the limb leads (46%) and a pseudo-infarct pattern (47%).[5] Echocardiography is a non-invasive diagnostic tool which can show an increase in wall thickness and diastolic dysfunction at an early stage. The myocardium may also have a granular or a sparkling appearance. However, this appearance has a low sensitivity and specificity (26–36% and 71–81%, respectively).[6] Other non-invasive diagnostic methods include cardiac MRI and Tc-PYP imaging.[7] Patients like the one presented here, who have contraindications to cardiac MRI, can undergo Tc-PYP imaging which has been proposed as a non-invasive modality to reliably diagnose cardiac amyloidosis. This modality is highly sensitive for ATTR amyloidosis.[8] Although endomyocardial biopsy was not obtained in our patient, evidence of amyloidosis was established in the bone marrow. The presence of M band and abnormal sFLC ratio pointed towards a diagnosis of AL amyloidosis while the Tc-PYP scintigraphy showing moderate uptake equal to bone (Grade 2) was suggestive of ATTR amyloidosis.[8] This posed a diagnostic dilemma. Technetium pyrophosphate scintigraphy is very sensitive for ATTR amyloidosis. Also, monoclonal gammopathy of undetermined significance (MGUS) can be seen in about 3.5% of the population above 50 years of age.[9] Hence ATTR amyloidosis with co-existent MGUS is the most likely diagnosis in our patient.

Medical management of cardiac amyloidosis consists of treatment of heart failure and treatment of the underlying disease. The cornerstone of medical management of heart failure due to cardiac amyloidosis consists of loop diuretics. The role of ACE inhibitors/angiotensin receptor blockers and beta-blockers is a subject of debate. Patients with severe heart failure may require left ventricular assist devices and those with significant conduction system disease may need permanent pacemaker insertion with or without an implantable cardioverter-defibrillator. Atrial fibrillation and thrombo-embolic disease may require rate control therapy and overall anticoagulation, respectively. Specific therapy for AL amyloidosis is chemotherapy followed by autologous stem cell transplantation. Familial ATTR amyloidosis requires liver transplantation; this is not indicated in senile systemic amyloidosis.[10] Tafamidis is a selective transthyretin kinetic stabilizer molecule that inhibits the amyloid cascade and is being investigated as a potential therapy for senile and familial ATTR amyloidosis.[11]

Conclusions

Cardiac amyloidosis is seen in about 20% of patients with systemic amyloidosis and can have diverse clinical presentations. Chronic non-resolving pericardial effusion or conduction abnormality like complete heart block due to infiltration of amyloid into the conduction system can occur rarely. Cardiac MRI and Tc-PYP imaging can be used in establishing the diagnosis of cardiac amyloidosis with ATTR amyloidosis, if endomyocardial biopsy is not feasible. ATTR amyloidosis can sometimes co-exist with MGUS.

Lead author biography

Dr Kevin John John is a doctor at the Believers Church Medical College Hospital, Tiruvalla. He completed his undergraduate training and internal medicine residency from Christian Medical College, Vellore, India. His areas of interest include heart failure, critical care medicine and health economics.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Acknowledgements

The authors would like to thank Dr John K. John for reviewing the manuscript.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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