Case Report

Cardiac amyloidosis presenting as recurrent acute coronary syndrome with unobstructed coronary arteries: Case report

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ABSTRACT

Amyloidosis is a systemic disorder characterized by the deposition of mis-folded protein molecules within various organs. Cardiac involvement may be the presenting feature of this condition or may be identified incidentally during investigation for amyloidosis affecting other organs. The presence and severity of cardiac involvement varies with the type of amyloidosis.

Irrespective of the subtype, patients with cardiac amyloidosis usually present with symptoms of heart failure with echocardiography showing features of restrictive cardiomyopathy. The usual cardiac symptoms noted in patients with amyloidosis include dyspnea, peripheral edema, and palpitations secondary to arrhythmias. Chest pain secondary to myocardial ischemia is an unusual presentation of cardiac amyloidosis, and is attributed to the deposition of protein molecules in the coronary microvasculature. We describe the case of a patient who presented with recurrent cardiac ischemia secondary to amyloidosis.

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1. Case presentation

A 75-year-old man was admitted to the coronary care unit with symptoms of chest pain for the past 4 h. He gave a history of exertional chest pain and breathlessness over the previous 3 months. His coronary risk factors included dyslipidemia, and he was an ex-smoker. There was no significant family history and he had no significant medical or surgical conditions. On examination, he was hemodynamically stable. Precordial auscultation revealed normal heart sounds with no added features and there was no dependent edema or visible jugular venous pulse. Examination of other systems did not show any significant abnormalities.

His initial ECG showed ST-segment depression involving precordial leads V4, V5, and V6 (Fig. 1a). His chest X-ray was unremarkable with no features of pulmonary edema. Serial cardiac markers showed a rise in the level of troponin T from an initial value of 50–73 after 12 h. The patient was managed as non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and also received intravenous nitrate infusion and morphine, and his pain subsided. Repeat ECG showed resolution of the dynamic changes noted initially (Fig. 1b) Serial cardiac markers showed a rise
in the level of troponin T from an initial value of 50–73 after 12 h.

Coronary angiography (Fig. 2a, b) demonstrated nonobstructive left anterior descending (LAD) and right coronary artery (RCA) disease. His echocardiogram showed mild-moderate mitral regurgitation with normal biventricular size and function. He developed further chest pain in the ward the day after the coronary angiography, with ECG showing ST-segment depression in V4 to V6. A repeat angiography was performed with intravascular ultrasound and optic coherence tomography (OCT) to assess the severity of the LAD and RCA lesions. This confirmed that these were only mild and nonobstructive, with no evidence of focal plaque rupture. During the procedure, coronary spasm was noted in the mid RCA, which resolved with intracoronary nitrates. It was felt that the patient’s symptoms could be secondary to coronary spasm and he was discharged the following day on medications including oral nitrate and calcium channel blocker.

He presented again the following week with further chest pain, shortness of breath, orthopnea, and paroxysmal nocturnal dyspnea. While his clinical examination did not reveal any new findings, chest X-ray showed features of pulmonary vascular congestion and ECG again showed dynamic ST depression involving v4 to v6. His blood tests revealed a troponin T of 1050 and NT-pro BNP of 5042. A diagnosis of NSTE-ACS was made.

Repeat echocardiogram showed mild impairment of his left ventricular (LV) function with an ejection fraction (EF) of 42% (Fig. 3a). A cardiac MR was performed, which also demonstrated mild LV impairment. T2-weighted images showed increased signal in the mid to apical anteroseptal wall. However, it did not reveal any evidence of contrast enhancement to suggest infiltration, fibrosis, or previous infarction; and there were no features of myocarditis (Fig. 2c, d). The patient responded to standard heart failure treatment including diuretics and was subsequently discharged.

The patient was readmitted a week later with further chest pain and breathlessness with a troponin T of 111 and 118 at

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**Fig. 1** – ECG at admission demonstrating ST changes (a), and ECG at baseline once symptoms have settled (b).

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**Fig. 2** – Coronary angiography demonstrating nonobstructed coronaries (a, b), and Cardiac MRI showing nonspecific patchy basal inferior and inferoseptal contrast enhancement (c, d).
admission and after 12 h, respectively. A repeat echocardiogram showed moderate LV impairment with an EF of 35%. A repeat cardiac MR was hence performed, which confirmed moderate LV impairment. It also showed mild wall thinning in basal inferior and inferoseptal wall extending to the mid LV with patchy contrast enhancement within the basal inferoseptal wall. A cardiomyopathy screening was performed.

Urine electrophoresis identified the presence of Bence Jones protein type K. Plasma electrophoresis showed a significantly elevated kappa to lambda ratio at 129.35 (0.26–1.65). Bone marrow aspirate cytology revealed small monoclonal kappa restricted plasma cells, suggestive of plasma cell dyscrasia. Bone marrow biopsy demonstrated active marrow with no evidence of myeloma; however, there were 7% plasma cells and occasional Mott cells. An abdominal fat biopsy was performed, which was also analyzed at the National Amyloidoid Centre, London. The presence of amyloid was demonstrated by the staining of amorphous material with Congo red that displayed apple-green birefringence when viewed under high-intensity cross-polarized light. Amyloid deposits were present throughout. Histochemical staining of the amyloid deposits was performed using monospecific antibodies reactive with serum amyloid A protein (SAA), transthyretin (TTR), and with kappa and lambda immunoglobulin light chains. The amyloid stained with antibodies to kappa light chains.

A radionuclide uptake scan (99mTechnetium PYP) showed extensive uptake of 99mTc within the heart that was equal to or more than that of sternal uptake (grade: 3–4), which was suggestive of cardiac amyloidosis (Fig. 3b, c, d).

2. Discussion

Amyloidosis is a rare systemic disorder, with an annual incidence of 1–5 cases per 100,000 people, and is characterized by deposition of abnormal amyloid fibrils in various tissues altering their normal physiological function.1-2 Amyloidosis AL is the commonest type of amyloidosis diagnosed, and is associated with cardiac involvement of variable extent in almost 70% of the cases.3 The disease typically presents as a restrictive cardiomyopathy secondary to interstitial amyloid deposition; however, it can uncommonly present with ischemic symptoms.4

The pathophysiology, behind this presentation, is the progressive luminal narrowing of small intramural coronary arteries caused by amyloid deposition in the arterial vessel wall resulting in myocardial ischemia and impairment.5 The patient typically presents with ischemic chest pain, ECG changes, and a rise in cardiac marker, and respond to antianginal therapy. A retrospective study involving histopathological review of myocardial tissue from 98 patients with AL amyloidosis showed that 66% patients had intramural amyloid deposits. However, only 25% of these patients had any symptoms suggestive of ischemia.5

The extent of vascular involvement in cardiac amyloidosis is variable and depends on the type of amyloidosis. A study looking at the endomyocardial biopsy samples of 100 patients with cardiac amyloidosis showed that vascular involvement was more common in AL amyloidosis (88%) compared to patients with senile amyloidosis (27%).6,7 There is, however, considerable variation in the extent of vascular involvement amongst patients. Literature review suggests that amyloidosis can sometimes be confined to the intramural coronary arteries, with minimal or no evidence of interstitial involvement, as in this case.5-7 These cases are rare, making up only 1–2% of patients with cardiac amyloidosis.1 The prognostic significance of amyloid deposits in the intramural coronaries remains unclear. While it can be argued that this results in ischemia and subsequent infarction with myocardial impairment, one study did not find any significant difference in the median survival interval from diagnosis to either death or transplant between patients with intramural coronary amyloidosis and patients without evidence of intramural amyloid deposition.5

Diagnosis, in this subgroup (without significant interstitial involvement), can be challenging since echocardiographic and cardiac MR findings are nonspecific. Similarly, the mild elevation left ventricular filling pressures, which may be noted in cardiac catheterization, are nonspecific. Coronary angiography is typically normal as the infiltration is predominantly microvascular. Consequently, the diagnosis of this form of cardiac amyloid is often delayed. The prognosis of AL amyloidosis depends on the extent of cardiac involvement and
elevation of the troponin and NT pro-BNP levels are adverse prognostic markers.\(^8\)

Management of cardiac amyloidosis AL involves management of heart failure and agents that suppress the underlying plasma cell dyscrasia. While the former includes standard heart failure therapies like fluid and salt restriction, diuretics, spironolactone, and beta-blockers, the latter involves chemotherapeutic agents. Intensive treatment using melphalan-dexamethasone based regimens coupled with autologous stem cell transplantation (ASCT) has been known to improve median survival.\(^9\) In younger patients with advanced heart failure due to AL amyloidosis, cardiac transplantation followed by high-dose melphalan-dexamethasone and ASCT has shown some benefit; however, this option is restricted by scarcity of donors and transplant-associated complications.\(^10\)

Recent introduction of the protease inhibitor bortezomib to a dexamethasone and cyclophosphamide based regime has demonstrated good response rates even in previously refractory cases and is currently considered as the standard regime in most centres.\(^11,12\) More recently, monoclonal antibodies, which identify an epitope expressed in the AL light chains thereby enabling its clearance from circulation, has been isolated; however, these agents are still in the early phases of development.\(^13,14\)

Similarly, management of transthyretin-related (TTR) cardiac amyloidosis involves suppression of TTR formation. Although liver transplantation, especially in the familial subtype, is the treatment of choice in these patients, in the recent years, therapeutic strategies involving potential disease modifying agents have emerged. The most promising amongst these are the TTR tetramer stabilizers and the RNA inhibitors. The TTR tetramer stabilizers bind to the transthyretin tetramer, thereby stabilizing it and preventing its dissociation into monomeric amyloid fibrils. Diflunisal, a nonsteroidal anti-inflammatory agent, and tafamidis, which is currently indicated for use in early polyneuropathy associated with hereditary TTR amyloidosis, work by binding to the tetramer and maintaining its stability.\(^14-16\) The RNA inhibitors, on the other hand, inhibit the synthesis of TTR (wild type and variant) in the liver. Small interfering RNA (siRNA) agents, like patisiran and revusiran, inhibit specific mRNA sequences resulting in reduced production of amyloidogenic proteins by 80%. Similarly, antisense oligonucleotide agents, which are short synthetic nucleotide chains, inhibit TTR protein synthesis by binding to the RNA.\(^14,17\)

Despite recent advances in the management of cardiac amyloidosis, the long-term prognosis of these patients remains poor, especially if there has been a delay in diagnosis. It is hence important to consider amyloidosis as a potential diagnosis in patients presenting with ACS, with no identifiable cause following coronary angiography and imaging by echocardiography and Cardiac MR.

**Conflict of interest**

The authors have none to declare.

**References**