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Case Report

Cardiac amyloidosis presenting with coronary artery embolization

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Amyloid light-chain (AL) amyloidosis is a multisystemic disease. Among its clinical manifestations, vein and arterial thromboembolic events are included. We report the unusual case of a 57-year-old female patient with AL amyloidosis presenting with an ST segment elevation myocardial infarction due to coronary artery embolization (CE). The patient reported a history of exertional dyspnoea along with episodes of haemoptysis for the last few months. Her coronary angiography demonstrated embolization of the distal segment of the left anterior descending artery. The main findings of her cardiac ultrasound included concentric left ventricular hypertrophy, mildly impaired left ventricular systolic function, left atrium enlargement and a restrictive-like filling pattern, while her chest computed tomography (CT) demonstrated bilateral pleural effusions. Cardiac magnetic resonance imaging that was performed afterwards, indicated areas of microvascular infarction, a small apex infarct and findings compatible with possible amyloidosis, a diagnosis that was confirmed later by fat tissue biopsy. Patient was referred for an oncology consultation, started therapy with direct oral anticoagulants, angiotensin converting enzyme inhibitor, statins and anti-plasma cell therapy. She has been improving since then and has been free of cardiovascular events for a follow-up period of 12 months. Cardiologists ought to be aware of amyloidosis as a rare but possible cause of coronary embolization, while close collaboration with oncologists is required for the establishment of the correct diagnosis.

Keywords

Cardiomyopathy; Constrictive/restrictive; Coronary blood flow/physiology/microvascular function; Diastolic dysfunction; Cardiac magnetic resonance imaging; Cardio-oncology

1. Introduction

Coronary embolization (CE) is an important cause of acute myocardial infarction with a reported incidence of 4% to 13% [1, 2]. CE is characterised by the absence of obstructive atherosclerotic disease and normal to near normal coronary arteries, as displayed in coronary angiography (CA) [2, 3]. Definite diagnosis can be difficult to be established and a number of diagnostic criteria have been proposed [1]. CE has been categorized as a potential cause of a type 2 myocardial infarction [4] while the use of imaging modalities such as intravascular ultrasound (IVUS) or optimal coherence tomography (OCT) have been proposed as diagnostic tools for the assessment of intravascular patency and the detection of intracoronary thrombus [5–7]. Moreover, cardiac magnetic resonance imaging (CMR) provides valuable information regarding late gadolinium enhancement (LGE), fibrosis/scarring and subendocardial or transmural oedema in the distribution area of the affected vessel [7, 8]. Key aspect in understanding the pathophysiology of coronary emboli formation is Virchow's triad in the context of possible clinical scenarios including: the interaction of blood stasis/slow flow (atrial fibrillation, left ventricular aneurysm, deep vein thrombosis), endothelial injury (vasculitis, arteritis, angioplasty, surgery), predisposing factors (atrial septal defect, ventricular septal defect, endocarditis, mitral stenosis) and hypercoagulability (cancer, thrombophilia, heparin induced thrombophilia, intravascular foreign material) [2, 9, 10]. The differential diagnosis for potential underlying causes in the face of CE can be challenging, requiring a thorough clinical and laboratory workup and the cooperation of many specialties.

2. Case presentation

A 57-year-old female, with a history of hypertension (treated with angiotensin II receptor blockers) and cigarette smoking (35 pack-years), presented to the emergency department, complaining of chest pain with concomitant shortness of breath that started approximately 2 hours before admission. Moreover, the patient reported exertional, gradually deteriorating dyspnoea, starting approximately 6 months ago, accompanied by infrequent episodes of haemoptysis. Three months prior to admission, the patient had undergone a cardiac (clinical examination, electrocardiogram (ECG), transthoracic echocardiogram (TTE)) and pulmonary workup (clinical examination, spirometry, chest radiography) by

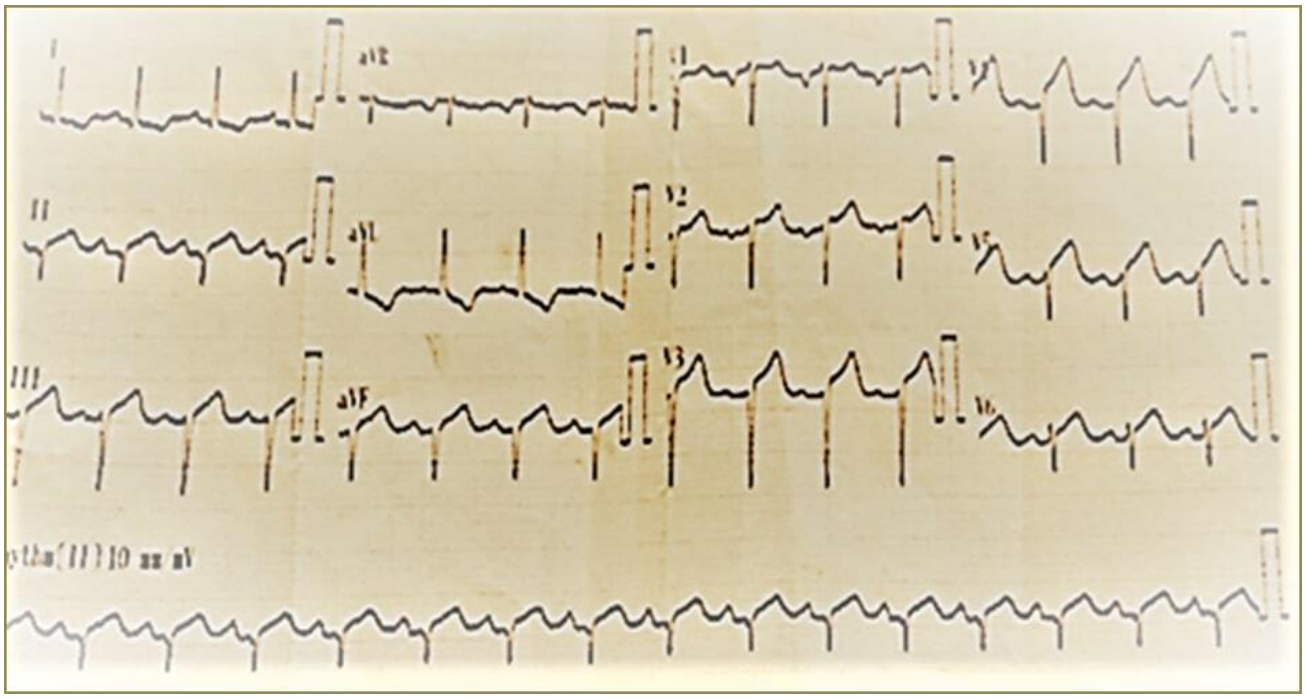

Fig. 1. Admission ECG in sinus rhythm with ST segment elevation in the anterior and inferior leads.

her family doctor (as an outpatient), that was reported to be without major pathologic findings and was also scheduled to undergo bronchoscopy. At admission her ECG showed ST segment elevation in the anterior and inferior leads and poor R progression in the precordial leads (Fig. 1). She had a blood pressure of 110/80 mmHg, a heart rate of 97 beats/min and a peripheral oxygen saturation of 93%. Auscultation of the heart and lungs revealed an S4, grade 1 murmurs in the mitral and tricuspid valves and bilateral mild attenuation of breath sounds. The diagnosis of ST segment elevation myocardial infarction was made and treatment with 180 mg ticagrelor, 325 mg aspirin and 5000 IU of unfractionated heparin was initiated. She was admitted directly to the catheterization laboratory for primary coronary intervention. Upon arrival in the cath-lab the pain had resolved. CA revealed an abrupt occlusion in the distal left anterior descending artery (LAD) while the rest of the coronary arteries displayed non-significant atherosclerotic lesions (Fig. 2). A CHOICE PT (Boston Scientific^{TM}, Natick, MA, USA) wire was advanced at the distal part of the LAD and thromboaspiration with an Export Advance catheter (MedtronicInc., Minneapolis, MN, USA) was attempted without any improvement in the vessel patency. A 1.5 mm $\times$ 15 mm Sprinter balloon (Medtronic Inc., Minneapolis, MN, USA) was advanced through the occlusion and repeated inflations were performed without success. With the working diagnosis of distal coronary embolism, no further intervention was performed, treatment with GpIIb/IIIa inhibitors was commenced and the patient was transferred to the coronary care unit with the indication of continuing p.o. antiplatelets, i.v. GpIIb/IIIa inhibitors and subcutaneous low molecular weight heparin.

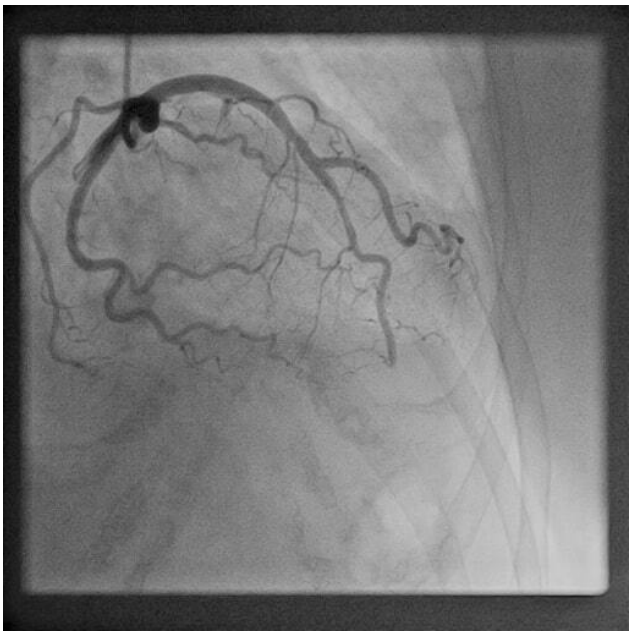

Fig. 2. Cranial view of the left coronary artery, revealing abrupt occlusion of the distal LAD.

The patient continued to complain of shortness of breath while her chest X-ray revealed pulmonary congestion along with bilateral pleural effusions. A brain natriuretic peptide (BNP) of 1520 pg/mL [Quidel Triage BNP Test^{TM} - San Diego, CA, USA, upper reference limit (URL): $<$100 pg/mL] and a high sensitive troponin I of 3600 pg/mL (PATHFAST^{TM} - LSI Medience Corporation, URL: $<$20 pg/mL) were measured, with a glomerular flitration rate of

96 mL/min/1.73 m^2. A twenty four-hour Holter rhythm monitoring did not reveal any episodes of atrial fibrillation/atrial flutter or episodes of tachyarrhythmias. TTE displayed concentric hypertrophy of the left ventricle (LV) (a LV regional wall thickness (RWT) of 0.69 and a LV mass index (LVMi) of 96 g/m^2 were calculated) [11] along with hypokinesia of the apical interventricular septum and the apex, slightly to mildly impaired systolic function (LV ejection fraction 47% assessed by the biplane Simpson's method), left atrium (LA) enlargement (the diameter of the LA was estimated to 42 mm), a restrictive-like filling pattern and small regurgitations from the mitral and tricuspid valves (Fig. 3). A contrast TTE study was performed to assess the potential presence of an apical thrombus, being negative. Right ventricular function was within normal limits (peak myocardial systolic velocity = 11 cm/sec, Tricuspid Annular Plane Systolic Excursion (TAPSE) = 17 mm) and the right ventricular systolic pressure was calculated to 47 mmHg. A right heart catheterization (RHC) was proposed next to differentiate further the pre-capillary or post capillary pathophysiologic dominant aspect contributing to the dyspnoea of the patient. RHC revealed pulmonary hypertension of 50 mmHg, a mean pulmonary wedge pressure of 18 mmHg pulmonary vascular resistance of 3.3 Wood Units and a diastolic pressure gradient of 2 mmHg. The patient was treated with intravenous furosemide which resulted in significant symptom improvement.

A computed tomography of the thorax and abdomen performed the following day displayed significant bilateral pleural effusions and hypertrophy of the cardiac walls with no evidence of pericardial effusion or thickening and no evidence suggestive of acute or chronic pulmonary thromboembolic disease (Fig. 4). Due to suspected diagnosis of an infiltrative cardiac disease, CMR was performed. Results included hyperintense signals in the areas of the apex of the LV and the apical interventricular septum in the T2 weighted scan. During the LGE phase, hyperintense signals in the apical areas of the LV and surrounding spots of low signal intensity were noticed, findings compatible with microvascular infarction, whilst the rest of the myocardium of the LV, especially the hypertrophic interventricular septum, displayed dispersed increased signals. Similar findings were noted in areas of the right ventricle and both of the atria. No intracardiac thrombus was detected. The demonstrated evidence advocated for a small infarct at the apex of the LV along with concomitant microvascular infarction and evidence of infiltrative myocardial disease, indicative of heart amyloidosis [12–14] (Fig. 5).

A serum protein electrophoresis revealed only hypogammaglobulinemia but immunofixation revealed a small λ-band and the free light chain assay increased free λ chains of 194 mg/L (normal reference range: 5.71–26.3 mg/L), with free κ of 9.80 mg/L (normal reference range: 3.3–19.4 mg/L) and a skewed serum κ/λ ratio of 0.05 (normal reference range: 0.26–1.65). Consequently, fat aspiration biopsy was performed, that demonstrated interstitial infiltration with fibrils stained with Congo-Red (+) followed by a bone marrow biopsy, establishing the diagnosis of amyloidosis (AL) amyloidosis of stage 3B.

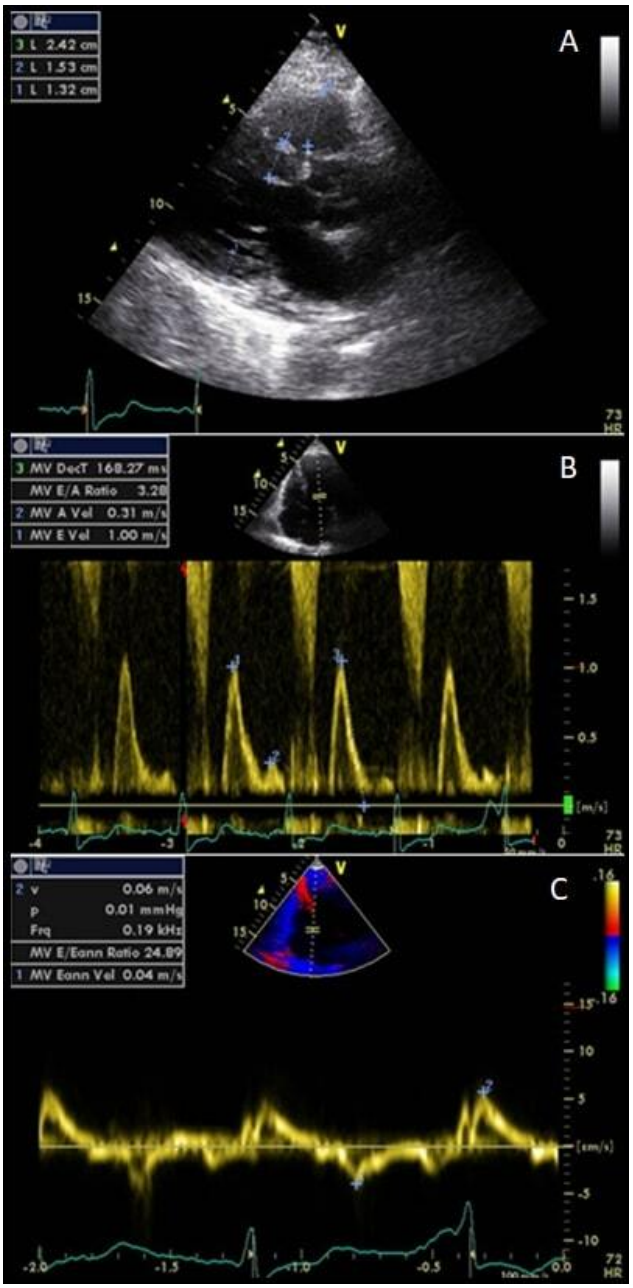

Fig. 3. The transthoracic echo of the patient displayed concentric hypertrophy of the walls of the left ventricle (A), with hypokinesia of the apical intraseptum and the apex, slightly to mildly impaired systolic function, left atrium enlargement and a restrictive-like filling pattern (B,C).

Therapy with a direct oral anticoagulant (DOAC), angiotensin converting enzyme inhibitor and statin along with bortezomib was commenced and the patient was discharged a few days later, clinically stable with a recommendation for frequent clinical follow-ups and to continue her oncology treatment as an outpatient. She received therapy with borte-

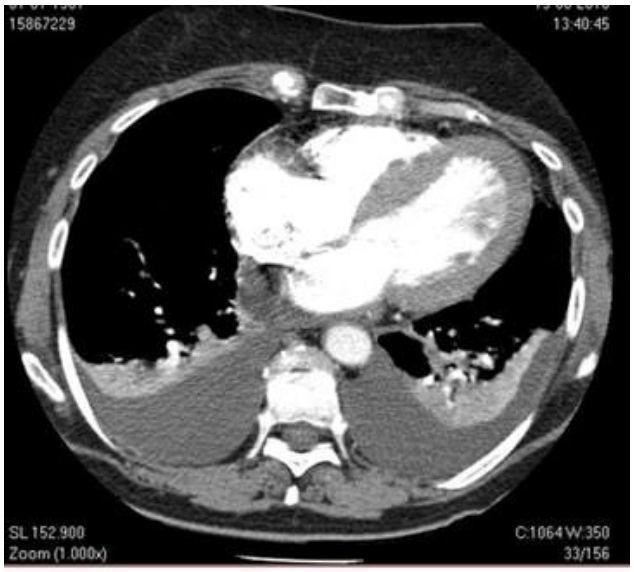

Fig. 4. Thorax-abdomen CT of the patient displaying significant bilateral pleural effusions and left ventricular hypertrophy.

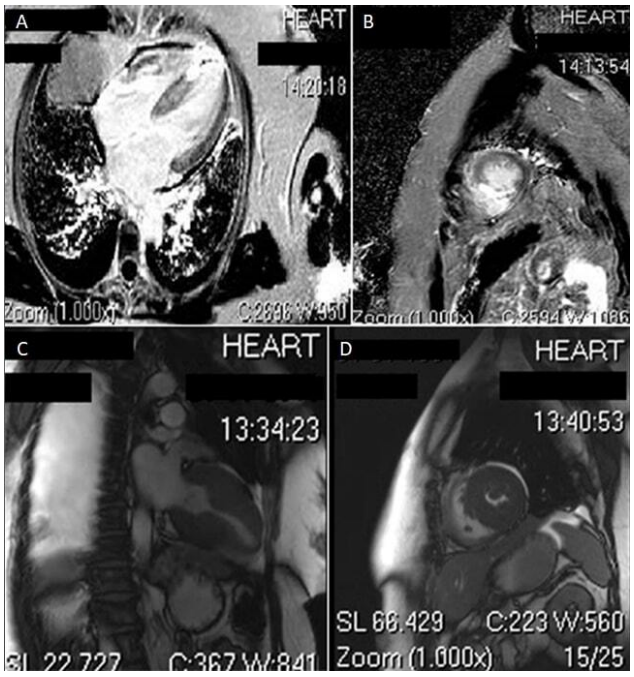

Fig. 5. During late gadolinium enhancement phase, hyperintense signals in the apical areas of the left ventricle and surrounding spots of low signal intensity were noticed (A,B), findings compatible with microvascular infarction, the rest of the hypertrophic myocardium of the left ventricle (C,D), especially the hypertrophic intraventricular septum, displayed dispersed increased signals, findings also noted in areas of the right ventricle and both of the atria (A,B).

zomib, lenalidomide and dexamethasone, achieved a very good partial response within 2 months, followed by daratumumab and finally achieving a complete hematologic response. A follow-up TTE at 3 months demonstrated a LV with mildly impaired systolic function (LV ejection fraction = 50% assessed by the biplane Simpson's method), concentric hypertrophy, grade 2 diastolic dysfunction, mild mitral regurgitation, mild dilatation of the atria with no other major findings. The follow-up CMR at 3 months recorded abnormal gadolinium kinetics and diffuse circumferential mesomyocardial LGE of the LV, transmural infarction of the apical inferior wall and LV apex with increased references at T1 mapping and marked increase of the extracellular volume (ECV = 45%). Her NTproBNP levels reduced from 14053 pg/mL to 3431 pg/mL (PATHFAST^{TM} - LSI Medience Corporation, normal reference range: <125 pg/mL) after 12 months [15], along with significant self assessed functional improvement in her daily activities.

3. Discussion

Amyloidosis is a multiorgan disease characterised by the extracellular aggregation of fibrillar proteins [14, 16]. Light chain AL, variant transthyretin and wild-type transthyretin amyloidosis are the most commonly described types affecting the heart [13, 15, 17]. Cardinal pathophysiologic features of systemic and/or localized amyloidosis include an overload of amyloid production, accumulated fractions of muted misfolding proteins and an increased propensity of amyloid formation by normal proteins [15]. Clinical symptoms are mainly dependant on the herald emerging accumulating protein type in the affected organs while kidneys, liver, heart, gastrointestinal tract and nervous system are the most common frequently reported targets of amyloid deposits [13, 15, 17, 18]. Early diagnosis, progressive multiorgan dysfunction and cardiac involvement have been proposed as some of the most crucial factors that determine survival [15, 19, 20]. In cases of lone cardiac involvement prognostic factors comprise free light chains-difference >18 mg/dL and the increase of cardiac biomarkers (troponin T >0.025 pg/mL and NTProBNP >1800 pg/mL) [13, 21]. The option of heart transplant might be suggested in a selected group of patients (characterised by complete response to standard AL therapy and low risk for early recurrence) with concomitant decompensated heart failure not responding to advanced heart failure standard of care treatments for a period of 6–12 months [15].

A recent position statement of the European Association of Cardiology (ESC) proposes a diagnostic algorithm for the diagnosis of cardiac amyloidosis [13]. In our case, the patient presented suggestive features on both TTE and CMR, whereas fat tissue biopsy documented amyloid infiltration.

Common cardiac and extracardiac clinical manifestations of AL amyloidosis, among others, include heart failure, arrhythmias, autonomic dysfunction, peripheral polyneuropathy, proteinuria, bilateral carpal syndrome and skin bruising [13]. Even though amyloidosis is known to predispose in thromboembolic events [18], there are relatively few cases in the literature of patients with cardiac AL amyloidosis and without atrial fibrillation, developing arterial thrombosis (peripheral artery emboli, mesenteric ischemia and stroke) [18, 22–24]. Intracardiac emboli have been described as

manifestations of AL amyloidosis with cardiac involvement [18, 25, 26] as also cases of AL mimicking coronary syndromes (but with non-occluding coronary arteries lesions) [27]. The hypercoagulable state that characterises AL amyloidosis is considered to play a critical role in the manifestation of venous and arterial thromboembolic events [28]. Park *et al.* [22] reported that patients with AL amyloidosis and high disease burden, as expressed in high serum concentrations of free light chains and b2 microglobulin, are prone to venous and arterial thromboembolism, due to the inflammatory cytokines (tumor necrosis a-factor, interleukin-6) cascade activation that in turn dysregulates endothelium function, platelets and coagulation factors. Additionally, Cho *et al.* [29] indicated that fibrils of amyloid penetrate into the intima of large epicardial coronary arteries as also the smaller microvascular arterioles and thus leading to embolic events, ischemia and mural thrombosis.

Antithrombotic treatment of patients with blood malignancies and arterial thrombosis can be challenging in daily clinical practice, while few reports in literature describe similar cases [30–33]. Clinical management of chronic anticoagulation treatment should carefully assess the ischemic risk and haemorrhagic danger of each patient individually. Contemporary literature supports the notion of DOAC's safe profile in the prevention of systemic embolism, even in cases with concomitant LV thrombus [34] in the present case the decision for chronic treatment with a DOAC was amenable to existent literature data displaying antithrombotic management in patients with systematic/arterial thromboembolic events [30–33]. Regarding cancer patients, the use of DOAC's has been described mainly in the context of deep vein thrombosis and pulmonary embolism [35].

A small number of cases report haemoptysis as the first clinical manifestation of cardiac AL amyloidosis. Frail microvascular pulmonary capillaries and/or parenchymal disease, characterised by the infiltration of amyloid fibrils, are considered as underlying causes, in addition to a non-compliant diseased myocardium with elevated LV filling pressures and left atrial myopathy, that in cases of increased workload or high systemic resistance can lead to episodes of flash pulmonary oedema [24, 36].

Careful screening is mandatory in order to exclude other causes of cardiomyopathy, including hypertensive heart disease, hypertrophic cardiomyopathy, high output heart failure, mitochondrial myopathies, mucchopolyscharidosis or Anderson-Fabry disease. Despite that all of the prementioned pathologies can ultimately lead to restrictive cardiomyopathy and heart failure, they can also share a common imaging phenotype (LV hypertrophy) at least in their early stages [17]. Prompt detection of concomitant clinical and laboratory/imaging evidence suggesting amyloidosis is required for the accurate differential diagnosis and treatment. Specifically for the cases of AL amyloidosis, a number of diagnostic "red flags" indicative of the disease have been proposed [13–15, 37, 38]. These key diagnostic signs and symptoms include polyneuropathy, dysautonomia, macroglossia, impaired kidney function-proteinuria for the extracardiac manifestations and hypotension, abnormal ECG findings (e.g., low voltage QRS), elevated NTProBNP and troponin levels along with echocardiographic (e.g., granular sparkling of myocardium, reduced longitudinal strain with apical sparing pattern, increased right ventricular wall thickness) as also CMR evidence (e.g., subendocardial LGE, increased extracellular volume, abnormal gadolinium kinetics) for the cardiac findings respectively [12, 13, 17].

4. Limitations

A number of limitations must be acknowledged regarding the present case report. Firstly, no intravascular imaging (IVUS, OCT) or follow-up CA data are available for further diagnostic information regarding the embolization of the LAD. Secondly, data on LA mechanics (such as LA strain) as well as on hypercoagulability screening tests were not available.

5. Conclusions

Amyloidosis can cause embolization of the coronary arteries and lead to acute coronary syndrome and heart failure. Careful clinical work up is required, whereas imaging techniques such as echocardiography and CMR, in conjunction with analytical and histological data, can be of great relevance to overall patient management. This case report highlights some of the potential manifestations of amyloidosis, showcasing the importance of an integrative approach and of the close collaboration between cardiologists and oncologists, in this challenging clinical entity.

Author contributions

CP, ET, EK, MAD designed the case report study and contributed to the manuscript conceptualization, preparation and draft of the manuscript and writing of the case report. IB, KT contributed to library searches and assembling relevant literature, data acquisition, data interpretation, writing of the case report and were the main contributors to the design of the figures. All authors contributed to the critical review and final approval of the manuscript.

Ethics approval and consent to participate

The study fulfills the ethical requirements of the Declaration of Helsinki, with regards to human subjects' research (ethical and scientific committee of Alexandra Hospital protocol number 457). Written consent was obtained from the patient.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://rcm.imrpress.com/EN/10.31083/j.rcm2203094.

Data availability

All relevant data are included in the manuscript.

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