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Cardiac Amyloidosis Presenting with Pre-Excitation Syndrome, Heart Failure, and Severe Factor X Deficiency as Part of Systemic Amyloid Light-Chain (AL) Amyloidosis – A Fatal Combination

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Conflict of interest:

None declared

None declared

Patient: Male, 37-year-old

Final Diagnosis: Cardiac amyloidosis

Symptoms: Palpitation • syncope

Medication: —

Clinical Procedure: —

Specialty: Cardiology • Hematology

Objective: Unusual clinical course

Background: Amyloid light-chain (AL) amyloidosis is a disease that results in systemic amyloid deposition, which may present with multi-organ dysfunction. It carries a poor prognosis at the time of diagnosis.

Case Report: A 37-year-old patient with a history of Wolff-Parkinson-White syndrome and thyroiditis presented with syncope and hypovolemia. ECG showed non-specific T wave inversions in the lateral leads with no signs of ischemia. Laboratory investigations revealed deranged coagulation parameters with prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) and follow-up factor assays revealed severe factor X deficiency. A transthoracic echocardiogram and subsequent cardiac MRI showed signs of cardiac amyloidosis. Bone marrow biopsy was consistent with AL amyloidosis, demonstrating period acid-Schiff (PAS)-positive adipose deposits and interstitial infiltration by clusters of lambda restricted plasma cells with aberrant expression of CD 56 and CD 117.

The patient was treated with bortezomib, cyclophosphamide, and dexamethasone, but died early during his treatment due to cardiac arrest, suspected to be secondary to conduction abnormalities caused by cardiac infiltration.

Conclusions: This case represents a novel pattern of disease in AL amyloidosis with cardiac, thyroid, and hematological involvement as a result of systemic amyloid deposition. Our report highlights the need for physicians to be aware of cardiac amyloidosis-related complications and the morbidity and mortality associated with concurrent hematological involvement in these cases.

Keywords:

Amyloidosis • Cardiomyopathy, Restrictive • Factor X Deficiency

Full-text PDF:

<https://www.amjcaserep.com/abstract/index/idArt/933398>

Background

Amyloidosis is a group of disorders which occur due to presence of misfolded protein depositions in various organs. These proteins are found normally in the body, but excess production or reduced filtration causes the formation of insoluble fibrils extracellularly, resulting in damage to the affected tissue or organ [1].

Amyloid light-chain (AL) amyloidosis is the most common type. It is a systemic disease caused by the depositions of light-chain proteins in the kidneys, heart, and the liver, among other organs, but it does not typically involve the central nervous system. Light-chain proteins are generally produced by the monoclonal proliferation of plasma cells, either as a primary disorder or in association with plasma cell neoplasms such as multiple myeloma and Waldenström macroglobulinemia [1,2].

The clinical presentation of AL amyloidosis includes constitutional symptoms such as fatigue, weight loss, and poor appetite, in addition to organ-specific symptoms. The most commonly affected organs in AL amyloidosis are the kidney and the heart, with the typical presentation being that of heart failure as a result of infiltrative heart disease. It is considered that cardiac disease, when present, is the main prognostic factor for patients with systemic amyloidosis, and it carries a poor prognosis, with survival of less than 3 years [1]. Amyloid depositions within cardiac tissue can affect the conduction system; particularly if present in the sinus node and bundle branches, this can result in various types of arrhythmias and conduction blocks [3]. The presence of cardiac arrhythmia has been linked to sudden death in patients with cardiac amyloidosis with abnormal echocardiogram and complex ventricular arrhythmia on ECG [4].

Renal disease most commonly presents with nephrotic syndrome, which may progress to end-stage failure; other manifestations include congestive heart failure, restrictive cardiomyopathy, peripheral neuropathy, orthostatic symptoms caused by autonomic dysfunction, macroglossia, hepatic infiltrative disease, and carpal tunnel syndrome [5,6].

AL amyloidosis can also result in bleeding tendency through several mechanisms: hepatic infiltrative disease, nephrotic syndrome, vascular damage secondary to amyloid deposition, platelet dysfunction, or factor X deficiency. A degree of factor X deficiency is seen in up to 14% of patients, with severe deficiency reported in 5% of cases. This deficiency is acquired and it is thought to be caused by the consumption of factor X by amyloid fibrils [7]. In fact, bleeding diathesis predisposes patients with AL amyloidosis to be at a high risk when undergoing procedures required to confirm the diagnosis, such as renal and bone marrow biopsy, and thus need frequent correction of the coagulation abnormality.

We present the case of a middle-aged man who presented with signs of conduction abnormality and thyroiditis, found to have severe factor X deficiency, with later confirmation of a diagnosis of AL amyloidosis.

Case Report

A 37-year-old man from Pakistan with a history of hypertension presented to the Emergency Department with loss of consciousness following a 20-day history of palpitations, upper abdominal pain, and recurrent vomiting. Systemic review was notable for dizziness on standing, hoarseness of voice, and 7 kg of unintentional weight loss over the preceding month. There was no history of chest pain, sweating, abdominal pain, bleeding, or seizures. One year prior, the patient had been investigated under the care of Cardiology for chest pain and palpitations. His ECG had revealed a Wolff-Parkinson-White pattern, and thyroid function studies and ultrasound were consistent with hyperthyroidism secondary to thyroiditis (Figure 1A). At the time, he was treated initially with propranolol and then carbimazole when his thyroid function failed to improve. He received regular outpatient follow-up and had reported improvement of his symptoms.

On presentation he appeared diaphoretic and ill and was noted to have postural hypotension. Physical examination revealed a tender hepatomegaly of 4 cm under the costal margin and right lower-limb swelling in the thigh. Initial laboratory investigations showed leukocytosis, mild normocytic anemia, thrombocytosis, and elevated troponins. A coagulation profile demonstrated a prolonged prothrombin time (PT) of 29 s (normal range: 9.4-12.5 s), an international normalized ratio (INR) of 2.9, and an activated partial thromboplastin time (aPTT) of 43 s (normal range: 25.1-36.5 s). He was initially suspected to have sepsis and was treated with intravenous hydration and antibiotics, with good response. An ECG showed non-specific T wave inversions in leads V2-V5 without any ischemic ST-T segment changes, with Wolff-Parkinson-White pattern, similar to the ECG done 1 year before. A Doppler ultrasound of the right lower limb was negative for deep venous thrombosis. A transthoracic echocardiogram revealed severe, concentric biventricular hypertrophy with an ejection fraction of 56%, left ventricular septum end-diastole was 1.5 cm, and strain analysis showed severe reduction in global longitudinal strain (GLS) of 8.8% with apical sparing.

Hypovolemia was corrected and cultures were subsequently negative, but the patient's coagulation parameters failed to improve. A mixing study led to correction of the PT and aPTT, suggesting a clotting factor deficiency, and a follow-up assay of clotting factors revealed severe factor X deficiency with a level of 7.3% (normal range: 70-120%). Mild deficiencies were also present in factor VII (54%) and factor IX (62%).

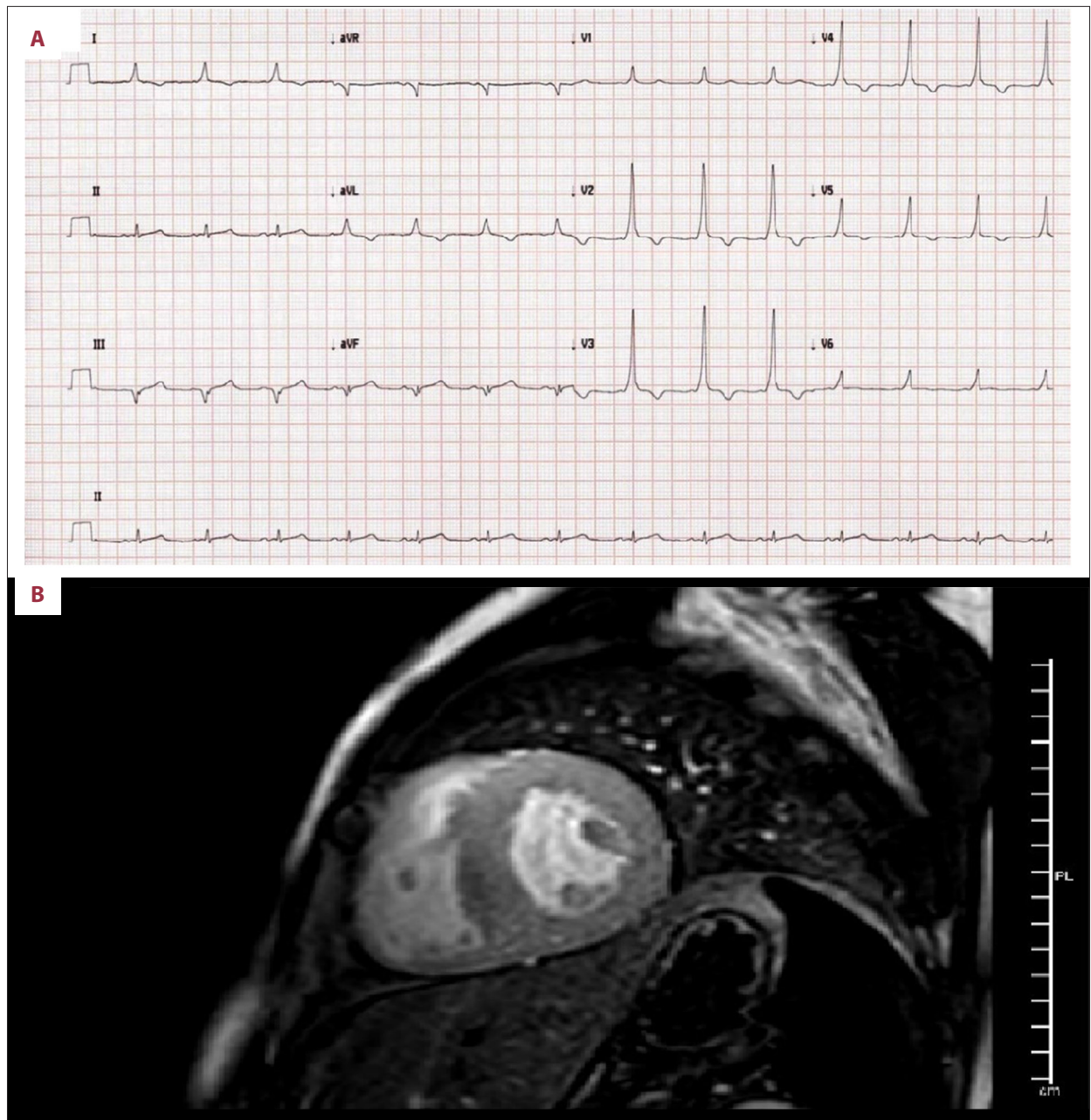


Figure 1. (A) ECG showing Wolff-Parkinson-White pattern (short PR interval and presence of delta waves). (B) MRI heart showing signs of infiltrative cardiomyopathy consistent with cardiac amyloidosis.

The patient was investigated for malignancy as a cause for acquired factor deficiency. An iodinated contrast enhanced computerized tomography (CT) scan of the neck, thorax, abdomen, and pelvis revealed thyroid enlargement, bilateral pleural effusion, and widespread lymphadenopathy in the cervical, hilar, mediastinal, and upper abdominal regions. A positron emission tomography (PET) scan revealed mesenteric and retroperitoneal lymph nodes with mild to moderate uptake, and the other previously visualized lymph nodes did not show any significant activity. In the absence of any obvious malignancy, the patient

was investigated for infiltrative disease. ECG-gated, gadolinium-enhanced cardiac magnetic resonance imaging (MRI) revealed diffuse subendocardial and mid-anteroseptal heterogeneous enhancement. There was circumferential myocardial hypertrophy and mild pericardial effusion. These findings were in keeping with infiltrative cardiac disease (Figure 1B). MRI of the liver showed no signs of infiltrative liver disease, and liver enzymes were normal.

Serum protein electrophoresis (SPE) showed polyclonal increase in gamma globulins, and immunofixation revealed free lambda

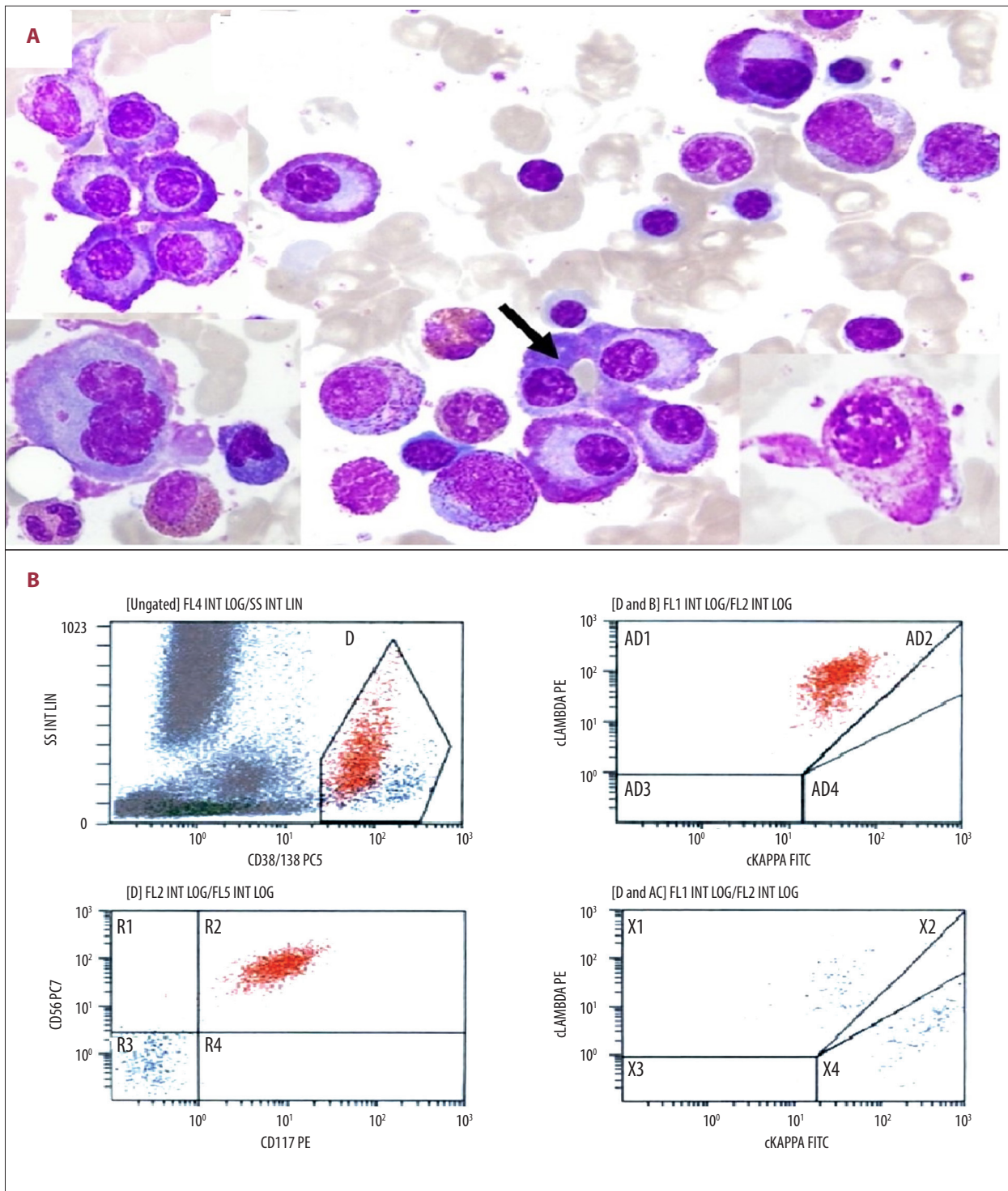


Figure 2. (A) BM aspirate smear (Wright's stain, 1000 \times) revealed scattered and clusters of plasma cells, averaged ~20%, morphologically abnormal, substantial number show deep condensed peripheral staining with flame plasma cell-like morphology, many appear granulated (**lower right insert**) or with immunoglobulin inclusions (Russell bodies, arrowed cell) and a few are binucleated (**lower left insert**) or have a pleomorphic nucleus. (B) Flow cytometry immunophenotyping on BM aspirate revealed 3% monotypic plasma cells (red population) expressing CD38/CD138 with cytoplasmic lambda light-chain restriction with aberrant CD56 and CD117 expression. Flow cytometry showed <1% residual polyclonal plasma cells (blue population).

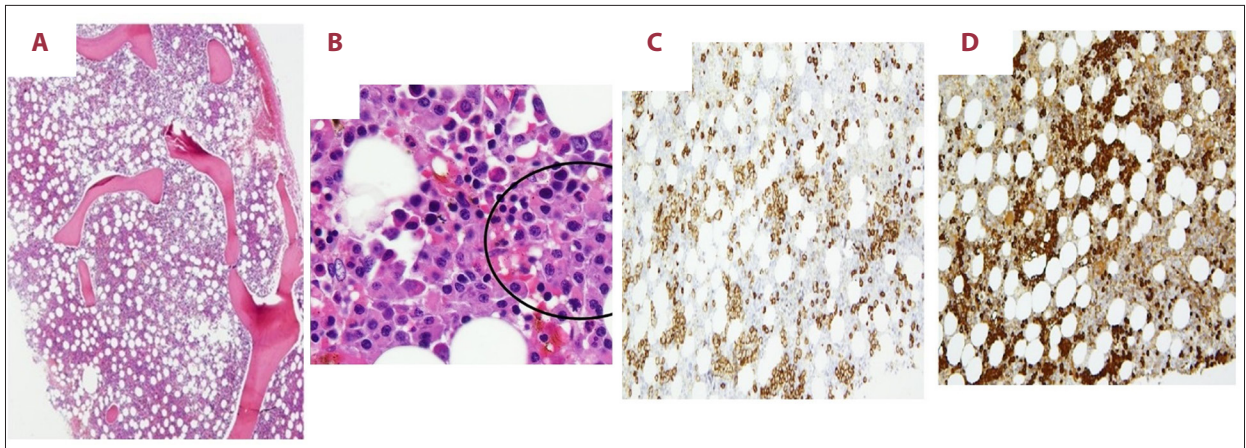


Figure 3. (A) BM biopsy is cellular to mildly hypercellular (H&E, $\times 40$). (B) Higher power ($\times 400$) show interstitial and clusters of plasma cells (circled), (C) BM biopsy, CD138 immunohistochemistry highlights scattered and clusters of plasma cells (roughly estimated at 20-30% of core cellularity), (D) lambda light-chain restriction, $\times 100$.

light-chain. Serum lambda free light-chain (LaFLC) was high at 978.3 mg per liter, serum kappa free light-chain (KaFLC) was 36.2 mg/L, with kappa-to-lambda ratio of 0.04, and urine was positive for Bence Jones protein (0.1 g/L). The patient underwent fat pad biopsy plus bone marrow aspiration and biopsy to confirm the diagnosis of suspected light-chain amyloidosis. He required high doses of prothrombin concentrate to correct his coagulopathy before these procedures.

At the time of the bone marrow collection, a complete blood count (CBC) showed mild normochromic normocytic anemia (hemoglobin 12.6 g/dL, normal range: 13-17), leukocytosis ($12.0 \times 10^3/\mu\text{L}$, normal range: 4-10), and thrombocytosis ($526 \times 10^3/\mu\text{L}$, normal range: 150-400), with rare circulating plasma cells noted on screening of the peripheral smear.

Bone marrow (BM) aspirate was hypercellular with active trilineage hematopoiesis and showed increased plasma cells with uneven distribution, scattered and in clusters, with an average of approximately 20%.

The plasma cells were morphologically abnormal, with many showing clearing of a large part of the cytoplasm, with deep condensed peripheral staining. Many cells appeared granulated with immunoglobulin inclusions (Russell bodies) and a few contained binucleated or pleomorphic nuclei (Figure 2A).

Immunophenotyping by flow cytometry on the bone marrow aspirate revealed 3% of monotypic plasma cells expressing CD38, CD138 with cytoplasmic lambda light-chain restriction, and aberrant CD56 and CD117 expression. The plasma cells were negative for CD19, CD20, and CD45. Flow cytometry showed <1% residual polytypic plasma cells, positive for CD19 and negative for CD56 and CD117, with a kappa-to-lambda ratio of 1.2. Four percent of B cells expressed CD19 and CD20,

with a Kappa/Lambda ratio of 1.38, with no immunophenotypic evidence of a monotypic B cell population (Figure 2B).

Bone marrow biopsy was cellular to mildly hypercellular when adjusted to the patient's age, with an average cellularity of 40-50%. There was trilineage hematopoiesis and interstitial infiltration with scattered clusters of lambda restricted plasma cells as highlighted by immunohistochemistry aberrantly expressing CD56 & CD117 (Figure 3A-3D). The infiltration was roughly estimated at 20-30% of the core cellularity. The section showed a deposition of a pink, amorphous, waxy-looking deposit, in the thickened blood vessels wall, mainly within the adipose tissue, with some focal interstitial deposits. The deposited material-stained pink to red by Congo red on standard light microscopy and produced a characteristic apple green birefringence under polarized light, consistent with amyloid deposition (Figure. 4A, 4B). The deposits stained positive for periodic acid-Schiff (PAS) and amyloid P (Figure 4C, 4D). The compiled findings confirmed bone marrow involvement by plasma cell neoplasm resulting in AL amyloidosis. Fat pad biopsy was not diagnostic.

The patient spent the whole duration of his work-up as an inpatient. The Cardiology and Hematology teams were involved early during the hospital stay. His right leg swelling, which was initially associated with pain, resolved spontaneously within 5 days of admission. But later, he complained of shortness of breath that was worse when lying flat, which was investigated with a transthoracic echo, described above. As his coagulation parameters failed to improve, the patient's home carbimazole therapy was stopped due to suspicion of carbimazole-induced coagulopathy. On day 20 of admission, after a pan CT and PET were unrevealing, the patient underwent abdominal fat pad biopsy and bone marrow biopsy in separate sittings, and both required prothrombin concentrate to

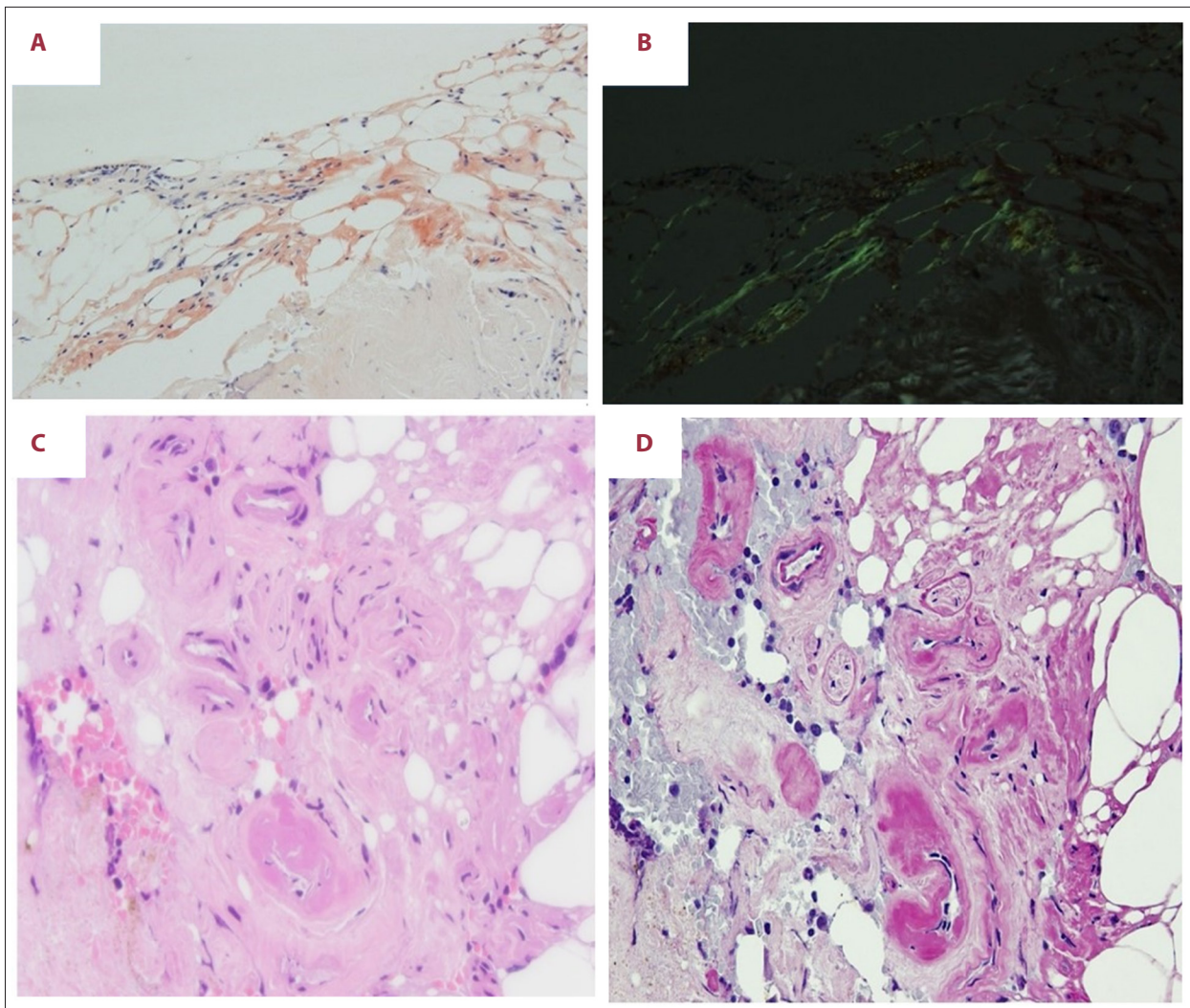


Figure 4. BM biopsy. (A) Amyloid deposits stain pink to red by Congo red by standard light microscopy. (B) The amyloid gives an apple green birefringence under polarized light. (C) (H&E stain), showed a deposition of pink amorphous, waxy-looking deposit, in the thickened blood vessels wall ($\times 500$). (D) The deposit is positive for PAS stain ($\times 500$).

achieve proper coagulation. A multidisciplinary team meeting was held, and the decision was made to resume his carbimazole due to persistent tachycardia, which was suspected to be due to hyperthyroidism.

Later, a bone marrow biopsy confirmed a diagnosis of plasma cell dyscrasia resulting in AL amyloidosis, and he was transferred to the local specialized cancer hospital for initiation of chemotherapy.

In summary, the patient was managed as a case of systemic AL amyloidosis secondary to plasma cell neoplasm manifesting with infiltrative heart disease, severe factor X deficiency, and possible thyroid involvement. The hepatomegaly was considered to be more due to cardiac hepatopathy than to amyloidosis. A thyroid or liver biopsy were not done due to high risk of bleeding.

On day 27 the patient developed tachypnea that was attributed to heart failure. This was managed with diuretics and continuation of his previous thyroid medications. He was started on bortezomib, cyclophosphamide, and dexamethasone chemotherapy. He continued to have tachycardia, with ECG showing sinus rhythm with non-specific T wave changes, so he was started on metoprolol, with a plan for ablation at a later date. A repeat transthoracic echocardiogram demonstrated a severe drop in ejection fraction over 4 weeks, with an ejection fraction of 25% and severe diastolic dysfunction.

The patient continued to experience persistent tachycardia and shortness of breath in spite of treatment. He was maintained on beta-blocker and diuretic therapy with cardiac monitoring as he was considered to be high risk for arrhythmia. On day 32 of admission, the patient developed cardiac arrest

with a rhythm of pulseless electrical activity. After 2 cycles of resuscitation the rhythm degraded to asystole. Unfortunately, despite 40 min of cardiopulmonary resuscitation, the patient could not be revived. Given the worsening tachycardia and WPW pattern on ECGs, the patient's cause of death was assumed to be arrhythmia secondary to conduction abnormalities as a result of infiltrative cardiac disease.

Discussion

Cardiac amyloidosis is a frequent feature of AL amyloidosis; it occurs due to the replacement of the normal myocardial contractile elements with interstitial deposits of amyloid, leading to alterations in cellular metabolism. Amyloid deposition within the myocardium affects the integrity of the tissue structure, causing it to become firm, rubbery, and noncompliant. Cardiac amyloidosis most commonly presents with restrictive cardiomyopathy and congestive heart failure [8].

In 2012 the incidence of cardiac amyloidosis was estimated to be 17 per 100 000 person-years in the United States, with a prevalence rate of 55 per 100 000 person-years in the same year [9].

Patients with cardiac amyloidosis usually present with signs of heart failure, including exertional and positional dyspnea, lower-limb edema, ascites, and syncope. Increased jugular venous pressure can be detected on physical examination. Conduction abnormality can be also a result of amyloid protein infiltration in the cardiac tissues, manifesting with nodal arrhythmia and heart block [10].

Cardiac involvement in amyloidosis is seen mainly in either AL amyloidosis or transthyretin amyloidosis (ATTR). In fact, up to 50% of patients with AL amyloidosis have cardiac disease at diagnosis and it is the principal determinant of prognosis. The estimated survival rate in cardiac amyloidosis is around 6 months in AL amyloidosis compared to a few years in transthyretin amyloidosis [11].

Transthyretin (TTR)-related amyloidosis is a result of accumulation of the protein transthyretin, a transport protein produced by the liver. The 2 subtypes of this condition are acquired TTR amyloidosis, also called senile systemic amyloidosis (SSA), or hereditary transthyretin-related amyloidosis (ATTR). In ATTR, patients are born with an inherited genetic defect in the TTR protein that results in excessive breakdown of this protein. Interestingly, ATTR tends to present much later in life, with symptoms of amyloidosis typically manifesting between the ages of 30 to 60 years. It is a heritable disorder wherein the defective gene is passed down to about 50% of offspring. On the other hand, in senile systemic amyloidosis (SSA), there is

breakdown of the normal TTR protein, for which the mechanism is not fully understood. Typically, it affects the heart, usually presenting with congestive symptoms in elderly men [12].

In vitro studies have demonstrated the effect of light-chain proteins on cardiac tissues in mice, mainly causing diastolic dysfunction. There is also evidence to suggest that light-chain protein has a direct toxic effect on cardiac tissue independent of fibril formation, which may be responsible for the rapid progression to cardiomyopathy in patients with AL amyloidosis [13].

Orthostatic hypotension has previously been reported, but unlike our patient, most of these reported cases were found to have heart block or sick sinus syndrome [14]. The resolution of orthostatic hypotension with i.v. fluids in our case suggests the etiology of hypovolemia was severe vomiting and/or autonomic dysfunction.

Amyloid fibril in the liver and the spleen can bind to factor X, causing deficiency evident primarily by abnormal coagulation profile (eg, PT, INR, and PTT) with correction after addition of normal plasma (mixing study), as in our patient. A study found that 28% of patients with AL amyloidosis had abnormal bleeding tendency and almost half of them (51%) had abnormal coagulation profile [15].

The diagnosis of systemic amyloidosis is confirmed by tissue biopsy from accessible sites like the abdominal fat pad, or from bone marrow biopsy, which are preferred to more invasive liver and cardiac biopsy despite lower diagnostic yield in primary amyloidosis. Coagulopathy, especially severe factor X deficiency, is a serious challenge in obtaining tissue samples. Our patient required high doses of prothrombin complex in order to obtain safe biopsies. Involvement of the thyroid in primary amyloidosis was also reported. Most of the patients were euthyroid and, less commonly, presented with a toxic goiter [16]. Our patient had signs of toxic thyroiditis, but we did not have the chance to obtain a thyroid biopsy to establish a diagnosis of AL amyloidosis-related thyroiditis.

In cardiac amyloidosis, echocardiography typically shows longitudinal left ventricular dysfunction with a possible restrictive pattern [17]. Other investigations include cardiovascular magnetic resonance (CMR) using gadolinium. The presence of subendocardial and then transmural late gadolinium enhancement is specific and can detect early disease before the development of left ventricular hypertrophy [18].

Nuclear scanning using Technetium-99 m pyrophosphate (Tc-99 m PYP), an isotope with high affinity to amyloid proteins, has very high accuracy and positive predictive value in diagnosing cardiac amyloidosis, especially ATTR [19]. Cardiac tissue

biopsy remains the criterion standard of diagnosis; it is done by obtaining around 4 or 5 pinhead-sized pieces from the right ventricle. Cardiac amyloid tissue stains light pink in color, disturbing the normal layout of the cardiac myocytes.

The association between pre-excitation syndrome and AL amyloidosis is unclear, but there is 1 case report of gastro-intestinal amyloidosis leading to GI bleeding in a patient with known WPW syndrome, but there were no signs of systemic amyloidosis or cardiac infiltrative disease, so it might have been incidental [20].

Management of cardiac amyloidosis is directed toward management and treatment of heart failure symptoms and treatment of the underlying disease. It should be noted, however, that the usual treatment for heart failure using beta blockers and angiotensin-converting enzyme (ACE) inhibitors is poorly tolerated, especially in light-chain disease, and these medications do not appear to add a prognostic benefit in such patients. Loop diuretics remain the mainstay of treatment to control heart failure symptoms in patients with cardiac amyloidosis. Non-dihydropyridine calcium channel blockers can improve diastolic function by relaxation time prolongation [21]. Advanced cardiac amyloidosis requires more specialized treatment including ventricular assistive devices and, less frequently, heart transplantation [22].

Delayed conduction due to infiltration of the conduction system by the amyloid protein may necessitate placement of a pacemaker, but the overall health status of the patient may limit or delay these interventions. Ventricular arrhythmia is typically managed conservatively through the use of beta blockers and non-dihydropyridine calcium channel blockers, but this carries a risk of severe systemic hypotension so use of this approach is limited. Implantable defibrillators may be considered depending on the clinical status [23].

Initiating treatment early in AL amyloidosis can improve the survival rate in heart failure patients. Therapy consists mainly of chemotherapy with cyclophosphamide or bortezomib. More recent trials with the CD 38 monoclonal antibody daratumumab have shown promising results and this has been used as an adjunct in treatment. For patients with plasma cell dyscrasia, autologous stem cell transplantation (ASCT) is considered. Our patient was started on chemotherapy and had a good initial response, but then had rapid worsening of cardiac disease.

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In ATTR, a newly introduced Tafamidis that can bind to transthyretin and slow the production of amyloid, was found to decrease all-cause mortality in patients with ATTR cardiac amyloidosis, but it is of limited use because of its high cost [24]. Otherwise, patients can benefit from liver transplantation in the early stages of the disease. For SSA, there is no specific treatment to act on the TTR products, so management is mainly directed toward treating the cardiac manifestations.

Conclusions

AL amyloidosis can present with various signs and symptoms as a result of diffuse involvement of multiple organ systems. This case report demonstrates the diagnostic challenge of a novel presentation of a well-known disease. Infiltrative disease is an important differential diagnosis that must be considered in cases of organ disease accompanied by unexplained coagulation abnormalities. Cardiac involvement in amyloidosis, in particular, is a predictor of poor prognosis and must be managed with specialized care due to the potentially fatal complications that can occur as a result of heart failure and conduction abnormalities.

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Ethics Approval

Medical Research Center, Hamad Medical Corporation, MRC: 04-20-1245.

Statement

Patient consent, as a signed form, has been obtained for publication of case details.

Declaration of Figures Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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