Syncope in cardiac amyloidosis and chronic ischemic heart disease: A case report

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Primary systemic amyloidosis is a relatively uncommon disease characterized by the production and deposition of pathological insoluble fibrillar proteins in organs and tissues. It has been estimated that between one-third and one-half of all patients with primary amyloidosis experience clinically significant cardiac involvement. The present study reports a case involving a 77-year-old woman with ischemic heart disease who presented to the cardiology department because of syncope due to slow atrial fibrillation. Laboratory tests revealed a monoclonal spike in the gamma fraction and impairment of renal function, normocytic anemia, mild hypercalcemia, hypoalbuminemia and increased levels of beta-2 microglobulin. Suspicion of cardiac involvement was supported by the echocardiographic pattern and increased levels of troponin I and brain natriuretic peptide, along with clinical signs of heart failure and systemic amyloidosis diagnosis, confirmed by abdominal fat aspiration.

Key Words: *Cardiac amyloidosis; Coronary artery disease; Syncope*

Systemic amyloidosis is a group of diseases sharing a common feature – extracellular deposition of pathological insoluble fibrillar proteins in organs and tissues (1). The most common form is primary amyloidosis, also known as light chain (AL) amyloidosis, which is characterized by production and, then, deposition of clonal immunoglobulin light chain proteins. The most common clinical manifestations are unexplained nephrotic syndrome, cardiomyopathy, hepatomegaly and peripheral neuropathy. AL amyloidosis is a relatively uncommon disease, with an incidence of approximately 2000 to 2500 new cases annually in the United States (2). Men are more frequently affected than women (ratio of 3:2), usually in the sixth decade of life (3). It has been estimated that between one-third and one-half of all patients with AL amyloidosis experience clinically significant cardiac involvement (4). We report a case of cardiac amyloidosis in a woman who presented with heart failure and slow atrial fibrillation, symptomatic for syncope.

CASE PRESENTATION

A 77-year-old woman was referred to the cardiology department for syncope and slow atrial fibrillation, and a history of progressive exertional dyspnea over the previous three months. She had a history of arterial hypertension, dyslipidemia and coronary artery disease (in 2003, she experienced an acute inferior myocardial infarction that was treated with fibrinolytic therapy; in 2004, she was treated for unstable angina and underwent a percutaneous transluminal angioplasty on the right coronary artery; and in 2005, inducible myocardial ischemia was detected on exercise test, and she underwent drug-eluting stent implantation on the same coronary artery due to restenosis).

At presentation, the patient was asymptomatic for angina and dyspnea at rest, with an arterial blood pressure of 120/60 mmHg and a heart rate of 40 beats/min. She was mentally sound, and had slightly pale skin and clear sclerae. Jugular venous distension was noted; however, no peripheral edema was present. The patient's heart sounds were irregular, with a grade 2/6 systolic murmur over the left sternal border. Inspiratory rales were heard at the bases of both lung fields. Abdominal examination revealed normal bowel sounds without any palpable mass. Other physical findings were unremarkable. Arterial blood gas analysis on room air showed an oxygen partial pressure of 90 mmHg, a carbon dioxide partial pressure of 32 mmHg, bicarbonate level of 21 mmol/L and a pH of 7.44. Laboratory tests revealed normocytic anemia, impairment of renal function, hypoalbuminemia, mild hypercalcemia, and increased lactate dehydrogenase and beta-2 microglobulin levels (Table 1). High levels of gamma-glutamyl transpeptidase and alkaline phosphatase were also found. Notably, troponin I levels remained slightly elevated during her hospital stay (ranging between 0.075 µg/L and 0.190 µg/L), whereas creatine kinase-MB levels were always found to be normal. Increased N-terminal pro-brain natriuretic peptide levels (4433 ng/L) were also found. Serum protein electrophoresis showed an 8.0 g/L monoclonal spike in the gamma fraction, and serum immunoelectrophoresis revealed a monoclonal lambda chain peak. A urine test for Bence Jones proteins was positive for lambda-free light chains (74 mg/L); nonselective glomerular proteinuria of 2.15 g in 24 h was also demonstrated. Immunochemistry revealed normal immunoglobulin (Ig) G, IgA and IgM levels, and cryoglobulins were absent.

The patient's chest radiograph revealed a slightly enlarged cardiac silhouette without pulmonary congestion. The electrocardiogram showed atrial fibrillation with low ventricular response, normal voltage in the limb leads, poor R wave progression, Q wave in anteroseptal precordial leads and voltage criteria for left ventricular hypertrophy with secondary repolarization abnormalities in the precordial leads (Figure 1). Abdominal ultrasonography showed normal size and morphology of the liver, pancreas, spleen and kidneys, and regular biliary ducts. The echocardiogram revealed increased thickness of the interventricular septum (15 mm) and biatrial dilation (left atrial volume of 45 mL/mq) (Figure 2A). Both left ventricular dimensions and left ventricular ejection fraction were normal. On the Doppler study and tissue Doppler imaging, the ratio of early mitral inflow to late filling velocity was 1.8, E wave deceleration time was 203 ms, the average mitral-to-myocardial early velocities ratio was 11, the ratio of mitral E-wave to colour M-mode propagation velocity was 4, the difference in duration of pulmonary vein and mitral flow at atrial contraction was 153 ms, and the estimated pulmonary artery systolic pressure was 45 mmHg (Figures 2B, 2C and 2D). These measurements suggested markedly elevated left ventricular filling pressure (5). The inferior ventricular wall was akinetic, and mild mitral and aortic regurgitation were found.

Laboratory findings, electrocardiogram and echocardiogram led to the suspicion of systemic amyloidosis; therefore, an abdominal fat aspiration was performed that resulted in amorphous pink deposits stained with Congo under light microscopy, which exhibited apple-green birefringence when examined using polarized microscopy.

Because low-dosage warfarin therapy caused excessive variability of international normalized ratio values (values reached 8), oral anticoagulation was discontinued.

During the patient's hospital stay, slow atrial fibrillation persisted and her heart rate remained very low despite the discontinuation of home therapy with beta-blockers (atenolol 100 mg/day, prescribed for chronic

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TABLE 1
Patient's laboratory test results

Laboratory test	Results	Reference range
White blood cells, $\times 10^9$/L	7700	4500–11,000
Hemoglobin, g/L	104	120–160
Hematocrit, %	32.7	36–46
Platelets, $\times 10^9$/L	198,000	150,000–450,000
Sodium, mEq/L	137	136–146
Potassium, mEq/L	4.8	3.5–5.1
Calcium corrected for albumin, mg/dL	10.8	8.7–10.3
Glucose, mmol/L	6	4.4–6.4
Blood urea nitrogen, mmol/L	34	6.1–17
Creatinine, µmol/L	107	38–84
Estimated creatinine clearance, mL/min	26	88–128
Albumin, g/L	23	34–48
Creatine kinase, IU/L	44	22–269
Creatine kinase-MB fraction, µg/L	1.8	0–4.5
Troponin I, µg/L	0.075	0–0.03
NT-proBNP, ng/L	4433	<450
Serum total protein, g/L	70	60–83
Lactate dehydrogenase, U/L	223	100–210
Beta-2 microglobulin, mg/L	7.4	<2.5
C-reactive protein, mg/dL	0.9	<0.5
Gamma-glutamyl transpeptidase, U/L	293	15–85
Alanine aminotransferase, U/L	26	5–40
Aspartate aminotransferase, U/L	34	5–45
Alkaline phosphatase, U/L	271	50–130

NT-proBNP N-terminal pro-brain natriuretic peptide

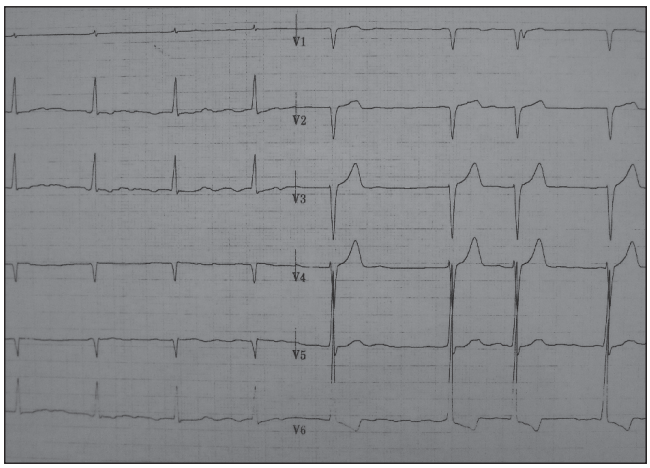

Figure 1) *Electrocardiogram showing atrial fibrillation with low ventricular response, normal voltage in the limb leads, QS wave pattern in anteroseptal precordial leads and voltage criteria for left ventricular hypertrophy with secondary repolarization abnormalities in the precordial leads*

ischemic heart disease). A unicameral pacemaker (VVI) was implanted to prevent recurrent syncopal episodes caused by slow atrial fibrillation. Permanent pacemaker implantation is indicated in cardiac amyloidosis patients meeting guideline conditions for device placement (6), although cardiac pacing improves only the symptoms, and not the survival rate (7).

At discharge, the patient was in good clinical condition. She was managed with angiotensin-converting enzyme inhibitors, low-dose furosemide, beta-blockers, aldosterone antagonists and acetylsalicylic acid. With the agreement of her hematologist and nephrologist, she was later prescribed a specific chemotherapeutic regimen.

DISCUSSION

We describe a case of cardiac amyloidosis in a patient with ischemic heart disease who presented with syncope and slow atrial fibrillation.

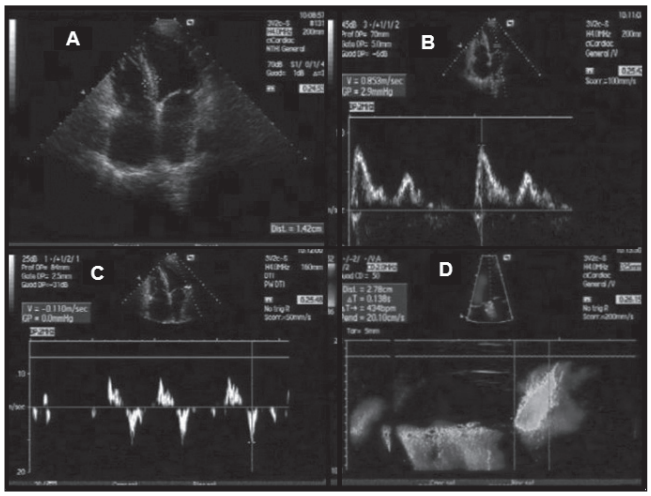

Figure 2) A *Two-dimensional echocardiogram in apical four-chamber view showing increased thickness of the interventricular septum (15 mm) and biatrial dilation (left atrial volume of 45 mL/mq).* **B and C** *Mitral inflow and anular Doppler tissue velocities showing an early mitral inflow to late filling velocity ratio of 1.8, a deceleration time of 203 ms and a mitral-to-myocardial early velocities ratio of 11.* **D** *Velocity propagation of early diastole and mitral E-wave to colour M-mode propagation velocity ratio of 4*

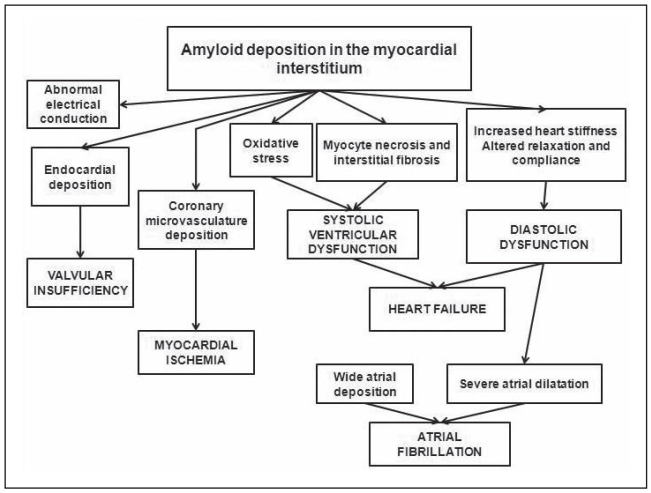

Figure 3) *Pathophysiology of cardiac amyloidosis and related heart diseases*

The presence of chronic coronary artery disease can confound the clinical picture, making the diagnosis of cardiac amyloidosis more difficult, because some signs of amyloidosis may be attributed to ischemic heart disease (atrial fibrillation, increased troponin levels, poor R wave progression and QS pattern on electrocardiogram, and signs and symptoms of heart failure). Moreover, some reports (8,9) indicate that AL amyloidosis can cause cardiac ischemia, owing to intramural vessel obstruction with apparently normal epicardial coronary arteries (Figure 3); therefore, amyloidosis could also worsen pre-existing ischemic heart disease, further reducing myocardial flow reserve.

The occurrence of syncope in patients with cardiac amyloidosis is not uncommon and confers a poor prognosis. Dubrey et al (3) found that syncope occurred in 20% of 232 patients with primary AL cardiac amyloidosis (3). Causal mechanisms reported in the medical literature included arrhythmias, conduction disturbance, orthostatic hypotension or vasovagal effects associated with neuropathy and, probably, dynamic left ventricular outflow tract obstruction secondary to asymmetric left ventricular hypertrophy of the basal septum (Figure 4) (2,3,10). In our case, syncope could be explained by several etiologies. Atrial fibrillation with slow atrioventricular conduction could be

related to biatrial dilation and to amyloid deposition in the S-A node and in the conduction system. The reduction of myocardial flow reserve could have contributed to arrhythmia and conduction disturbance. Atrial fibrillation is one of the most common arrhythmias in cardiac amyloidosis because of widespread atrial deposition of amyloid and diastolic dysfunction, resulting in severe atrial dilation (Figure 3).

In the present case, plasma cell dyscrasia, laboratory data (increased beta-2 microglobulin levels and normocytic anemia) and multiorgan involvement led us to suspect systemic amyloidosis with cardiac involvement. Electrocardiography revealed poor R wave progression and QS pattern in anteroseptal precordial leads (not referable to previous inferior myocardial infarction), and voltage criteria for left ventricular hypertrophy in the precordial leads. The patient's electrocardiogram did not show low voltages in the limb leads (one of the typical electrocardiographic signs of cardiac amyloidosis) (Figure 1). However, Dubrey et al (3) found a high prevalence of electrocardiographic pseudoinfarction pattern and low-voltage amplitudes (74.7% and 70.7%, respectively) in the 'cardiac amyloidosis population', whereas Murtagh et al (11) reported lower prevalences (47% and 46%, respectively). Although electrocardiographic signs of left ventricular hypertrophy in the precordial leads are not common in cardiac amyloidosis, they have been described in some patients, especially in association with conditions such as hypertension (11).

The patient's echocardiogram showed the typical amyloidosis pattern of severe diastolic dysfunction, increased wall thickness with normal left ventricular dimension and ejection fraction (Figure 2). Diastolic dysfunction is one of the earliest pathophysiological impairments and is a common finding on echocardiography. It worsens as myocardial infiltration progresses (12), whereas systolic function usually decreases in end-stage disease (13).

Increased levels of troponin I and brain natriuretic peptide are typical findings in patients with cardiac amyloidosis. The former is probably elevated because of myocyte necrosis (caused by amyloid deposition) and myocardial ischemia related to intramural vessel occlusion (14); the latter is probably related to elevated filling pressures and myocyte necrosis (15). Increased troponin I and brain natriuretic peptide levels correlate with poor prognosis (16,17).

The suspicion of cardiac involvement was not confirmed by endomyocardial biopsy; however, it was supported by the echocardiographic pattern, along with persistently increased levels of troponin I and brain natriuretic peptide, and clinical signs of heart failure in the presence of systemic amyloidosis.

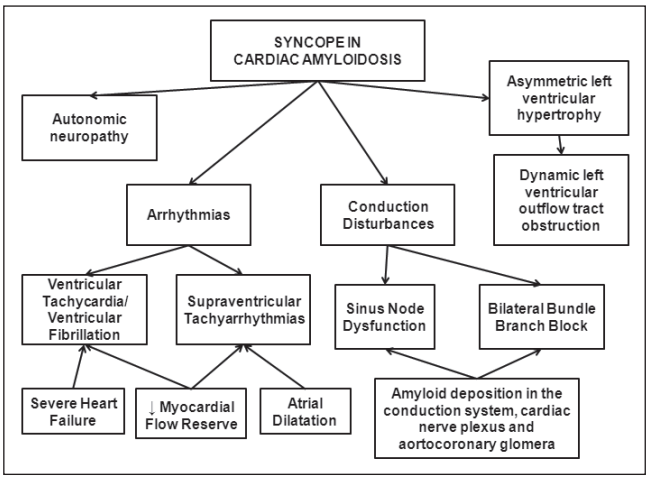

Figure 4) *The causal mechanisms of syncope in cardiac amyloidosis*

CONCLUSION

We have described an unusual case of cardiac amyloidosis in a patient with ischemic heart disease who presented with syncope and mild heart failure. Cardiac amyloidosis should always be considered a possibility in patients older than 60 years of age with heart failure and typical echocardiographic findings (diastolic dysfunction, biatrial dilation and increased ventricular wall thickness), electrocardiographic signs (pseudoinfarction pattern and/or low voltages in the limb leads), plasma cell dyscrasia and systemic involvement (especially hepatic, renal or gastrointestinal impairment) (3). Early recognition of AL amyloidosis is very important because specific treatment for this disease can significantly improve outcomes.

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