An Interesting Case of Cardiac Amyloidosis Initially Diagnosed as Hypertrophic Cardiomyopathy

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Cardiac involvement occurs frequently in primary amyloidosis and is associated with heart failure hospitalizations and poor survival. The initial presentation of the disease may be misleading, resulting in under-diagnosis of cardiac amyloidosis and late initiation of treatment. We present a case of cardiac amyloidosis initially misdiagnosed as hypertrophic cardiomyopathy and we discuss the key findings of the disease along with the latest evidence regarding the management and prognosis of cardiac amyloidosis.

Cardiac amyloidosis refers to a rare group of disorders caused by the extracellular deposition of insoluble abnormal fibrils, called amyloid, which are composed of a variety of serum proteins. Cardiac involvement may occur, with or without clinical manifestations, as a part of systemic amyloidosis or as a localized phenomenon, and is associated with poor prognosis.1,2 We present a case of biopsy-proven cardiac amyloidosis in a woman with symptoms of congestive heart failure who was referred to our hospital with the diagnosis of hypertrophic cardiomyopathy, and we discuss the key ECG and echocardiographic findings that a clinician should evaluate in order to eliminate under-diagnosis of cardiac amyloidosis, along with the current data concerning prognosis and treatment.

Case presentation

A 48-year-old woman was admitted to our clinic with dyspnea on exertion, fatigue, anorexia and lower limb edema. She so mentioned exertional chest pain. The patient was free of any personal history until three months before presentation, when peripheral edema and ascites first occurred. The diagnosis by her cardiologist was hypertrophic cardiomyopathy, based on asymmetrical hypertrophy of the left ventricle on echocardiography. She had no family history of cardiovascular disease, sudden cardiac death or syncope.

On physical examination she had blood pressure 90/70 mmHg, heart rate 66 beats/min, a second heart sound with an increased intensity of the pulmonic component, a 2/6 apical systolic murmur and normal lung auscultation. Jugular vein dilatation and a palpable liver with positive hepatojugular reflux were present, along with signs of ascites. There was a first degree atrioventricular block on the ECG and a pseudo-infarct pattern without signs of left ventricular hypertrophy (Figure 1). The chest X-ray on admission showed cardiomegaly. Blood count was normal. Serum biochemistry was normal except for elevated creatine kinase (CPK), 435 U/L,
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with the myocardial isoenzyme CK-MB equal to 25 U/L, and elevated lactate dehydrogenase. Serum homocysteine levels were also increased (14.7 μmol/L, normal range 9-12 μmol/L). Testing for connective tissue diseases was negative (Ra test, antinuclear and anti-mitochondrial antibodies).

Echocardiographic study showed asymmetric hypertrophy of the left ventricle, with the posterior wall thicker than the septum (20 and 16 mm, respectively) and a granular “sparkling” texture. The left and right atria were dilated and there was a small pericardial effusion (Figure 2). Transmitral Doppler flow revealed a restrictive filling pattern (Figure 3) with an E wave equal to 1.3 m/s, an A wave equal to 0.6 m/s, and an E/A ratio >2; reduced deceleration time ≤150 ms; and the diastolic wave of pulmonary vein flow higher

Figure 1. Twelve-lead ECG on admission showed a QS complex in lead V1, Rsr complex in V2, rS in V3, QS in V4, rS complexes in V5 and V6, and QS waves in leads II, III, aVF, consistent with a pseudo-infarct pattern. A first-degree atrioventricular block is also present, with a PQ duration of 325 ms.

Figure 2. Parasternal short axis view (A) and apical four-chamber view (B) revealed thickened left ventricular walls with a granular “sparkling” appearance, enlarged atria and a small pericardial effusion. LV – left ventricle; LA – left atrium; RV – right ventricle; RA – right atrium; IVS – interventricular septum; LVPW – left ventricular posterior wall; PE – pericardial effusion.
than the systolic. Tissue Doppler imaging revealed reduced systolic and diastolic mitral annular velocities. There was mild mitral and tricuspid regurgitation and the estimated right ventricular systolic pressure was 34 mmHg.

The patient was on atenolol 50 mg/day and a hydrochlorothiazide-amiloride combination (25/2.5 mg). Amiodarone 200 mg twice daily was added because of multifocal ventricular premature beats and an episode of non-sustained ventricular tachycardia on the 24-hour ECG. On the fifth day of treatment with amiodarone the patient experienced a presyncopal episode with nausea, dizziness, hypotension (systolic arterial pressure equal to 65 mmHg) and a slow junctional rhythm of 38 bpm. A temporary pacemaker was implanted while atenolol and amiodarone were withdrawn. The pacemaker was removed three days later when sinus rhythm was restored and amiodarone was started again in a smaller dose of 200 mg once daily.

Coronary angiography showed normal coronary arteries. Ventriculography revealed a reduced ejection fraction and mild to moderate mitral regurgitation. Right heart catheterization had the following findings: mean right atrial pressure 9 mmHg, right ventricular pressures 35/0-10 mmHg (systolic/diastolic-mean), pulmonary artery pressure 36/12-24, mean capillary wedge pressure 18 mmHg and increased left ventricular end-diastolic pressure of 19 mmHg (systolic 105 mmHg). An endomyocardial biopsy was taken, which revealed severe lesions consistent with cardiac amyloidosis with muscle cell necrosis (Figures 4 & 5).

Once the diagnosis of amyloidosis was established by echocardiographic and biopsy findings, methylprednisolone 16 mg daily was added and we sought to differentiate between primary amyloidosis (PA) and secondary amyloidosis (SA). PA is often associated with multiple myeloma, which was ruled out using appropriate tests. Urine protein immunoblotting indicated a lambda light monoclonal chain, which is diagnostic for PA.

The patient was treated with amiodarone 200 mg daily, furosemide 40-80 mg, spironolactone 50-100 mg and folic acid. During six months of follow up, symptoms of right heart failure with ascites and pe-

Figure 3. Transmirtal Doppler flow showed a restrictive filling pattern with E/A >2, reduced deceleration time and reduced isovolumic relaxation time. E – early diastolic velocity; A – late diastolic velocity.

Figure 4. Extended degeneration of the myocardium, vacuolization and disruption of the cardiac myocytes. Focal necrosis and interstitial fibrosis are also seen.

Figure 5. Amyloid (black arrows) was identified on immunohistochemical testing with the use of monoclonal antibodies.
Peripheral edema were prominent and resulted in repeated hospitalizations. Chemotherapy cycles with melphalan hydrochloride 14 mg and methylprednisolone 16 mg three times daily were added without any improvement. One month after diagnosis, the patient’s condition was complicated by thrombosis of the celiac aortic bifurcation and the right deep femoral artery (Figure 6). Thrombectomy with a Fogarty catheter was performed and dicoumarol was added. Repeated hospitalizations due to congestive heart failure continued until nine months after diagnosis when the patient died suddenly while asleep. A 24-hour ECG fifteen days before death was negative for malignant arrhythmia.

Discussion

Our patient presented with symptoms of right heart failure and echocardiographic findings of asymmetric hypertrophy of the left ventricle. The initial diagnosis by the referring cardiologist was hypertrophic cardiomyopathy. A closer observation, however, of the echocardiographic and ECG findings was sufficient to call into question the diagnosis of hypertrophic cardiomyopathy. Moreover, it is interesting that our patient had a typical disease course, which was complicated by both arrhythmias and thrombosis, and typically died suddenly while asleep, nine months after cardiac involvement occurred.

The ECG in hypertrophic cardiomyopathy shows signs of left ventricular hypertrophy, while our patient presented low voltage R waves. A normal ECG may be present in 15% of hypertrophic cardiomyopathy patients, usually those with localized hypertrophy. Low voltage waves in the limb and the precordial leads are the most common ECG finding in cardiac amyloidosis and are present in over 50% of patients with PA. The largest series of ECG findings, in 127 patients with PA and biopsy-proven cardiac involvement, comes from the Mayo Clinic. The two main ECG abnormalities were the presence of low voltages and a pseudo-infarct pattern in 46% and 47% of patients, respectively. Both ECG findings were present in 25% of patients. Our patient had low voltages and poor R-wave progression in the precordial leads, as well as abnormal Q waves in the limb and the precordial leads.

Thickening of the left ventricular wall due to amyloid infiltration can be misdiagnosed as true left ventricular hypertrophy. The increased left ventricular wall thickness in cardiac amyloidosis, however, is associated with low voltages on the ECG and this feature is a specific finding for infiltrative diseases, of which amyloidosis is the most common. Rahman et al showed that a septal thickness >1.98 cm combined with low voltages on ECG has a sensitivity of 72% and a specificity of 91% for the diagnosis of cardiac amyloidosis.

The granular “sparkling” appearance of the myocardium in echocardiography is characteristic, but not specific to amyloidosis. In one series this finding was present in 26% of patients. This echocardiographic criterion has a sensitivity of 87% and a specificity of 81% for the diagnosis of cardiac amyloidosis, but when atrial enlargement is also present it can reach a sensitivity of 100%.

Doppler transmitral flow measurements showed a restrictive filling pattern with an E/A ratio > 2. Restrictive physiology in cardiac amyloidosis is attributed to amyloid infiltration, which results in a stiff myocardium. Systolic function impairment is a late phenomenon. Tissue Doppler imaging in cardiac amyloidosis has been shown to detect early diastolic dysfunction, even with minimal wall thickening. Moreover, a tissue Doppler mitral annular early diastolic velocity (E') < 8 cm/s can discriminate between restrictive cardiomyopathy and constrictive pericarditis.

Differential diagnosis between PA and SA is important in order to specify further management and prognosis. Cardiac involvement occurs in 50% of patients with PA and has been associated with severe
cardiac impairment and a worse prognosis than cardiac involvement due to SA; the median survival is 1.08 years and is shorter in the presence of heart failure.9

PA involves extracellular tissue and cardiac deposition of fibrils, called amyloid, that are composed of light chain immunoglobulin (AL) produced by monoclonal plasma cells.10 Multiple myeloma and Waldenstrom macroglobulinemia are the two main diseases associated with PA.1 Multiple myeloma and amyloidosis may coexist, or the diagnosis of multiple myeloma may come before or after the presentation of amyloidosis or cardiac amyloidosis. Amyloid deposition in the heart may involve the myocardium and the conductive system. Other sites where amyloid can be found are the intima, media and adventitial layers of the epicardial11 and endomyocardial coronary arteries, the cardiac valves and the pericardium. Extensive amyloid deposition in coronary arteries may result in typical anginal symptoms with normal coronary angiography.12

Amyloid deposition in the conductive tissue may cause atrioventricular conduction abnormalities, mainly second- and third-degree atrioventricular block. Patients with cardiac amyloidosis are sensitive to digitalis, nifedipine and verapamil. It is possible that this increased sensitivity to antiarrhythmics was the substrate for the manifestation of junctional rhythm in our patient, as a response to treatment with the combination of atenolol and amiodarone, while a reduced dosage of amiodarone alone was well tolerated.

Our case was complicated by thrombosis of the celiac aortic bifurcation and the right deep femoral artery. Even though amyloidosis may be associated with hemorrhagic diathesis, the occurrence of thromboembolic episodes is common even in sinus rhythm. In one series of patients with PA, 9 out of 15 patients who were not receiving anticoagulation therapy had arterial thromboembolic events involving ischemic stroke, multiple peripheral emboli and mesenteric ischemia. All 9 patients were in sinus rhythm and only one had a visible thrombus on echocardiography.13 It is generally believed that amyloid deposition in atrial walls results in a mechanic atrial standstill, which favors thrombus formation. This is the rationale behind the recommendation of dicoumarol prescription in patients with severe cardiac amyloidosis and abnormal atrial function.

The prognosis of PA is poor, with a mean survival of 13 months without treatment, which may be prolonged to 17 months after cyclic melphalan and methylprednisolone treatment.14 Cardiac involvement is associated with an even worse prognosis. Mean survival from onset of heart failure symptoms is no more than 6 months and predisposes to sudden death.15

Heart transplantation remains controversial because of the potential for amyloid deposition in the graft, or for multiple myeloma occurrence during follow up. There are a few patients who have received a cardiac transplant and shown variable survival. Early postoperative results do not differ from other heart transplantation patients, but survival rates drop 30 months after transplantation in amyloidosis patients.1 The survival of 7 patients with PA treated with heart transplantation and chemotherapy in the United Kingdom was 71% at 1 and 2 years, but 36% at 5 years.16 High-dose intravenous melphalan in combination with stem cell autologous transplantation is currently used for systemic PA, but its efficacy has not yet been proved. The overall survival of 92 patients who received this treatment in the United Kingdom was 5.3 years and survival among those who survived beyond day 100 was 8.5 years.17 Alternatively, a more aggressive treatment with sequential heart and stem cell transplantation has been applied in selected patients; after a median of 95 months follow up, 3 out of 5 patients were asymptomatic, without evidence of cardiac or extra-cardiac amyloid accumulation.18 Recently, new chemotherapy regimens have been developed and various specific anti-amyloid drugs have shown very promising results.19

In conclusion, cardiac amyloidosis is a severe disease with a poor prognosis. The clinical cardiologist should suspect cardiac amyloidosis in a patient with right heart failure symptoms and thickened left ventricular walls, with a restrictive filling pattern of the left ventricle combined with low voltages on the ECG. In addition, anticoagulation treatment with dicoumarol is recommended in patients with severe cardiac amyloidosis, even those in sinus rhythm, in order to avoid thromboembolic events.

References

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