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Cardiac amyloidosis and hypertrophic cardiomyopathy: A dangerous liaison

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CLINICAL CASE

This is a case of a 50-year-old woman complaining of easy fatigability, anorexia and hypotension since 2009. She also reported alopecia, a 15 kg weight loss, and amenorrhea. A year after the beginning of the symptoms she sought medical attention: a diagnosis of nephrotic syndrome with proteinuria >10 g/L was made. A renal biopsy showed focal segmental glomerulosclerosis. Steroids and cyclosporin were then started. The patient did quite well until November 2011 when she was hospitalized for the recurrence of the symptoms. Because of persistent hypotension, Rituximab therapy instead of Bortezumib was instituted. At that time the ECG showed sinus rhythm with low QRS voltages and Q waves in the inferior leads and from V1 to V4. An echocardiogram showed severe symmetric left ventricular hypertrophy (21 mm of the interventricular septum and 20 mm of the posterior wall diastolic thickness). The left ventricular walls showed an inhomogeneous granular pattern. During systole, a virtual left ventricular cavity was evident with a left ventricular ejection fraction (LVEF) around 60%. A severe dynamic left ventricular outflow tract (LVOT) obstruction was present with a left ventricular-aortic gradient of 120 mmHg at rest and 250 mmHg during the Valsalva maneuver. Moderate mitral regurgitation with a systolic anterior motion (SAM) of the mitral valve was demonstrated. Severe diastolic dysfunction was present, with an E/E' ratio of 12.3 cm/s (Figure 1).

The clinical and echocardiographic picture raised the diagnostic issue of a systemic amyloidosis with cardiac involvement or the presence of hypertrophic cardiomyopathy (HCM) in a patient with nephrotic syndrome. No family history of HCM was reported. To establish a correct diagnosis a more detailed work-up was then carried out: the renal biopsy specimens were reanalyzed with the Congo red staining and resulted positive for amyloid fibrils (Figure. 2). A diagnosis of λ light chain (AL) systemic amyloidosis was entertained based on the results of the immunological blood work (monoclonal immunoglobulin on urine and serum, serum immunofixation, quantitative measurement of serum κ and λ free light chains) and the results of the abdominal fat aspiration and bone marrow biopsies which were positive for amyloid. In addition, a cardiac magnetic resonance imaging (MRI) demonstrated, with the late gadolinium subendocardial enhancement (LGE), an endocardial-epicardial signal intensity gradient typical for heart amyloidosis, with the early gadolinium clearance from the blood pool. This pattern of gadolinium distribution suggested cardiac amyloidosis (Figure 1). At this point the diagnosis of systemic amyloidosis with a cardiac involvement seemed to be corroborated. Therefore therapy with cyclophosphamide, thalidomide and dexamethasone was initiated. However, for the completeness of a diagnostic work up, a genetic typing test for HCM was also sent to the lab.

After an initial clinical improvement, the patient experienced symptoms of severe heart failure. She was hospitalized and Bortezumib was started. Unfortunately the renal function progressively worsened and dialysis was necessary. After three cycles of chemotherapy the patient improved her functional class and was discharged home on dialysis three times a week. No more episodes of heart failure

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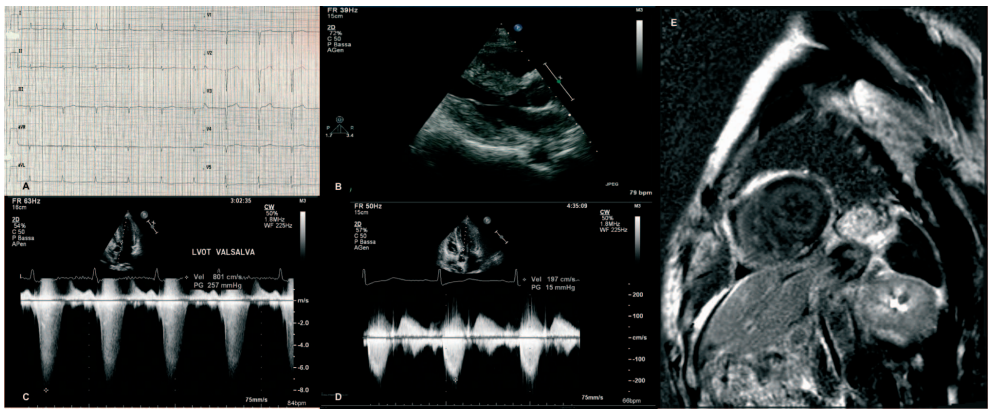

Figure 1. ECG showing sinus rhythm, low QRS voltages, Q waves on the inferior leads and on V1-V4 (A). Echocardiography showing increased ventricular mass and granular sparkling pattern (B) and severe LVOT gradient on Continuous-wave Doppler (C). Decreased LVOT gradient after starting chemotherapy (D). MRI: LGE image demonstrating an endocardial-epicardial signal gradient and disappearance of the contrast agent from the blood pool (E).

occurred in the follow-up. Follow-up echocardiography at 3, 6 and 12 months demonstrated a gradual improvement. The 12-month echocardiogram showed a reduced septal thickness of 17 mm and the peak LVOT gradient decreased significantly from 120 mmHg to 15 mmHg at rest without an increase with the Valsalva maneuver. LVEF improved to 70%, mitral regurgitation was mild with no more evidence of SAM and diastolic dysfunction improved to a pseudonormal filling pattern with a E/E' ratio of 10 cm/s.

Surprisingly, the results of the genetic typing came back positive for a double heterozygous mutation on p.Arg1079Gln for MYH7 gene (suggesting HCM) and on p.Cys566Ser for MYBPC3 (a novel mutation, never described in the literature, in a highly conserved amino acid).

At the present time the patient is doing well with diuretic therapy (Furosemide 50 mg per day, Spironolactone 25 mg per day, potassium chloride 600 mg tid), prednisone and chemotherapy cycles.

DISCUSSION

AL amyloidosis is an uncommon disease with a dire prognosis.[1–3] Cardiac involvement is usually part of a systemic disease; when heart failure develops, death can ensue within 4–6 months.[4–5] By contrast, HCM is relatively common with a more favorable prognosis.[6] The presence of LVOT obstruction has been reported only in a few cases of amyloidosis[7–11] and the AL type amyloidosis is probably the rarest one. In addition the LVOT gradients described are not as high as it was in our patient.

Differential diagnosis between cardiac amyloidosis and HCM is mandatory since the prognosis is very different. Our patient experienced symptoms and signs of nephrotic syndrome associated to

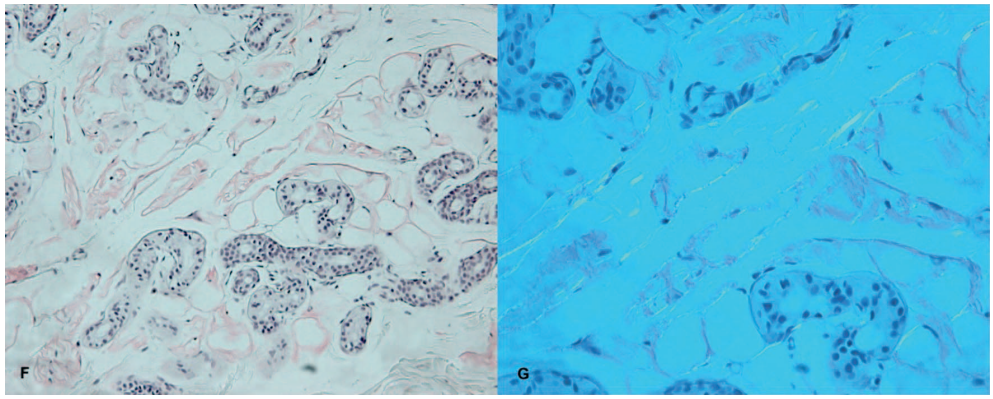

Figure 2. Renal biopsy. Light microscopy of hematoxylin and eosin-stained kidney showing infiltration by collagen-type extracellular material (F). Polarized microscopy of Congo red-stained kidney showing apple-green birefringence, diagnostic of amyloid (G).

episodes of heart failure. The ECG demonstrated low QRS voltages with pathological Q waves in the inferior and anterior leads pointing towards an infiltrative disease. However, the echocardiographic findings of severe septal wall thickness, the presence of SAM of the mitral valve with mitral regurgitation and the demonstration of a dynamic LVOT gradient suggested a diagnosis of HCM, whereas the typical granular appearance of the cardiac walls favored a cardiac involvement of systemic amyloidosis (Figure 1).[12] The clinical picture, the ECG and the echocardiographic findings were somewhat discordant. To settle the diagnostic issue a cardiac MRI was performed. The LGE images demonstrated a circumferential endocardial-epicardial signal gradient typical for amyloid infiltration. As an extracellular fluid tracer, gadolinium accumulates in expanded interstitial spaces, which are increased secondary to extracellular amyloid infiltration. This behavior determines the early gadolinium disappearance from the blood pool (Figure 1). These features are highly sensitive and specific for amyloid involvement of the heart.[13] A diagnosis of systemic amyloidosis with a cardiac involvement was favored and, in addition to heart failure treatment, the patient was started on chemotherapy for the systemic amyloidosis (Cyclophosphamide, Bortezumib and Dexamethasone cycles) to which she responded very well. Surprisingly, genetic typing resulted positive for a double heterozygous mutation on p.Arg1079Gln for MYH7 gene and on p.Cys566Ser for MYBPC3, diagnostic of HCM. The positivity of genetic testing for mutations diagnostic of HCM raises the question of the clinical meaning of the genetic testing. To our knowledge the possible coexistence of amyloidosis and HCM has never been described in the literature. It seems unclear if we face a case of cardiac amyloidosis with a positive genetic typing for HCM without a real phenotypic expression or, on the other hand, we assist to an atypical clinical presentation of HCM in a patient with systemic amyloidosis. The answer is difficult and maybe only the clinical follow-up will clarify the issue. Moreover, the role of the novel mutation in a highly conserved amino acid has to be followed out.

CONCLUSIONS

To our knowledge, this is the first reported case of a patient with cardiac involvement of systemic amyloidosis and genotyped HCM presenting with neprothic syndrome and heart failure.

The multimodality diagnostic approach including ECG, echocardiogram, renal and abdominal fat biopsies, cardiac MRI and the genetic testing allowed to diagnose the presence of both the diseases in the same patient.

The predominant role of one pathology versus the other one in determining the clinical scenario and the response to the treatment has not been completely clarified yet.

COMPETING INTERESTS

No authors have conflicts of interests.

AUTHORS' CONTRIBUTIONS

E.E.: contributed to the conception and design of the study, contributed to the acquisition, analysis and interpretation of data, drafted the manuscript and given final approval to the manuscript version submitted for publication.

P.D.D.: contributed to the conception and design of the study, contributed to the acquisition, analysis and interpretation of data, drafted the manuscript and given final approval to the manuscript version submitted for publication.

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F.G.: contributed to the conception and design of the study, revised the manuscript critically for content and given final approval to the manuscript version submitted for publication.

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All authors read and approved the final manuscript.

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