Heart Failure and Cardiac Involvement as Isolated Manifestation of Familial Form of Transthyretin Amyloidosis Resulting From Val30Met Mutation With No Clinical Signs of Polyneuropathy

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A 63-year-old white man with a 6-month history of progressive exertional dyspnea was referred for evaluation. In 1997, he presented an episode of unconsciousness as first symptom of a cardiac disease. In 2003, arterial hypertension, as well as atrioventricular block Mobitz type I, was diagnosed. A worsening of the biventricular heart failure over the last 2 years led to his admission at our clinic in 2008, with dyspnea at rest and bilateral pleural effusions. At admission, the patient appeared to be well, with a blood pressure of 142/76 mm Hg and a pulse of 97 bpm. Jugular venous pulse was not elevated, but mild bilateral edema of the lower extremities was noted. The lungs were clear to auscultation, with attenuation on the right side because of pleural effusion. The patient’s symptoms improved slightly through pharmacological therapy, but he remained in New York Heart Association functional class III heart failure. Laboratory studies revealed normal blood cell counts and electrolyte panel, with signs of load on the right side of the heart. The highest B-type natriuretic peptide was 818.6 pg/mL (normal, <100 pg/mL). The 24-hour urine protein collection was outside of normal limits at 0.27 g (normal, <0.15 g), and glomerular filtration rate according to the modified Cockcroft-Gault was 58 mL/min (stage III chronic renal insufficiency according to Kidney Disease Outcome Quality Initiative (K/DOQI)). ECG was a pacemaker ECG. Transthoracic echocardiography revealed an increased wall thickness with increased left-ventricular myocardial mass, increased left-ventricular filling pressure, septal and inferior hypokinesia of the left ventricle, mitral (valve) insufficiency grade 1, left-ventricular filling pattern, and missing a-wave by phase-contrast imaging of the mitral valve inflow. Left ventricular end-diastolic volume (141 mL), end-systolic volume (63 mL), and ejection fraction (63%) were within physiological parameters. Left ventricular myocardial mass was 344 g: the resulting left ventricular myocardial mass index was elevated with 171 g/m² (normal, <95 g/m²). In the late phase (late gadolinium enhancement) after administration of contrast material (0.2 mmol/kg body weight), we noticed an exactly circumscribed circular subendocardial accumulation in the myocardium of the entire left ventricle. Additionally, several small circumscribed islands with considerable late gadolinium enhancement were enclosed in the ventricular septum. The entire right ventricular myocardium strongly and homogeneously accumulated contrast material.

Cardiac catheterization revealed restrictive cardiomyopathy, with an equalization of the left ventricular and right ventricular end-diastolic pressure, nonstenosed coronary heart disease, and pulmonary-arterial hypertension (mean, 51 mm Hg) class II, according to the revised clinical classification as proposed at the Venice conference. The patient’s peak oxygen uptake was diminished to 8.8 mL/min per kg (Weber D), and right ventricle catheterization revealed a cardiac index of 2.47 L/min per m². Chest x-ray showed effusion of the right pleura, with cardiomegaly (heart-lung quotient: 18.5/32) and signs of chronic pulmonary congestion, as well as mainly right-sided pleural effusion. Although there was no family history of amyloid disease, the clinical features in this case were consistent with amyloidotic cardiomyopathy. Diagnosis of familial transthyretin (TTR)-associated amyloidosis was considered after endomyocardial
Figure 1. A, Echocardiographic 4-chamber view. Typical for cardiac amyloidosis are thickened walls with normal ventricular diameter, thickened valves, bialtrial enlargement, and increased myocardial echogenicity. B, Cardiac amyloidosis in MRI. Late enhancement and the so-called “zebra-pattern” are typical for amyloidosis.
Figure 2. Diagnosis of amyloid, exhibited in a tissue sample of the right ventricle. By using electron microscopy, distinct changes could be noticed, which are typical for amyloid deposits in the extracellular space. Those deposits are marked by arrows.
biopsy revealed amyloid plaques in the patient’s heart. The cardiac interstitium was widened by pericardiomycyal deposits and widespread hyalinosis. These deposits were not tingeable by Congo red staining, using light microscopy or fluorescence microscopy, but in polarization microscopy, they presented typical green birefringence. In some patients with type 1 familial amyloid polyneuropathy, amyloid deposits are resistant to pretreatment with potassium permanganate in Congo red staining. Here, TTR was identified through immunohistochemistry. Electron microscopy of the extracellular deposits showed changes characteristic of amyloid (Figure 2). Immunohistochemical analyses with antibodies against TTR, serum amyloid P-component, AA-amyloid, apolipoprotein A1, fibrinogen, lysozyme, k-light chain, and w-light chain resulted only in a strong and homogeneous reaction with the anti-TTR but not against serum amyloid P-component. Total body bone scan with administration of 99mTc-3,3-diphosphono-1,2-propano-1,2-dicarboxylic acid (99mTc-DPD) revealed an increased pan-myocardial accumulation of 99mTc-DPD both during blood pool and in mineralization phases.

As we suspected TTR amyloidosis, we initiated sequence analysis of all 4 coding regions in the TTR gene. This revealed a Val30Met mutation (GTG>ATG) in codon 30 of exon 2, a mutation that results in increased amino acid mass by ~30 Da and usually causes autonomic neuropathy, polyneuropathy, and amyloid deposits in the vitreous body as well as the leptomeningeal membranes. Patients with type 1 familial amyloid polyneuropathy have been reported to develop ocular disorders and central nervous symptoms, especially after liver transplantation. Ophthalmologic examination revealed a stage III hypertonic fundus. Intraocular pressure was within physiological parameters on both eyes (15 mm Hg), visual acuity was 20/20, and pupils were round and reacted normally. Neurological examination revealed only a slight pallhypesthesia of the left foot and the right medial malleolus (5/8).

More than 400 cases with individuals carrying the Val30Met TTR mutation have been published. It is rare that a patient carrying this mutation primarily develops amyloid cardiomyopathy. Other authors report that patients with the Val30Met mutation usually show sensorimotor peripheral neuropathy; cardiac involvement is uncommon and rarely functionally significant.

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Disclosures
None.

References
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