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ORIGINAL ARTICLE

Amyloid Cardiomyopathy in the Rare Transthyretin Tyr78Phe Mutation

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Abstract

Tyr78Phe is a rare pathogenic transthyretin (TTR) mutation. Few previous reports described a late-onset hereditary transthyretin-related amyloidosis (ATTR-m) form with a variable phenotype, mainly dominated by neurological manifestations. We describe the case of a 69-year-old male with massive but asymptomatic cardiac infiltration and only subclinical neurological involvement, and review the literature to depict characteristics of the Tyr78Phe TTR mutation.

Keywords Transthyretin · Amyloidosis · Amyloid cardiomyopathy · Tyr78Phe · Transthyretin familial amyloid polyneuropathy

More than 120 mutations in the transthyretin (TTR) gene have been reported to cause hereditary transthyretin-related amyloidosis (ATTR-m), with a variable clinical expression of the disease [1]. Tyr78Phe is a rare mutation whose clinical phenotype has not been previously completely elucidated.

We report the case of an asymptomatic 69-year-old man with no family history of cardiomyopathy, no cardiovascular risk factors, who had always been an active person, at that time regularly playing tennis. At the age of 55, he had surgery for bilateral carpal tunnel syndrome (CTS). Due to his recreational sport activity, he has undergone periodical clinical assessment since 2006. In 2015, a transthoracic echocardiogram (TTE) demonstrated left ventricular hypertrophy (LVH) (23 mm in the basal interventricular septum), interpreted as "athlete's heart." No other investigation was performed until May 2017, when hypertrophic cardiomyopathy (HCM) was for the first time suspected. The first visit to our clinic was in October 2017. Electrocardiogram showed sinus rhythm, first-degree atrio-ventricular block, and diffuse ST-T segment abnormalities (Fig. 1a). TTE was repeated demonstrating significant symmetric LVH (24 mm in the basal septum and 19 mm in the posterior wall), normal systolic function, grade-I diastolic dysfunction, significant thickening of atrio-ventricular valves and of the interatrial septum, slight bi-atrial enlargement, right ventricular hypertrophy (9 mm), and no pulmonary hypertension nor pericardial effusion (Fig. 1b). Given the suspicion of an amyloidotic infiltrative disease, further testing was pursued. A light-chain etiology was excluded due to a lack of abnormal findings (protein electrophoresis, serum-free light-chain assay and immunofixation, urine Bence-Jones protein research). Cardiac magnetic resonance confirmed LVH (Fig. 1c) with patchy non-specific late gadolinium enhancement in the interventricular septum. Finally, a bone scintigraphy with (99 m)technetium-hydroxymethylene diphosphonate showed low-to-moderate uptake of the radionuclide in the myocardium (reported Perugini score 2) (Fig. 1d). DNA sequencing found the Tyr78Phe mutation in the TTR gene. A neurological evaluation highlighted a mild weakness involving the dorsal and plantar flexion of halluces and a distal sensory impairment to vibration. No signs of autonomic involvement were identified. An electromyography study showed an axonal sensory neuropathy with a decrease of both sensory nerve action potentials recorded by antidromic technique (left 2.2 μV, right 4.3 μV; n.v. > 5 μV). To date, Tyr78Phe has been reported in four cases, after the recognition of its pathological potential in an in vitro model [2]. It was firstly reported by Anesi et al. [3] in a 70-year-old male with both severe cardiac and neurological symptoms, preceded by a history of bilateral CTS 10 years before.

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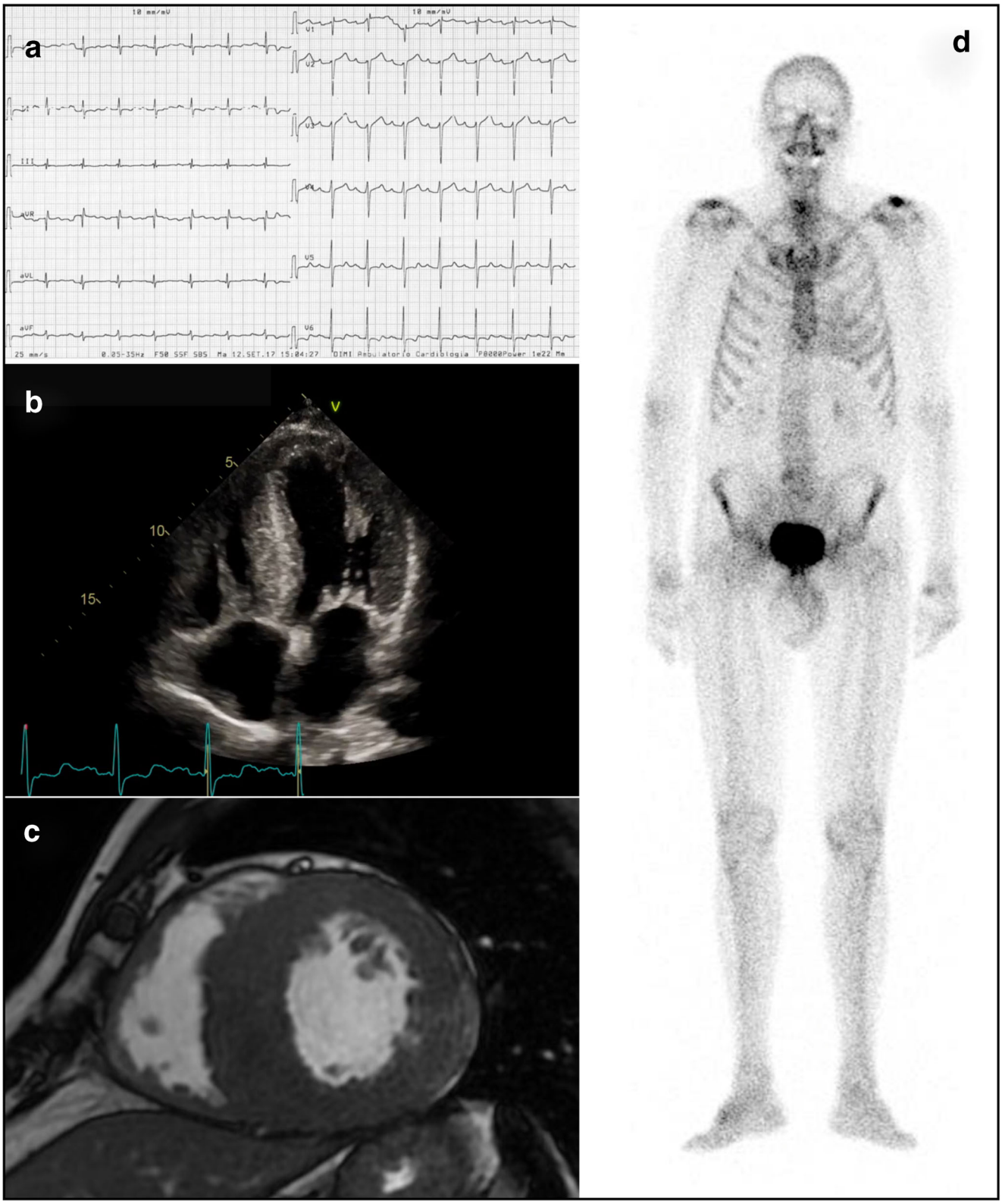

Fig. 1 Electrocardiogram (ECG) showing sinus rhythm, first-degree atrio-ventricular block, and diffuse ST-T segment abnormalities (**a**). Transthoracic echocardiogram (TTE) (**b**) and cardiac magnetic resonance study (**c**) show symmetric left ventricular hypertrophy, significant thickening of the atrio-ventricular valves and interatrial septum, as well as right ventricular hypertrophy. (99 m)technetium-hydroxymethylene diphosphonate bone scintigraphy (**d**) shows low-to-moderate radionuclide uptake in the myocardium (reported as Perugini score 2)

The patient suffered also from macroglossia, hepatomegaly, proteinuria, weight loss, and gastrointestinal symptoms. In 2009, Magy et al. [4] described the mutation in a 78-year-old man, who presented with a 5-year history of lower limbs paraesthesia and a surgery for bilateral CTS 15 years before. Clinical conditions were characterized by an axonal sensory-motor neuropathy of the lower extremities and by skin infiltration, with no evidence of cardiac involvement. Riboldi et al. [5] in 2011 reported the mutation in a case with only neurological manifestations. The 63-year-old male patient presented with dysphagia and lower limbs weakness which began 4 years before, and had had a history of bilateral CTS, treated surgically at the age of 44 and 55 years. He had a severe and rapid neurological progression with mainly motor involvement and only minimal sensory signs. Finally, in a contemporary Italian series of 186 ATTR-m patients, only one Tyr78Phe subject was identified, with isolated cardiac involvement [1].

In our case, the patient has subclinical cardiac and neurological involvement. Neurological findings are mild, while cardiac infiltration had been present for at least 2 years (without symptoms) before the suspicion of an underlying pathological condition was raised. Nevertheless, cardiac findings led to the recognition of neurological involvement. This early diagnosis may significantly impact the prognosis of our patient, having allowed the initiation of an etiological treatment. Tyr78Phe probably presents with late-onset intermediate clinical manifestations, with neurological involvement likely to be dominant and cardiac manifestations of less importance. However, it carries a significant phenotypical heterogeneity. The mutation appears to have a definite Italian geographical context. Beyond the patient in the Italian registry and the one herein described, one subject was a French man of Italian origin [4], whereas the two others reported by Italian investigators may be assumed to be Italian [3, 5]. Family history is reported only in the case by Magy: among 9 siblings (one dead), the mutation was found in 4 of them, with only one reported to have phenotypic evidence of the disease [4]. Unfortunately, no information regarding age or clinical conditions of the mutation-positive siblings was given. Nonetheless, the fact that among 4 carriers only one had an overt phenotypical manifestation of the disease is in line with the subclinical presentation of our patient.

Compliance with Ethical Standards

This study complied with all ethical standards involving human subjects. The patient consented to participation into clinical surveys by signing an informed consent.

Conflict of Interest The authors declare that they have no conflict of interest.

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