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Case Report

Early Diagnosis of Hereditary Cardiac Amyloidosis in a Carrier of the Ile88Leu Mutation: Is Endomyocardial Biopsy Indicated?

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Abstract

Variant transthyretin amyloidosis (ATTR-v) is an inherited systemic rare disease associated with high mortality. Disease-modifying drugs are more effective the earlier they are started. Identification of early cardiac involvement is a clinical priority in order to start therapy as early as possible. A 56-year-old man was shown to be a carrier of the Ile88leu mutation of the transthyretin (TTR) gene in the context of a family screening. The initial identification of disease allowed for an early start of specific therapy.

Keywords: Cardiac Amyloidosis; Tranthyretin; Endomyocardial Biopsy; Therapy.

Introduction

Variant transthyretin amyloidosis (ATTR-v) is an inherited systemic rare disease associated with high mortality, due to misfolded transthyretin (TTR) protein accumulation in the form of amyloid fibrils within the extracellular space of various organ especially peripheral nervous system and myocardium caused by mutation in TTR gene [1]. Deposition of misfolded TTR protein in the heart leads to restrictive cardiomyopathy, heart failure and arrhythmias [2].

Disease-modifying drugs are more effective the earlier they are started. Identification of early cardiac involvement is a clinical priority in order to start therapy as early as possible [3].

Here we present the case of a patient carrier of the TTR gene mutation in whom early identification of disease allowed early treatment to begin.

Case Report

A 56-year-old man was shown to be a carrier of the Ile88leu mutation of the TTR gene in the context of a family screening. The patient was symptomatic for palpitations. Blood tests, including cardiac Troponin and NTproBNP were normal. Serum and urine immunofixation electrophoresis were negative for monoclonal gammopathy. The ECG showed sinus rhythm, within normal atrioventricular and intraventricular conduction but frequent ventricular ectopic beats (VEBs) (Figure 1 panel A). Transthoracic echocardiogram documented normal ventricular size and thickness and preserved left ventricular systolic function (Figure 1 panel B), also strain rate evaluation was normal; no valvulopathy or

pericardial effusion was present. In order to identify early cardiac involvement, the patient underwent cardiac magnetic resonance imaging (MRI) and biphosphonate scintigraphy (Figure 1 panel C) that were negative for cardiac involvement. Neurological examination showed initial bilateral carpal tunnel syndrome. However, Holter monitoring revealed the presence of frequent monomorphic VEBs (> 1000/24h).

Due to the presence of VEBs, the patient underwent an endomyocardial biopsy which showed a mild focal positivity to Congo Red staining, and immunohistochemistry (Figure 1 panel D) confirmed a mild focal positivity for transthyretin as well as immunofluorescence staining (Figure 1 panel E). Electron microscopy (Figure 1 panel F) documented modest accumulations of fibrillar material mainly localized around the vessels and occasionally close to the myocardiocytes with an increase in intercellular spaces (arrows).

The patient started Tafamidis and 12 months after, biphosphonate scintigraphy remained negative and the ventricular thicknesses remained unchanged.

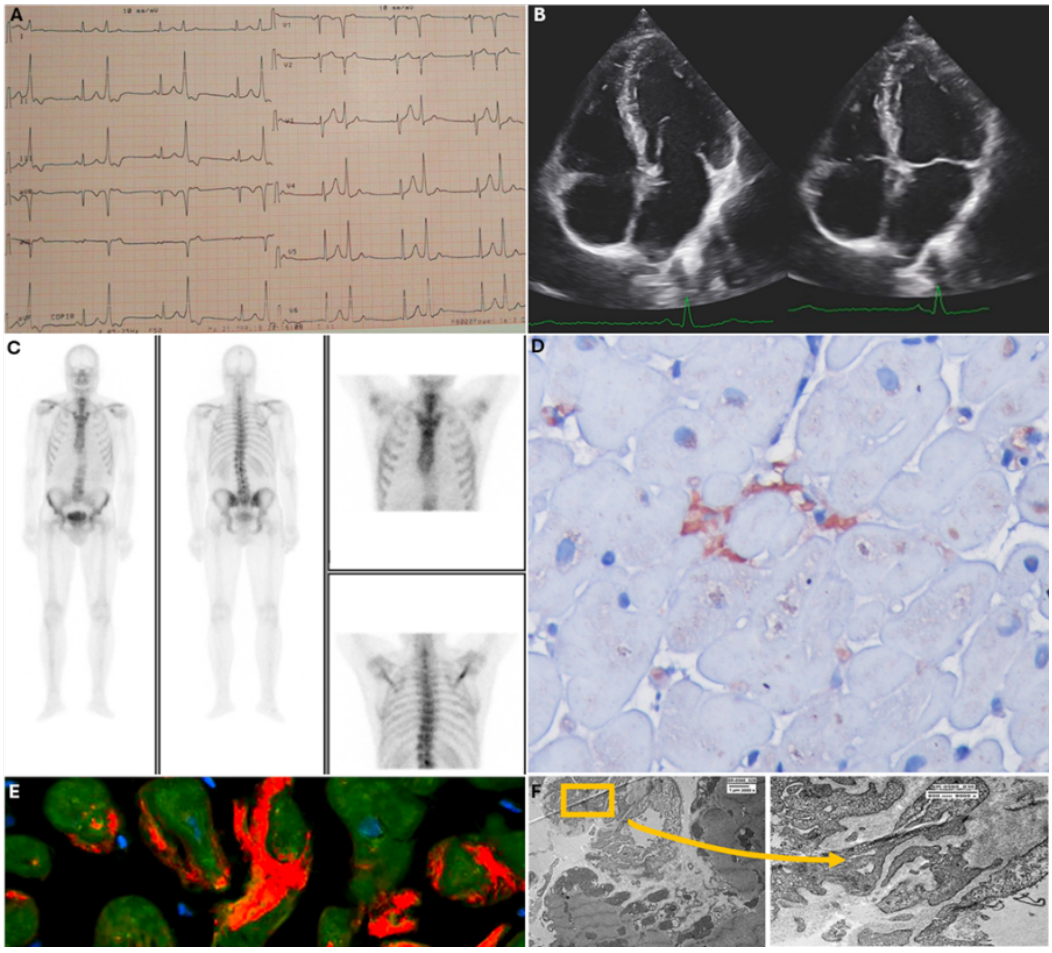

Figure 1: Clinical, instrumental and pathological characteristics of the 56-year-old patient carrier of the Ile88leu mutation of the TTR gene. Panel A: The ECG showed sinus rhythm, with frequent ventricular ectopic beats (VEBs). Panel B: Transthoracic echocardiogram shows normal ventricular size and thickness and preserved left ventricular systolic function. Panel C: Biphosphonate scintigraphy is negative for cardiac involvement**.** Panels D-E: at endomyocardial biopsy, immunohistochemistry (panel D) confirms a mild focal positivity for transthyretin as well as immunofluorescence staining (panel E). Panel F: Electron microscopy documents modest accumulations of fibrillar material mainly localized around the vessels and occasionally close to the myocardiocytes with an increase in intercellular spaces (arrows).

Discussion

ATTR-v is a rare, adult-onset, autosomal dominant genetic disorder caused by mutations in the TTR gene (1,2). Prognosis depends on age of onset, time between disease onset and diagnosis, mutation type and phenotype. Although ATTR is a systemic disease, the main predictor of mortality in both wild-type and inherited forms is the severity of cardiac involvement.

The growing availability of effective therapies determining a greater benefit the earlier they are started, highlights the importance of identifying cardiac involvement [4].

Advances in the possibility of non-invasive diagnosis and the development of disease-modifying therapies such as TTR stabilisers and gene silencers have transformed ATTR from a rare and incurable disease to a prevalent disease with possibilities for early diagnosis and specific therapy.

This case shows that in TTR gene mutation carriers, an initial cardiac involvement can be present even in the absence of left ventricular hypertrophy and positive bisphosphonate scintigraphy. In the presence of clinical symptoms and/or suspicious signs of disease, such as arrhythmias [5], an endomyocardial biopsy may be indicated in order to start disease modifying therapy earlier.

Family screening, which must be initiated when a proband is identified, and initial cardiac involvement demonstration allow to begin disease-modifying treatment earlier.

Conclusion

ATTR-v is a rare, adult-onset, autosomal dominant genetic disorder caused by mutations in the TTR gene. The growing availability of effective therapies determining a greater benefit the earlier they start, highlights the importance of identifying initial cardiac involvement even in the absence of left ventricular hypertrophy.

Contributors: All authors contributed to planning, literature review and conduct of the review article. All authors have reviewed and agreed on the final manuscript.

Competing interests: None.

References

1. Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, et al. (2013) Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 8:31.
2. Porcari A, Fontana M, Gillmore JD. (2023) Transthyretin cardiac amyloidosis. Cardiovasc Res. 118(18):3517-3535. doi: 10.1093/cvr/cvac119.
3. Arbelo E, Protonotarios A, Gimeno JR, Arbustini E, Barriales-Villa R, et al (2023) ESC Scientific Document Group.2023 ESC Guidelines for the management of cardiomyopathies. Eur Heart J. 44:3503-3626.
4. Rapezzi C, Elliott P, Damy T, Nativi-Nicolau J, Berk JL, et al (2021) Efficacy of Tafamidis in Patients With Hereditary and Wild-Type Transthyretin Amyloid Cardiomyopathy: Further Analyses From ATTR-ACT. JACC Heart Fail. 9:115-123.
5. Seferović PM, Tsutsui H, McNamara DM, Ristić AD, Basso C. et al. (2021) Heart Failure Association of the ESC, Heart Failure Society of America and Japanese Heart Failure Society Position statement on endomyocardial biopsy. Eur J Heart Fail. 23:854-871.