Recurrent suspected myocarditis combined with infrahisian conduction disturbances revealing a desminopathy

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Introduction

Desminopathies are rare inherited diseases caused by mutations in the desmin gene. Diagnosis of desminopathies is challenging because of their low incidence and the broad spectrum of clinical presentations. The present report (1) describes a new clinical presentation mimicking recurrent myocarditis, extending the clinical phenotype associated with desmin mutations; and (2) demonstrates that the Purkinje system is involved in the pathogenesis of conduction disturbances related to desminopathies.

Case report

We report the case of a 50-year-old woman with an unusual cardiac phenotype related to a dominant mutation in the desmin gene. The patient did not have any significant medical history except asthma during childhood. There was no family history of cardiomyopathies, sudden death, or cardiac device implantation. She was first admitted to our hospital for an episode of chest pain radiating to her jaw and down her left arm. Her physical examination was strictly normal. Electrocardiogram at admission revealed a first-degree atrioventricular block associated with nonspecific intraventricular conduction disturbances (Figure 1A). A second electrocardiogram exhibited an episode of alternating bundle branch block (Figure 1B). Laboratory investigations showed elevated troponin T (84 ng/l; normal <50 ng/l) and creatine kinase (397 UI/l; normal <200 UI/l). C-reactive protein was normal (4 mg/l; normal <6 mg/l). The echocardiogram was normal (left ventricular ejection fraction = 60%), as well as the coronary angiogram, which excluded coronary artery disease. The diagnosis of myocarditis was suspected and symptoms spontaneously resolved within 12 hours. Given the unusual electrocardiographic features, an electrophysiologic study (EPS) was performed, revealing advanced His-Purkinje system disease (Figure 1C and D). No programmed ventricular stimulation was performed during the EPS. A dual-chamber pacemaker was therefore implanted immediately. The patient was readmitted 3 months later for a recurrence of a retrosternal chest pain associated with an increase in troponin T level (75 ng/l). Cardiac magnetic resonance revealed a large area of subepicardial late gadolinium enhancement located in the lateral wall of the left ventricle (Figure 2). A deltoid muscle biopsy was performed, and histopathologic findings revealed features of myofibrillar myopathy with desmin-positive protein aggregates (Figure 3). Genetic molecular analysis revealed a heterozygous missense mutation (c.38C>T; p.Ser13Phe) in the desmin gene (GenBank accession number NM001927.3) (Supplementary Figure, available online). The variant fulfilled all the criteria for a disease-causing mutation. Additionally, this mutation was already published as pathogenic[1–3] and is located in the head domain of the protein. No mutation was identified in the lamin A/C gene. Following these results, the pacemaker was upgraded to an implantable cardioverter-defibrillator (ICD); genetic screening of relatives is ongoing. After 24 months of follow-up, no recurrence of chest pain occurred and echocardiograms remain normal, without evidence for structural cardiomyopathy on echocardiography.

Discussion

Desminopathies are rare diseases related to mutations in the desmin gene located on chromosome 2q35. The spectrum of clinical presentations is broad, including variable association of progressive skeletal muscle weakness and cardiac involvement. Cardiac manifestations are mostly represented by cardiomyopathies (the most frequent being dilated and

KEYWORDS Desminopathy; Myocarditis; Cardiomyopathy; Atrioventricular block; Pacemaker; Desmin; Purkinje

ABBREVIATIONS **EPS** = electrophysiologic study; **ICD** = implantable cardioverter-defibrillator

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KEY TEACHING POINTS

- Desminopathies are rare genetic diseases caused by mutations in the desmin gene located on chromosome 2q35. The spectrum of clinical presentations is broad, including variable associations of progressive skeletal muscle weakness and cardiac involvement.
- The present report describes a new clinical presentation characterized by an isolated cardiac phenotype mimicking recurrent myocarditis combined with conduction disturbances, thereby extending the clinical phenotype associated with desmin gene mutations.
- This report provides evidence of the involvement of the Purkinje system in the pathogenesis of conduction disturbances related to desminopathies.

restrictive cardiomyopathies[4]) and conduction disturbances.[5] The present report highlights remarkable features related to a desmin gene mutation (c.38C > T; p.Ser13Phe).

First of all, the cardiac presentation fulfilled criteria for suspected acute myocarditis.[6] This cardiac phenotype of myocarditis has not yet been reported in desminopathies, the most frequent types of cardiomyopathies described in this disease being dilated and restrictive cardiomyopathies. Even if the causal relationship between gene mutation and myocarditis cannot be stated with certainty, this unusual presentation revealing the disease might represent an early stage of the pathologic process and questions the possible interrelations between myocarditis and genetic cardiomyopathies (as observed in arrhythmogenic right ventricular cardiomyopathy or dilated cardiomyopathy). It also highlights the possibility of overlapping between clinical phenotypes induced by desmin mutations, as has been reported for mutations in other genes.[7,8] This clinical presentation of "pseudo-myocarditis" has already been reported in other genetic cardiomyopathies, such as arrhythmogenic right ventricular cardiomyopathy.[9,10] Acute myocarditis may reflect an "active phase" of the underlying genetic cardiomyopathy and may play a role in the acceleration of myocardial involvement.[11,12] This suggests complex interactions between genetic and environmental factors for the production of a given phenotype. Finally, the report illustrates the quite late expression of a genetic disease.

Secondly, isolated cardiac signs revealed the disease, as there was no skeletal muscle weakness. Isolated cardiac

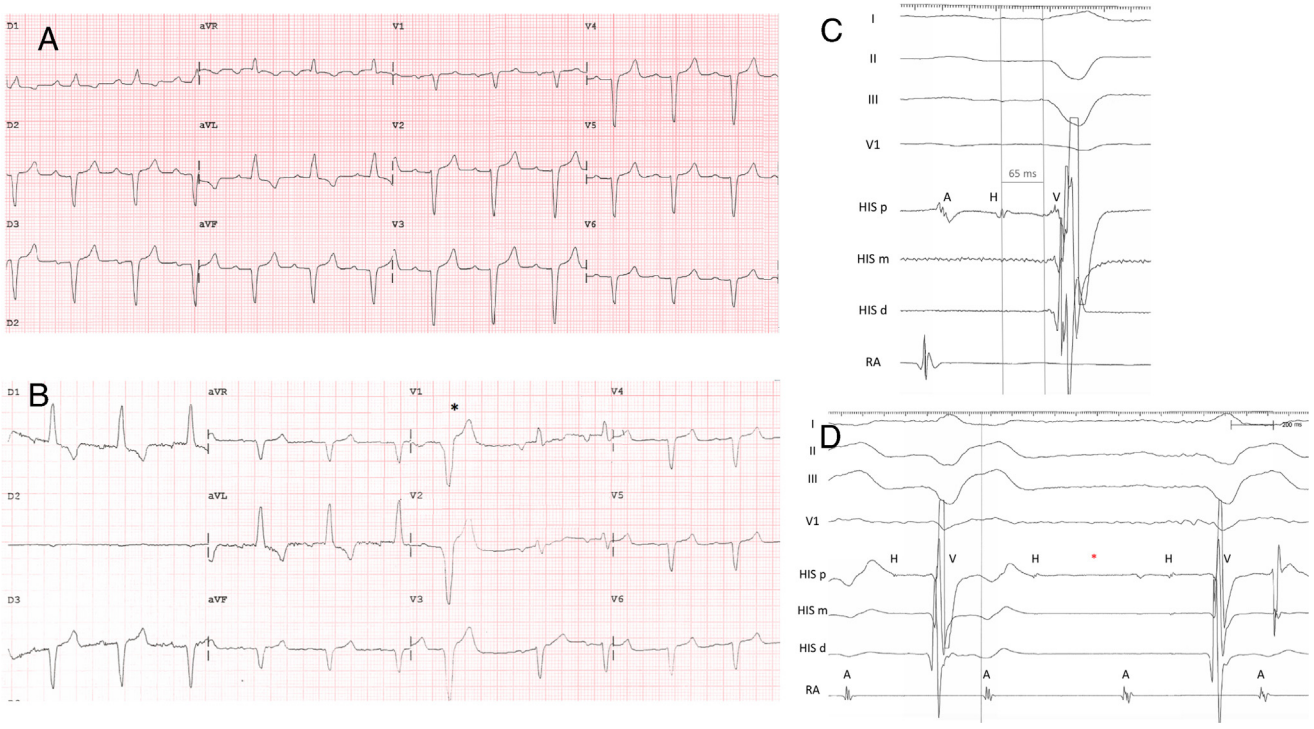

Figure 1 **A:** Baseline 12-lead electrocardiogram (25 mm/s, 10 mm/mV) showing a first-degree atrioventricular block (PR duration = 230 ms) combined with a nonspecific intraventricular conduction disturbance (QRS duration = 150 ms without criteria for left or right bundle branch block) and a marked left-axis deviation (−70°). **B:** Second electrocardiogram showing conduction disturbances. The first QRS beat (asterisk) is preceded by a premature atrial beat, causing aberration in the form of left bundle branch block. Thus, this beat shows a left bundle branch block pattern with prolonged PR interval (300 ms), whereas the 2 following beats show a right bundle branch block pattern with shorter PR interval (240 ms). **C, D:** Results from electrophysiologic study (200 mm/s, 10 mm/mV). Two quadripolar catheters were used: the first one was positioned on the tricuspid annulus to record the His bundle electrogram (leads labeled "HIS p," "HIS m," and "His d"); the second one was positioned on the right atrium free wall (lead labeled "RA"). **C:** At baseline, a prolonged HV interval (65 ms; normal <55 ms) was noted. **D:** Pharmacologic challenge (ajmaline infusion, 1 mg/kg) induced a 2:1 second-degree infrahisian block, demonstrated by the absence of ventricular electrogram after the hisian potential (asterisk). A, atrial electrogram. H, hisian electrogram. V, ventricular electrogram.