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

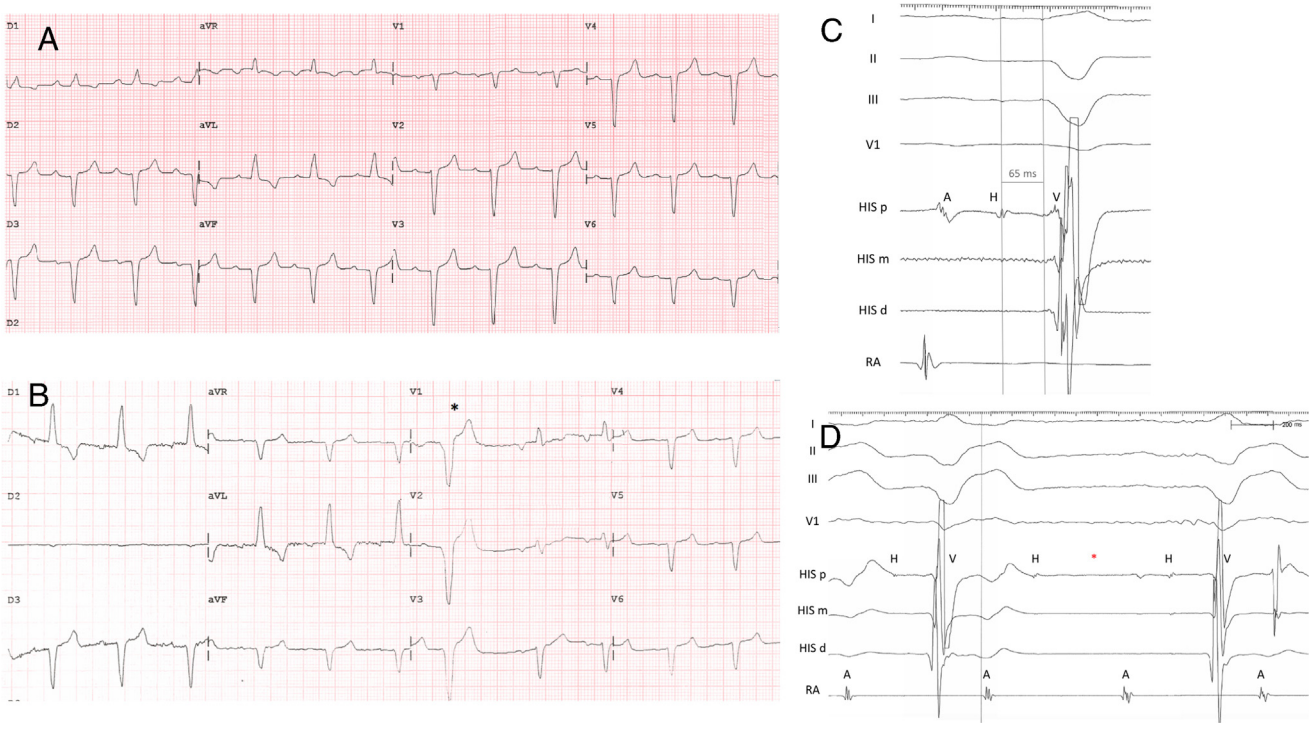

Figure 1 **A:** Baseline 12-lead electrocardiogram (25 mm/s, 10 mm/mV) showing a first-degree atrioventricular block (PR duration = 230 ms) combined with a nonspecific intraventricular conduction disturbance (QRS duration = 150 ms without criteria for left or right bundle branch block) and a marked left-axis 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.

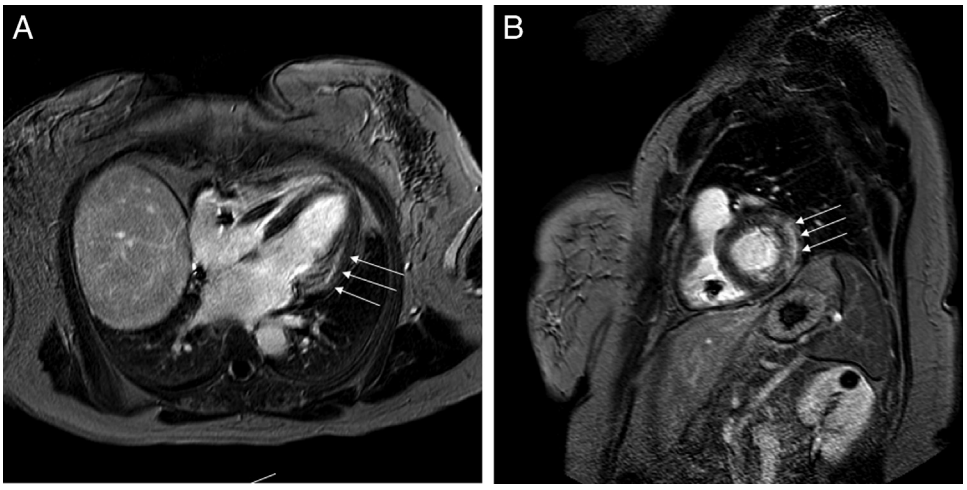

Figure 2 Cardiac magnetic resonance findings. T1-weighted late gadolinium images showing a large area of subepicardially distributed late gadolinium enhancement of the lateral wall of the left ventricle (*arrows*). Note the nonischemic regional distribution of the lesion, which excludes the subendocardial layer. There was no increased global myocardial early gadolinium enhancement ratio between myocardium and skeletal muscle in gadolinium-enhanced T1-weighted images. Finally, no myocardial signal intensity increase was noted in T2-weighted edema images (images not shown). **A:** Four-chamber view. **B:** Short-axis view.

phenotypes with neither neurological signs nor myopathy or muscular weakness have less frequently been described in carriers of desmin gene mutations. The location of the mutation (head, helix domains, or tail) might influence the phenotype. In the present case, the mutation (p.Ser13Phe) was located in the head domain. A meta-analysis[4] demonstrated that mutations in the head or tail domain of the desmin gene are both rarely observed and more likely to result in an isolated cardiac phenotype. In the present case, the p.Ser13Phe mutation is located at a protein kinase-C phosphorylation site within a highly conserved nonapeptide sequence in the head domain of the desmin protein. It was first described by Bergman et al[3] in 2007 in 2 Dutch families presenting a phenotype varying from isolated dilated cardiomyopathy to a generalized skeletal myopathy with mild respiratory problems. Pica et al[2] in 2008 published

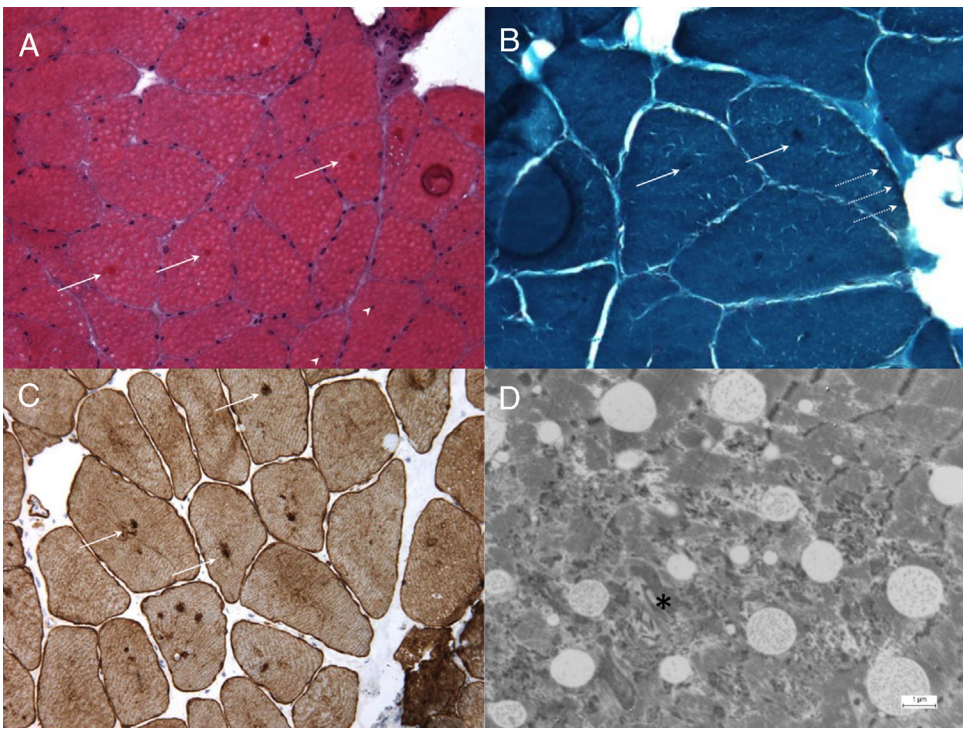

Figure 3 Histopathologic findings. **A:** Hematoxylin–eosin sections. Note the heterogeneity of the diameter of muscular fibers. Arrows indicate the presence of sarcoplasmic aggregates. Arrowheads indicate the centralization of nuclei. **B:** Gomori trichrome. Solid arrows indicate sarcoplasmic protein aggregates; dotted arrows indicate subsarcolemmal protein aggregates. **C:** Desmin immunostaining. Arrows indicate desmin-positive protein aggregates within the sarcolemma. **D:** Electron microscope findings showing granulofilamentous material (*asterisk*).

the mutation in a Chinese patient presenting a complete heart block associated with mild proximal and distal limb weakness. In 2009, van Tintelen et al[1] gave a precise description of the clinical presentation of 27 patients from 5 families. The p.Ser13Phe mutation was fully penetrant and responsible for a cardiac involvement characterized by atrioventricular block at young ages and right ventricular involvement particularly in 2 patients who fulfilled the diagnostic criteria for arrhythmogenic right ventricular cardiomyopathy.

Thirdly, an EPS provided evidence that the conduction block was located below the atrioventricular node, within the His-Purkinje system. If cardiac conduction disease is recognized as one of the clinical manifestations of desminopathies, there are no data in wider literature regarding the precise location of conduction delays within the conduction system. To the best of our knowledge, results of electrophysiologic studies have not been reported yet in this pathology. The present report demonstrates that electrocardiographic abnormalities are a result of an impairment in infrahisian conduction, whereas atrioventricular nodal conduction remains strictly normal. Of note, the conduction disturbances persisted after resolution of myocarditis, this finding strongly supporting a causal relationship between the desmin mutation and the conduction disease. In an animal model, Schrickel et al[13] found slower conduction velocities in the ventricles of desmin knockout mice, which is consistent with the fact that desmin is a major component of the Purkinje network. They did not observe any prolongation of AH and HV intervals, but this animal model was associated with a lower incidence of both atrioventricular conduction disturbances and ventricular tachyarrhythmias than what is observed in humans with heterozygous mutations.

Finally, owing to the very low prevalence of desminopathies, there is no consensus regarding indications for prophylactic ICD implantation in this pathology. In patients with severe conduction disturbances caused by LMNA mutations, it is recognized that an ICD rather than a pacemaker should be implanted, because these patients exhibit a high risk of sudden death despite pacemaker implantation.[14] In the present case, the decision to upgrade the pacemaker to an ICD was based on previously published work[5] reporting the occurrence of ventricular tachyarrhythmias in 4 out of 28 carriers of DES mutations, as well as sudden death in 1 other patient and in 6 out of 14 relatives who had pacemakers for conduction disturbances. Even if it was not possible to draw any significant association between sudden death or ventricular tachyarrhythmias and left ventricular function owing to the limited number of patients, these data support the prophylactic implantation of an ICD rather than a pacemaker in patients presenting with severe conduction disturbances, regardless of left ventricular function. This strategy of prophylactic ICD implantation is also supported by another publication[15] reporting the case of a 24-year-old patient who received a prophylactic ICD in the setting of DES mutation with subnormal left ventricular ejection fraction (50%) and no inducible tachyarrhythmias during EPS. This patient subsequently experienced an episode of fast ventricular tachycardia terminated by shock, despite the absence of left ventricular dysfunction. Finally, the presence of late gadolinium enhancement might increase the risk of ventricular tachyarrhythmias and has also been taken into account in our decision to upgrade the pacemaker to an ICD.

Conclusion

In conclusion, this report (1) extends the spectrum of phenotypes related to desmin mutations, and (2) provides evidence that conduction disturbances are located within the Purkinje system.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrcr.2015.04.002.

References

1. Van Tintelen JP, Van Gelder IC, Asimaki A, et al. Severe cardiac phenotype with right ventricular predominance in a large cohort of patients with a single missense mutation in the DES gene. Heart Rhythm 2009;6:1574–1583.
2. Pica EC, Kathirvel P, Pramono ZAD, Lai P-S, Yee W-C. Characterization of a novel S13F desmin mutation associated with desmin myopathy and heart block in a Chinese family. Neuromuscul Disord 2008;18:178–182.
3. Bergman JEH, Veenstra-Knol HE, van Essen AJ, van Ravenswaaij CMA, den Dunnen WFA, van den Wijngaard A, van Tintelen JP. Two related Dutch families with a clinically variable presentation of cardioskeletal myopathy caused by a novel S13F mutation in the desmin gene. Eur J Med Genet 2007;50:355–366.
4. Van Spaendonck-Zwarts KY, van Hessem L, Jongbloed JDH, de Walle HEK, Capetanaki Y, van der Kooi AJ, van Langen IM, van den Berg MP, van Tintelen JP. Desmin-related myopathy. Clin Genet 2011;80:354–366.
5. Wahbi K, Béhin A, Charron P, Dunand M, Richard P, Meune C, Vicart P, Laforêt P, Stojkovic T, Bécane HM, Kuntzer T, Duboc D. High cardiovascular morbidity and mortality in myofibrillar myopathies due to DES gene mutations: a 10-year longitudinal study. Neuromuscul Disord 2012;22:211–218.
6. Caforio ALP, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2013;34:2636–2648. 2648a–2648d.
7. Quarta G, Syrris P, Ashworth M, Jenkins S, Zuborne Alapi K, Morgan J, Muir A, Pantazis A, McKenna WJ, Elliott PM. Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. Eur Heart J 2012;33:1128–1136.
8. Elliott P, O'Mahony C, Syrris P, Evans A, Rivera Sorensen C, Sheppard MN, Carr-White G, Pantazis A, McKenna WJ. Prevalence of desmosomal protein gene mutations in patients with dilated cardiomyopathy. Circ Cardiovasc Genet 2010;3:314–322.
9. Lopez-Ayala JM, Pastor-Quirante F, Gonzalez-Carrillo J, Lopez-Cuenca D, Sanchez-Munoz JJ, Oliva-Sandoval MJ, Gimeno JR. Genetics of myocarditis in arrhythmogenic right ventricular dysplasia. Heart Rhythm 2015;12(4):766–773.
10. Christensen AH, Svendsen JH. Myocarditis mimicking arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol 2009;54:663–664.
11. Patrianakos AP, Protonotarios N, Nyktari E, Pagonidis K, Tsatsopoulou A, Parthenakis FI, Vardas PE. Arrhythmogenic right ventricular cardiomyopathy/

dysplasia and troponin release. Myocarditis or the "hot phase" of the disease? Int J Cardiol 2012;157:e26–e28.
12. Frustaci A, Verardo R, Caldarulo M, Acconcia MC, Russo MA, Chimenti C. Myocarditis in hypertrophic cardiomyopathy patients presenting acute clinical deterioration. Eur Heart J 2007;28:733–740.
13. Schrickel JW, Stöckigt F, Krzyzak W, Paulin D, Li Z, Lübkemeier I, Fleischmann B, Sasse P, Linhart M, Lewalter T, Nickenig G, Lickfett L, Schröder R, Clemen CS. Cardiac conduction disturbances and differential effects on atrial and ventricular electrophysiological properties in desmin deficient mice. J Interv Card Electrophysiol 2010;28(2):71–80.
14. Anselme F, Moubarak G, Savouré A, Godin B, Borz B, Drouin-Garraud V, Gay A. Implantable cardioverter-defibrillators in lamin A/C mutation carriers with cardiac conduction disorders. Heart Rhythm 2013;10:1492–1498.
15. Luethje LGC, Boennemann C, Goldfarb L, Goebel HH, Halle M. Prophylactic implantable cardioverter defibrillator placement in a sporadic desmin related myopathy and cardiomyopathy. Pacing Clin Electrophysiol 2004;27:559–560.