Time to change the family diagnosis: Arrhythmogenic left ventricular cardiomyopathy

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SOUHRN

Arytmogenní kardiomyopatie je dědičná kardiomyopatie charakterizovaná fibrotukovou přeměnou srdeční svalové tkáně, vysokým rizikem komorových arytmií a náhlé srdeční smrti. Toto onemocnění myokardu je typicky přenášeno autozomálně dominantně a je způsobeno patogenními variantami v desmosomálních a extradesmosomálních genech. V této kazuistice představujeme rodinu se třemi členy, kterým byla diagnostikována arytmogenní kardiomyopatie levé komory. Bylo zjištěno, že tento stav je způsoben nonsense mutací (c.1754 T>G (p. Leu585Ter)) v genu desmoplakinu (DSP). Bohužel, u dvou z těchto rodinných příslušníků byla zpočátku mylně diagnostikována ischemická choroba srdeční a byli pro ni léčeni, což nebyla správná diagnóza. Tento případ ukazuje důležitost anamnézy, přesné diferenciální diagnostiky a užitečnost zobrazování magnetickou rezonancí (MR) pro stanovení správné diagnózy arytmogenní kardiomyopatie.

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Keywords:
Arrhythmogenic cardiomyopathy
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Late gadolinium enhancement
Misdiagnose
Myocardial infarction with non-obstructive coronary arteries

ABSTRACT

Arrhythmogenic cardiomyopathy is an inherited cardiomyopathy characterized by fibrofatty replacement and a high risk of ventricular arrhythmias and sudden cardiac death. This myocardial disorder is typically transmitted through autosomal dominant pattern and caused by pathogenic variants in the desmosomal and extradesmosomal genes. In this case, we are presenting a family with three members who have arrhythmogenic left ventricular cardiomyopathy. The condition was found to be caused by a nonsense mutation (c.1754 T>G (p. Leu585Ter)) in the desmoplakin (DSP) gene. Unfortunately, two of the family members were initially misdiagnosed and treated for coronary artery disease, which was not the correct diagnosis. This case demonstrates the importance of accurate differential diagnosis and the usefulness of magnetic resonance imaging (MRI) in establishing the correct diagnosis of arrhythmogenic cardiomyopathy.

Clinical case report

A 19-year-old woman was hospitalized in a foreign hospital following an out-of-hospital cardiac arrest. After experiencing a syncopal episode and retrosternal pain, the patient was resuscitated in the airport hall and subsequently admitted to the local hospital's cardiology department. A selective coronary angiography was performed, revealing the occlusion of a small branch of the circumflex artery. No other issues were found with the coronary arteries. The patient received conservative management and was diagnosed and treated for coronary artery disease with statin and antiplatelet therapy.

Upon returning to the Czech Republic, the patient underwent an examination at our centre for young survivors of myocardial infarction. A follow-up was conducted at the Prague site.

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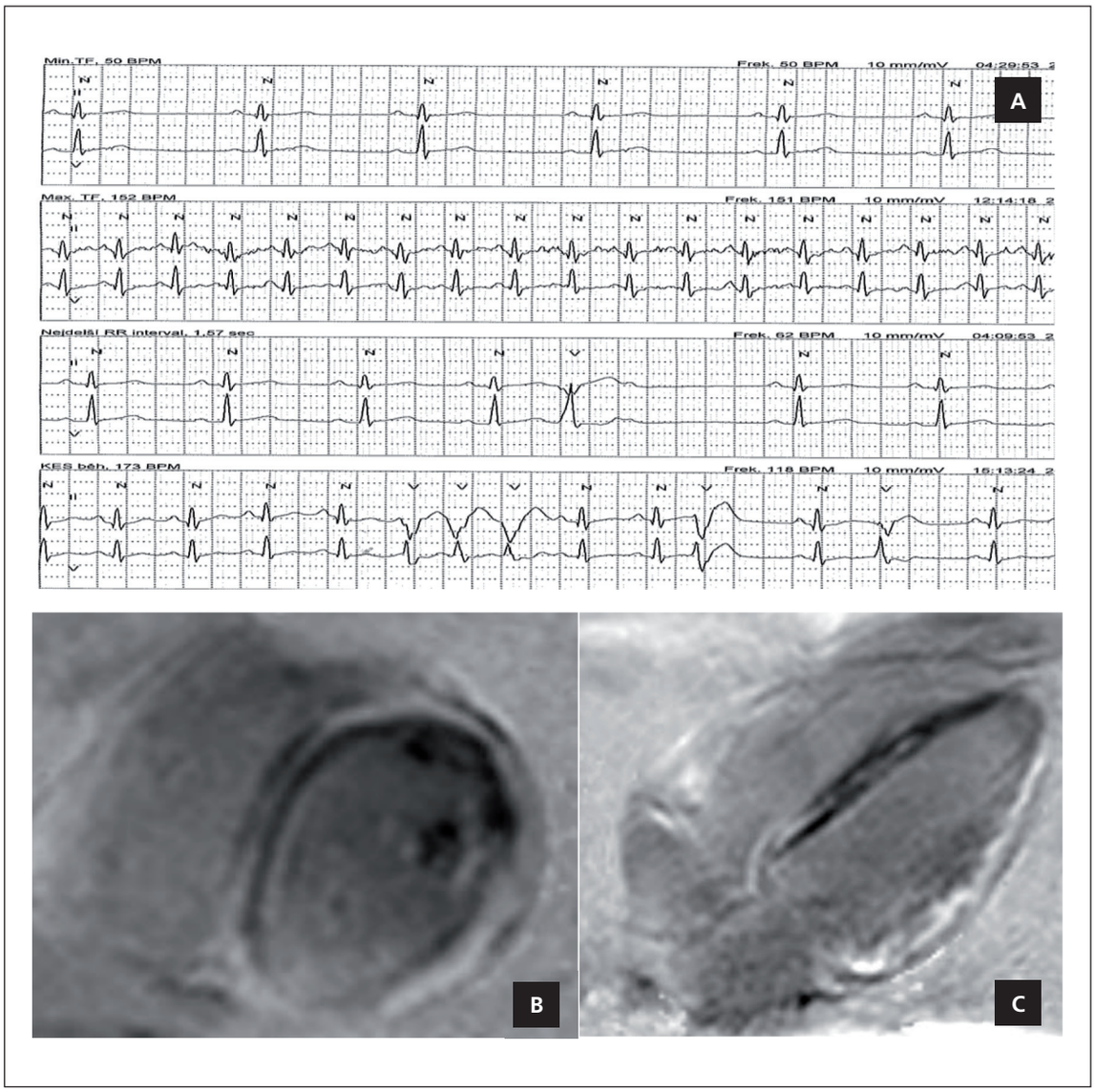

Fig. 1 – Proband's stress test ECG record (A) and CMR scans (B, C). (A) ECG Holter monitoring – 4 strips with normal sinus rhythm, sinus tachycardia 150 beats per minute, and sinus rhythm followed by frequent ventricular extrasystoles – triplets (three premature ventricular contraction with frequency 173 beats per minute) followed by bigeminy. (B) Phase – sensitive inversion – recovery (PSIR), short axis view, midmyocardial and subepicardial circumferential late gadolinium enhancement (LGE). (C) PSIR, four-chamber view, midmyocardial and subepicardial LGE of the lateral wall and interventricular septum.

In our clinical examination, we observed a low voltage on the ECG and a prolonged QTc interval. The ECG Holter and stress test monitoring revealed a higher incidence of ventricular extrasystoles (**Fig. 1A**). During the echocardiography examination, the hypokinesis of the posterior and lateral wall was detected, despite this fact the ejection fraction was described as borderline normal. The cardiac magnetic resonance examination (CMR) was indicated and detected not only mild global left ventricular systolic dysfunction with an ejection fraction 42% but also a non-ischemic pattern of delayed enhancement in the left ventricle. It showed a subepicardial up to midmyocardial almost circumferential late gadolinium enhancement (**Figs 1B, 1C**). There were findings that contradicted a previous diagnosis of myocardial infarction and were highly suspicious of arrhythmogenic left ventricular cardiomyopathy. Additionally, a repeat selective coronary angiography showed normal findings. To confirm the diagnosis, a genetic examination was recommended.

The genetic test confirmed arrhythmogenic cardiomyopathy with a pathogenic mutation in the desmoplakin DSP gene (c.1754T>G, p. Leu585Ter). The patient's family members were subsequently confirmed to have the same mutation. The incorrect diagnosis of coronary artery disease was corrected for both the patient and her father. In his case, after 22 years of being treated for the non-causal diagnosis of his syncope with the medication for coronary artery disease including acetylsalicylic acid,

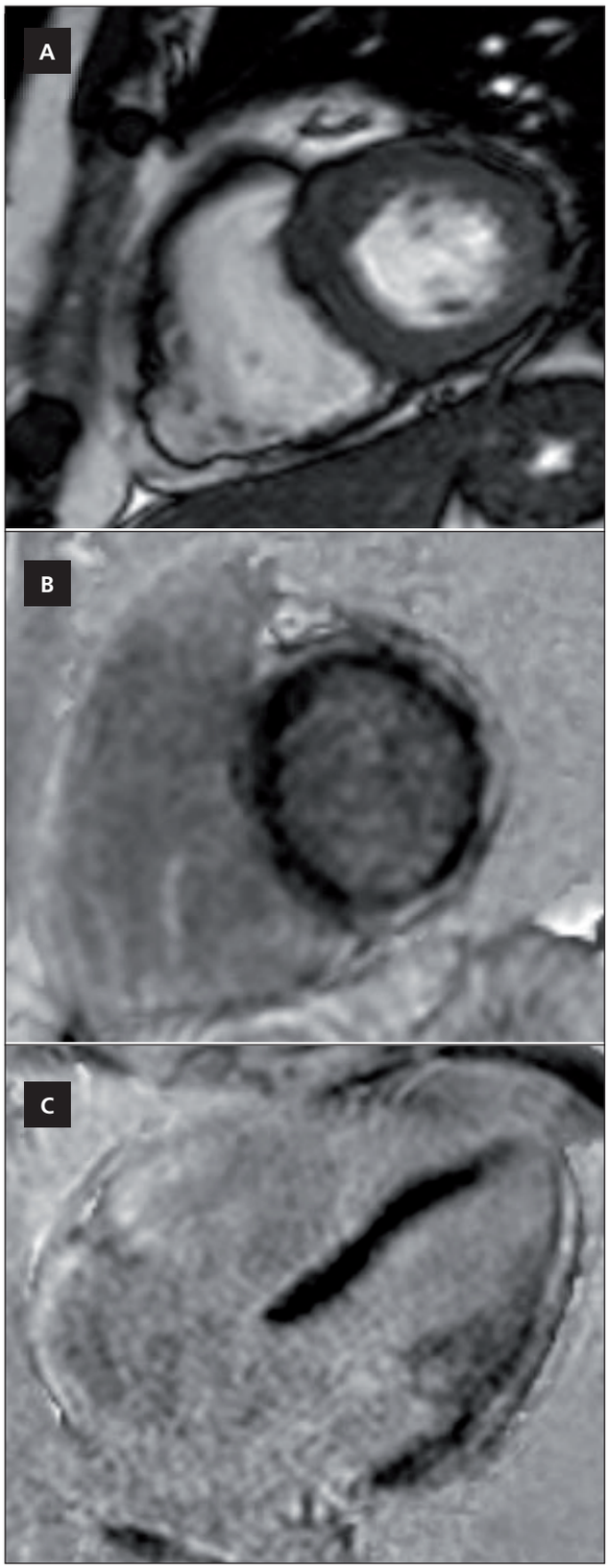

Fig. 2 – Proband's father CMR scans. (A) Short axis view, inferolateral aneurysm of right ventricle in systolic phase. (B) PSIR, short axis view, midmyocardial and subepicardial LGE of the inferolateral wall. (C) PSIR, four-chamber view, midmyocardial and subepicardial LGE of the lateral wall.

statin, and beta-blocker. The CMR examination of the father of the proband also confirmed the presence of an arrhythmogenic cardiomyopathy. In his case, biventricular involvement was detected (**Figs 2A–2C**). Moreover, in the proband's brother the same pathogenic mutation in DSP gene was found.

The patient, along with her father, was treated by discontinuing acetylsalicylic acid and statins. All three family members were implanted with defibrillators and are regularly seen in our outpatient clinic.

Discussion

There has been an increase in occurrences of myocardial infarction in the young women in recent years, often identified as MINOCA (myocardial infarction with non-obstructive coronary arteries).[1–3] It is important to consider the overall well-being of patients despite the rising cases of myocardial lesions. For young individuals, family history can be a valuable tool in distinguishing between myocardial infarction and cardiomyopathy.[4,5] It is important to begin every patient follow-up by reviewing their medical history. In cases of inherited diseases, it is common to observe similar symptoms in relatives. An ECG can help to diagnose both myocardial infarction and arrhythmogenic disorders. In case of inconclusive echocardiography, cardiac magnetic resonance should be performed. Typically, in arrhythmogenic left ventricular cardiomyopathy, there is a non-ischemic type of late gadolinium enhancement (LGE). Genetic tests can be useful, particularly when a close family member has experienced similar symptoms or illnesses. In our situation, both a daughter and her father were misdiagnosed with myocardial infarction at a young age. However, thanks to the early diagnosis of the proband, the medical management of the entire family was altered.

Brief summary

After examining with advanced imaging techniques and genetic testing, we were able to modify the patient's diagnosis from myocardial infarction to arrhythmogenic cardiomyopathy. As a result, the entire approach to the patient's treatment was altered. The genetic mutation was present not only in the patient but also in her father and younger brother. This serves as a reminder of the importance of considering each patient's unique circumstances and utilizing complex diagnostic methods when uncertain about the final diagnosis.

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Conflict of interest
Michaela Veselá, Gabriela Dostálová, Zuzana Hlubocká, Petr Kuchynka, Vladimír Tuka, Tomáš Kovárník, Martin Mašek, and Aleš Linhart declare that they have no conflict of interest.

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Ethical statement
The case report was conducted in accordance with the ethical standards of the institution and the Declaration of Helsinki. Approval from the institutional ethics committee was not required due to the nature of the case report.

Informed consent
Written informed consent was obtained from the patient for the publication of this case report and accompanying image.

Authors' contributions
All authors contributed to the case report study conception and design. Material preparation, data collection, and figures were performed by all authors. The first draft of the manuscript was written by Michaela Veselá and Gabriela Dostálová and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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