A 51-year-old woman experienced a respiratory tract infection with fever followed by persistent fatigue and muscle pain in her extremities for >2 months. Family history revealed a 30-year-old wheelchair-bound son with advanced myopathy suffering from Duchenne muscular dystrophy (DMD; deletion in the dystrophin gene). Blood analysis in the mother revealed an elevated total creatine kinase (CK) level of 479 U/L (normal, <190 U/L) with a normal creatine kinase-MB (CK-MB) level of 17 U/L (normal, <25 U/L). Additional workup of (skeletal) myopathy was composed of a calf muscle biopsy with normal histopathologic findings (Figure 1): in particular, there were no signs of structural abnormalities, inflammation, or dystrophin deficiency. Genetic analysis of blood cells revealed a heterozygous dystrophin gene mutation, and the female patient was identified as a possibly symptomatic–DMD carrier.

In addition to muscle pain, she was also experiencing dyspnea on exertion and fatigue and, therefore, presented to our hospital. She was in an acceptable general condition, and her physical examination was unremarkable. Her resting ECG demonstrated sinus rhythm without any repolarization abnormalities. A cardiovascular magnetic resonance imaging (CMR) study was performed on a clinical scanner (1.5-T Aera; Siemens, Erlangen, Germany) as part of an ongoing clinical project. CMR cine images demonstrated regional hypokinesia of the left ventricular myocardium, that was performed after ruling out coronary artery disease (Figure 3). Interestingly, histopathologic endomyocardial biopsy workup demonstrated some structural abnormalities and areas of fibrosis but no signs of myocardial inflammation (Figure 4). However, dystrophin staining revealed an impressive mosaic pattern with clear absence of dystrophin in the cell membrane of some cardiomyocytes and coexistent presence of dystrophin in other neighboring cells, proving the diagnosis of a genetic cardiomyopathy. Hence, the nonischemic pattern of late gadolinium enhancement observed in the preceding contrast images was assessed as a characteristic finding of cardiac involvement in a female (heterozygous) DMD carrier.

This female patient had also a 25-year-old clinically healthy daughter who agreed to undergo a CMR study as participant in our ongoing clinical project. Her resting ECG was unremarkable. Blood analysis revealed an elevated total CK level of 872 U/L (normal, <190 U/L) but normal values for CK-MB, troponin T, and N-terminal pro–B-type natriuretic peptide. CMR cine images showed mild hypokinesia in the inferolateral wall similar to the finding in her mother (Figure 5, top panel; Movies IV–VI in the online-only Data Supplement), and left ventricular ejection fraction was 66%. However, contrast images revealed exactly the same pattern of myocardial damage as was observed in her mother (Figure 5, bottom panel). Hence, additional genetic analysis was performed and revealed the same heterozygous dystrophin gene mutation as was identified previously in her mother.
This case report is unique because it not only demonstrates a striking mosaic pattern of cardiac dystrophin deficiency in a female DMD carrier with normal dystrophin expression in the skeletal muscle but also highlights the presence of the same pattern of cardiac involvement (detected by CMR cine and contrast imaging) in a symptomatic female DMD carrier and her asymptomatic DMD carrier daughter. The different involvement of skeletal and cardiac muscles found in this patient indicates a need for thorough cardiac investigations even in those DMD carriers who have normal skeletal biopsy findings. The elevated serum CK concentration (with normal CK-MB) that was detected in our patient is a common finding in female DMD carriers and does neither reflect the current severity of skeletal myopathy nor allow a prognostication regarding the future development.²,³

Previously, the severity of skeletal myopathy was mainly explained by nonrandom patterns of X-chromosome inactivation. However, in a recent study there was no relationship between the pattern of X-chromosome inactivation and transcriptional behavior of the DMD gene.⁴ Hence, the exact reason for the similar cardiac findings in our carriers remains unclear. However, even if one would hypothesize that the pattern of X-chromosome inactivation is possibly different in skeletal compared with heart muscle, such a difference, per se, cannot sufficiently explain the occurrence of a potentially similar pattern of X-chromosome inactivation in the mother compared with her daughter. Therefore, more comprehensive and systematic approaches are required to better understand the reason for cardiac involvement in female carriers of muscular dystrophy.

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Disclosures
None.

References

Figure 1. Hematoxylin-eosin (HE) staining of a skeletal muscle biopsy sample taken from the female Duchenne muscular dystrophy carrier: regular-sized and -shaped myocytes can be seen. Inserted images show immunohistochemical dystrophin stainings (DYS) with 3 different dystrophin antibodies: there are no signs of dystrophin deficiency.

Figure 2. Cardiovascular magnetic resonance imaging (CMR) cine images (top) and late gadolinium enhancement (LGE) images (bottom) of the female Duchenne muscular dystrophy carrier. Top panels show cine images in diastole in the short-axis, 4-chamber, and 3-chamber views, respectively. Bottom panels show LGE images in the respective views (red arrows indicate areas of positive LGE).
Figure 3. Coronary angiograms of the left coronary artery (left) and the right coronary artery (right) of the female Duchenne muscular dystrophy carrier. Coronary artery disease was ruled out before invasive endomyocardial biopsy.

Figure 4. Different stainings of endomyocardial biopsy samples taken from the female Duchenne muscular dystrophy carrier: A and B, Dystrophin stainings showing a mosaic pattern with clear absence of dystrophin in the cell membrane of some cardiomyocytes and coexistent presence of dystrophin in other neighboring cells (stained brown). C, Trichrome staining showing irregular-sized cardiomyocytes and diffuse interstitial fibrosis. D, CD3 staining for T lymphocytes: lymphocytes as possible sign of myocardial inflammation were not detected.

Figure 5. Cardiovascular magnetic resonance imaging (CMR) cine images (top) and late gadolinium enhancement (LGE) images (bottom) of the daughter (also a female Duchenne muscular dystrophy carrier). Top panels show cine images in diastole in the short-axis, 4-chamber, and 3-chamber views, respectively. Bottom panels show LGE images in the respective views (red arrows indicate areas of positive LGE).
Cause of Cardiac Disease in a Female Carrier of Duchenne Muscular Dystrophy: Myocarditis Versus Genetic Cardiomyopathy Without Skeletal Myopathy?
Anca Florian, Anna Ludwig, Peter Ong, Karin Klingel, Reinhard Kandolf, Antje Bornemann, Udo Sechtem and Ali Yilmaz

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**Movie Legend:**

**Movie 1.** Cine-CMR in the short-axis view of the female DMD carrier. Best viewed with Windows Media Player.

**Movie 2.** Cine-CMR in the long-axis four-chamber view of the female DMD carrier. Best viewed with Windows Media Player.

**Movie 3.** Cine-CMR in the long-axis three-chamber view of the female DMD carrier. Best viewed with Windows Media Player.

**Movie 4.** Cine-CMR in the short-axis view of the daughter (also a female DMD carrier). Best viewed with Windows Media Player.

**Movie 5.** Cine-CMR in the long-axis four-chamber view of the daughter (also a female DMD carrier). Best viewed with Windows Media Player.

**Movie 6.** Cine-CMR in the long-axis three-chamber view of the daughter (also a female DMD carrier). Best viewed with Windows Media Player.