Microvascular Angina as Prehypertrophic Presentation of Fabry Disease Cardiomyopathy

Andrea Frustaci, MD; Matteo A. Russo, MD; Marco Francone, MD, PhD; Cristina Chimenti MD, PhD

Angina is a common manifestation of Fabry disease (FD), an X-linked lysosomal storage disorder, attributable to deficiency of the enzyme α-galactosidase A. The level of involvement is usually the coronary microcirculation, and the mechanism of hypoperfusion includes endothelial dysfunction with reduced NO production and hypertrophy/hyperplasia of the smooth muscle cells with lumen narrowing in response to glycosphingolipid cell infiltration. Microvascular angina, however, usually manifest along with cardiomyocyte and left ventricular hypertrophy. Because of skewed inactivation of X chromosome, specific cell types, such as smooth muscle cells, may overexpress the disease in female before myocardial hypertrophy would occur.

A 36-year-old female, daughter of a 60-year-old female affected by FD cardiomyopathy (maximal left ventricular wall thickness 17 mm causing dyspnea with New York Heart Association class 2/3; α-Gal gene mutation c.668G>A), came to the attention because of chest pain induced by emotional stress and moderate exercise. Resting ECG and 2-dimensional echocardiogram were normal. Cardiac magnetic resonance showed normal left ventricular wall thickness (maximal value 10 mm) with normal volumes and function and no signal abnormalities even at T1-mapping evaluation (Figure, A). Effort ECG induced precordial pain and a 1.5 mm deflection of ST segment from stage 2 of Bruce protocol. After gene analysis and assessment of the enzyme α-galactosidase A in peripheral leukocytes showing the same mother’s gene mutation (c.668G>A) and a very low enzymatic activity (0.6 nmols/h/mL; nv >3), the patient underwent cardiac catheterization, coronary angiography, and left ventricular endomyocardial biopsy. Cardiac catheterization documented normal intracavitary pressures and coronary arteries with slow flow. Histology of endomyocardial samples showed a mosaic of normal and mildly hypertrophied cardiomyocytes (Figure, B; mean diameter at nuclear level 16±0.5 μm) containing perinuclear and cytoplasmic vacuoles that at ultrastructural examination consisted of membrane-bound myelin bodies denoting FD cardiomyopathy. In contrast to mild cardiomyocyte involvement, intramural arterioles and small arteries showed a severe lumen narrowing attributable to hypertrophy and proliferation of smooth muscle cells, all provided of perinuclear vacuoles (Figure, B and C). At electron-microscopy the vacuoles consisted of myelin bodies denoting glycosphingolipid cell infiltration (Figure, D). The patient was treated with diltiazem 120 mg bid, aspirin, and α-agalsidase 0.2 mg/kg every other week.

Comparing mother and daughter cardiac histology revealed a divergent structural phenotype with the disease being expressed in the former mostly in cardiomyocytes and leaving the coronary vessels nearly unaffected (Figure, E and F). This was paralleled by the presence of LV hypertrophy at ECG and at cardiac magnetic resonance (Figure, G) being responsible of dyspnea (New York Heart Association class II/III) and no angina.

Microvascular angina can be the first manifestation of FD cardiomyopathy preceding the development of left ventricular hypertrophy. It is attributable to overexpression of the disease on vascular smooth muscle cells as a result in female of skewed inactivation of X-chromosome. It is unknown whether, at this early stage of FD, enzyme replacement therapy may improve or revert vascular obstruction.

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Disclosures

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References


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Figure. Cardiac magnetic resonance (CMR) and histopathology from daughter and mother with Fabry disease (FD) cardiomyopathy. A, Daughter’ CMR showing normally thickened and normally size left ventricular chamber on cine images (SSFP sequence; left image) without any sign of edema on T2 weighted short tau inversion recovery short-axis sequence (t2-STIR; central image) nor evidence of late gadolinium enhancement (LGE; right image). B, Endomyocardial biopsy from the same patient showing mosaic of normal and minimally affected cardiomyocytes with a severe lumen narrowing of a 200-μm-thick small artery attributable to hypertrophy and hyperplasia of vacuolated smooth muscle cells (Masson trichrome, ×200). C, Resorcin-stained resin embedded semitin section from the daughter showing severe glycolipid accumulation in myocardiocytes and 2 small arterioles also heavily infiltrated by glycolipids with severely narrowed lumen (L). D, Transmission electronmicroscopy from the same patient showing a small arteriole with smooth muscle cells infiltrated by glycolipid bodies. The inset shows a high magnification detail of myelin-like arrangement of glycolipids. E, Endomyocardial biopsy of patient’s mother showing severe glycolipid accumulation of myocardiocytes, while a small arteriole is nearly unaffected. Scale bar, 100 μm. F, Transmission electronmicroscopy from the mother showing tiny and focal glycolipid accumulation in the arteriole smooth muscle cells. Scale bar, 5 μm. G, CMR from the mother showing a moderate hypertrophy (SSFP sequence; left image) with combined diffused edematous imbibitions (arrowhead on T2-STIR; mid image) and a typical LGE midwall stria located within the inferolateral wall of the left ventricle (arrows; right image).
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