Progression of Left Ventricular Fibrosis in a Woman with Anderson-Fabry Disease: Longitudinal Observations Using Two-Dimensional Speckle-Tracking Echocardiography

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INTRODUCTION

Anderson-Fabry disease (AFD) is a rare X-linked genetic lysosomal storage disease with an estimated prevalence of 1:40,000 to 1:60,000 in men.[1] Early detection of cardiac involvement in patients with AFD is important because early medical intervention with enzyme replacement therapy (ERT) helps preclude irreversible fibrosis in the heart and may prevent cardiovascular complications.[2] Here, we present a case of AFD in a woman who developed myocardial fibrosis that could be observed by serial echocardiography using two-dimensional (2D) speckle-tracking imaging, which is a novel modality for assessing cardiac function.

CASE PRESENTATION

A 62-year-old woman with previous palpitations who had been diagnosed with hypertrophic cardiomyopathy and treated with a β-blocker (bisoprolol 3.75 mg/day) for 5.5 years was hospitalized for further medical evaluation. The most recent transthoracic echocardiographic study, performed 5.5 years after the first visit, demonstrated normal left ventricular diastolic dimension (48 mm) and left ventricular ejection fraction (58.9%) and marked left ventricular hypertrophy (LVH) with increased interventricular septal thickness (20 mm). Moreover, although the patient had not experienced any specific symptoms related to cardiovascular disease after the first visit, transthoracic echocardiography unexpectedly detected localized thinning of the basal left ventricular posterior wall (Figure 1, *top, arrows*, Video 1). Physical examination of the patient revealed a pulse rate of 71 beats/min, blood pressure of 133/88 mm Hg, and a loud systolic heart murmur at the fourth left sternal border. She had an elevated serum creatinine level of 0.91 mg/dL, a troponin T level of 0.032 ng/mL, a brain natriuretic peptide level of 518 pg/mL, and otherwise normal blood test results. Electrocardiography revealed a short PQ interval of 0.112 seconds and T-wave inversion in precordial leads V_3 to V_6, findings that were similar to those of 5.5 years previously (Figure 2). Chest radiography revealed cardiomegaly (cardiothoracic ratio 56.0%). Although coronary computed tomographic angiography revealed no organic coronary lesion, cardiac magnetic resonance (CMR) demonstrated a thinned basal posterior wall (Figure 3C, Video 2) and late gadolinium enhancement mostly in the epicardial layer of the left interventricular septum and basal posterior wall (Figures 3A and 3B). Endomyocardial biopsy specimens from the interventricular septum revealed myocytes with perinuclear cytoplasmic vacuolization, which were accompanied by interstitial fibrosis on light microscopy (Figure 4, *left*) and numerous lysosomal inclusions characterized by a concentric lamellar configuration on electronic microscopy (Figure 4, *right*). After obtaining written informed consent, blood specimens were collected from the patient. Alpha-galactosidase (GLA) activity measurement and genetic analysis were performed at the laboratory of the National Center for Child Health and Development (Setagaya, Tokyo, Japan). The patient's GLA activity was 4.03 pmol/punch/h, which was 12.5% of the normal value and met the criteria for AFD for women (<30%). Genetic analysis detected a novel mutation in the GLA gene (exon 5, c. 772G>T, p.G258X [GGA/TGA]). The patient had four sons (aged 33, 31, 29, and 26 years): the oldest son, who had reported pain in his extremities with an unknown cause, had the same genetic mutation but without LVH and left ventricular dysfunction on echocardiography. On the basis of these findings, a diagnosis of AFD was established, and ERT was started for the patient.

We retrospectively performed 2D speckle-tracking analysis using digitally stored echocardiographic image data sets of this patient; created serial left ventricular deformation images along with longitudinal strain on a bull's-eye map; and further calculated global longitudinal strain, mean circumferential strain, and radial strain at the basal level. Longitudinal strain of the posterolateral wall at the basal level (Figure 1) and the value of global longitudinal strain (Table 1), as well as the mean value of radial strain at the basal level (Table 1), started to deteriorate from 2.5 years after her first visit before admission (3 years before admission).

DISCUSSION

A characteristic cardiac phenotype of AFD is LVH, which is also typical for more common cardiac conditions such as hypertrophic cardiomyopathy, hypertensive heart disease, and even athlete's heart.[3] In 2003, Moon *et al.*[4] first described a specific pattern of myocardial fibrosis in

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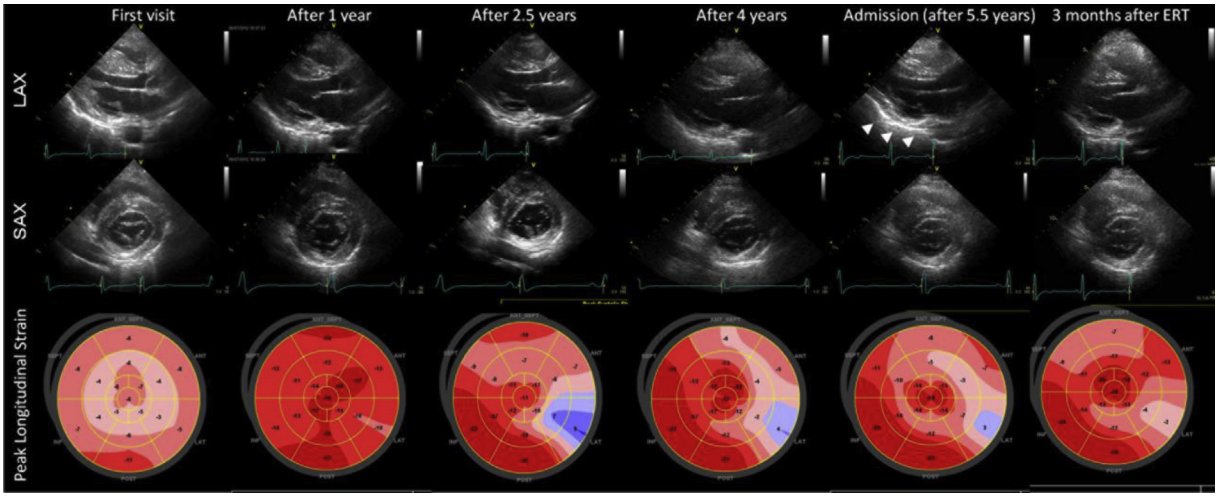

Figure 1 Serial echocardiograms with 2D speckle-tracking images. *Arrowheads* indicate localized thinning of the basal left ventricular posterior wall. The deterioration of longitudinal strain at the basal posterolateral wall 3 years before the admission can be seen. *LAX*, Long axis; *SAX*, short axis.

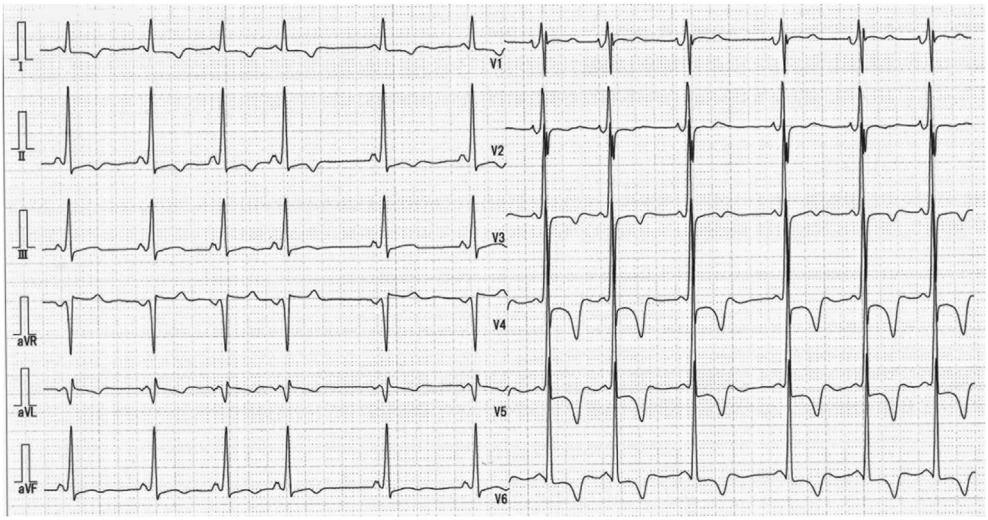

Figure 2 Electrocardiogram on admission. A supraventricular ectopy, short PQ interval of 0.112 seconds, and T-wave inversion in precordial leads V_3 to V_6 are shown.

patients with AFD, which was visualized as late gadolinium enhancement on CMR and was characterized by the involvement of the basal posterior to inferior wall with a mesocardial distribution that spared the subendocardium. This finding was further confirmed by other investigators[5] and is currently thought to be a clue for identifying AFD among cardiomyopathies that present as LVH.[3]

Recent studies have reported that ERT failed to show an impact on mortality rate in patients with advanced AFD.[6] ERT should be considered in patients at an earlier stage of cardiac involvement of AFD to enhance the benefit of treatment.[2] Therefore, the development of diagnostic tools for screening such patients is needed, although a short PQ interval on electrocardiography has been reported to be sensitive for early detection.[7]

In our patient, who had been diagnosed with HCM and treated accordingly, the recognition of localized thinning of the basal left ventricular inferoposterior wall on follow-up echocardiography prompted our conducting a systemic workup for AFD, including GLA measurement and genetic analysis. Although this finding has already been reported by a few investigators,[8,9] neither the precise pathophysiologic mechanism nor the clinical significance of this finding in AFD is clear. Therefore, it can be postulated that this finding might be the late consequence of the progression of myocardial fibrosis that could have been detected if we had performed CMR earlier.

Recently, cross-sectional studies have shown the usefulness of 2D speckle-tracking imaging for screening cardiac involvement of AFD at an early stage.[10,11] These studies could detect early impairments in the regional wall motion as left ventricular strain (longitudinal, radial, and circumferential) abnormalities. Conversely, in our retrospective longitudinal analysis, 2D speckle-tracking imaging could have detected earlier evidence of myocardial fibrosis in the basal posterior wall, which was later confirmed using CMR as late gadolinium enhancement. To date, only a few longitudinal studies regarding AFD have used 2D speckle-tracking echocardiography. Therefore, our case with a long-term longitudinal echocardiographic follow-up might