CASE REPORT

Advanced Anderson-Fabry disease presenting with left ventricular apical aneurysm and ventricular tachycardia

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Abstract

A 54-year-old female with Anderson-Fabry disease (AFD)-R342Q missense mutation on exon 7 in alpha-galactosidase A (*GLA*) gene - presented with sustained ventricular tachycardia. Imaging confirmed the presence of a new left ventricular apical aneurysm (LVAA) and a significantly reduced intra-cavitary gradient compared to two years prior. AFDcv is an X-linked lysosomal storage disorder caused by GLA enzyme deficiency. The phenotypic expression of AFD in the heart is not well described. Cardiac involvement can include left ventricular hypertrophy (LVH), which is typically symmetric, but can also mimic hypertrophic cardiomyopathy (HCM). Left ventricular apical aneurysm is a rare finding in HCM. We suggest a shared mechanism of LVAA formation in AFD and HCM, independent of the underlying cardiomyopathy. Mechanisms of LVAA formation in HCM include genetic predisposition and long-standing left ventricular wall stress from elevated intra-cavitary systolic pressures due to mid-cavitary obstruction. Both mechanisms are supported in this patient (a brother with AFD also developed a small LVAA). Screening for AFD should be considered in cases of unexplained LVH, particularly in patients with the aneurysmal variant of HCM.

Key words: Anderson-Fabry disease; Sustained ventricular tachycardia; Left ventricular apical aneurysm; Hemodynamic compensation; Transthoracic echocardiography; Magnetic resonance imaging; Hypertrophic cardiomyopathy

Core tip: Left ventricular apical aneurysm (LVAA) is a very rare phenomenon in patients with Anderson-Fabry disease (AFD); however, this patient with genetically confirmed AFD presented with a new LVAA. The authors believe that formation of the LVAA is the result of long-

standing elevated intra-cavitary systolic pressures and possibly genetic predisposition, similar to what can be seen in hypertrophic cardiomyopathy.

INTRODUCTION

Anderson-Fabry disease (AFD) is an X-linked lysosomal storage disorder caused by alpha-galactosidase (GLA) enzyme deficiency. The phenotypic expression of AFD in the heart is not well described. Cardiac involvement can include left ventricular hypertrophy (LVH), which is typically symmetric, but can also mimic hypertrophic cardiomyopathy (HCM). We report the case of a middle-aged female previously diagnosed with AFD who developed a left ventricular apical aneurysm (LVAA), which has been rarely reported in AFD. We suggest a shared mechanism of LVAA formation in AFD and HCM, independent of the underlying cardiomyopathy.

CASE REPORT

A 54-year-old female with AFD and well controlled hypertension presented with chest pain, palpitations and dizziness after missing two doses of metoprolol. Her initial electrocardiogram (ECG) displayed sustained monomorphic ventricular tachycardia (VT) with a cycle length of 214 ms. The VT had a right bundle, superior axis morphology suggesting a left ventricular (LV) apical origin (Figure 1)[1]. She initially received a bolus of amiodarone that failed to terminate the VT. Post direct current cardioversion, serial ECGs showed atrial fibrillation with persistent ST segment elevation in the inferior leads (Figure 2). A coronary angiogram demonstrated non-occlusive coronary artery disease. Transthoracic echocardiogram (TTE) revealed that her ejection fraction was newly reduced from 75% to 40% and identified a thin-walled LVAA that was not seen on TTE two years prior (Figure 3A and B). The mid and basal segments of the LV still had marked concentric hypertrophy with systolic mid-cavitary obliteration; however, the intra-cavitary gradient at rest was significantly lower than on the prior study; it had decreased from 71 to 16 mmHg (Figure 4). Contrast-enhanced cardiovascular magnetic resonance (CMR) confirmed these findings and demonstrated late gadolinium enhancement (LGE) of the aneurysmal LV apex extending to the lateral and inferolateral walls, consistent with myocardial scarring (Figure 5). The patient was restarted on metoprolol and had no further episodes of VT. A defibrillator (ICD) was implanted prior

to discharge.

DISCUSSION

AFD is a rare, X-linked lysosomal storage disorder caused by GLA enzyme deficiency, which results in an abnormal accumulation of sphingolipid catabolites in multiple organs, including the heart. Although the prevalence of AFD is likely underestimated, mutations are present in 1:6000 to 1:40000 females. Clinical manifestations in heterozygous females vary widely from no apparent clinical disease to full expression of the disease[2]. Cardiac involvement can lead to myocardial hypertrophy, restrictive cardiomyopathy, coronary artery disease, arrhythmias (atrial and ventricular) as well as aortic and mitral valvulopathy[3]. Our patient's disease manifested in childhood with acroneuropathy and hypohydrosis, and subsequently progressed to include cutaneous lesions, lacunar infarcts and LVH. A few years prior to presentation she was diagnosed with hypertension, but there was no manifest renal involvement from AFD. Her blood pressure was well controlled with a combination of an angiotensin converting enzyme inhibitor and a beta blocker. The diagnosis of AFD was established at age fifteen by genetic testing with a R342Q missense mutation on exon 7 in the *GLA* gene. A brother had the same mutation. The R342Q mutation has been shown to lead to a complete loss of the GLA activity, and to be associated with a classical phenotypic presentation of AFD[4,5].

Despite a relatively early diagnosis, our patient had been reluctant to initiate AFD therapy until her symptoms worsened. Enzyme replacement therapy with Agalsidase beta (Fabrazyme®, Genzyme, Cambridge, MA, United States) had been initiated eighteen months prior to presentation. She received monthly infusion of 65 mg for one year, followed by an infusion of 60 mg every 2 wk. Despite being compliant with the treatment, her disease slowly progressed, with worsening of her neuropathy, cutaneous lesions, development of cerebral vasculopathy and formation of the LVAA.

LVH is a relatively common finding in AFD and has been shown to correlate with severity of the disease. LVH in AFD can mimic HCM and has been identified among the causes of late onset HCM in women. In addition, women tend to present at a later age than men, and often have milder symptoms, making the diagnosis of AFD more challenging in female patients[6,7]. The pattern of hypertrophy in AFD is typically symmetric, as opposed to asymmetric with preferential septal involvement in HCM. Contrast-enhanced CMR typically demonstrates evidence of LGE, particularly in the LV subepicardial and mesocardial inferior and inferolateral segments. The LGE is believed to be the result of both intra-myocyte accumulation of sphingolipids and fibrosis[8]. Development of a LVAA is uncommon in HCM (reported in only 2% of patients) but portends a poor prognosis with a high adverse event rate, including sudden death,
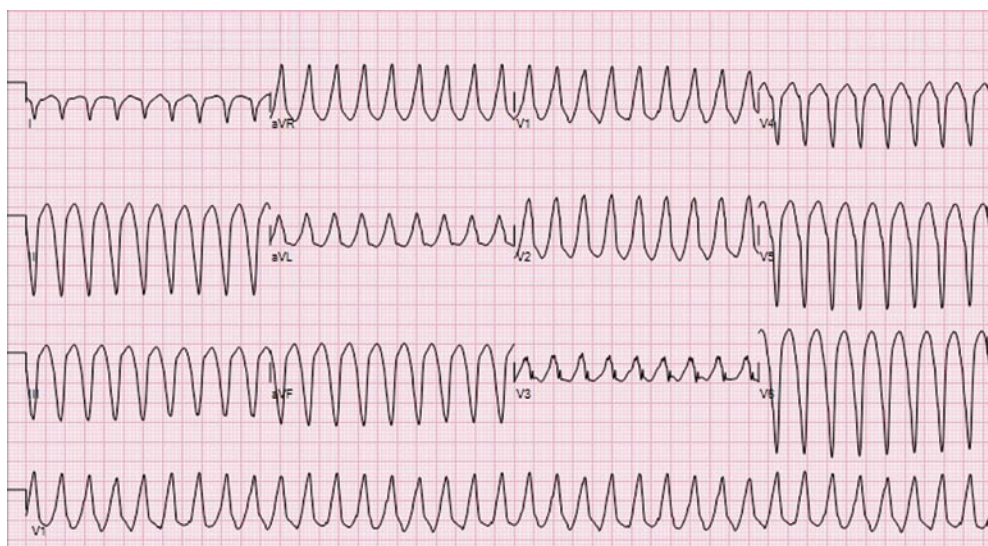
Figure 1 12-lead electrocardiogram (5 mm/mV) during ventricular tachycardia. The QRS shows a right bundle morphology with superior axis, suggesting a left ventricular apical source.
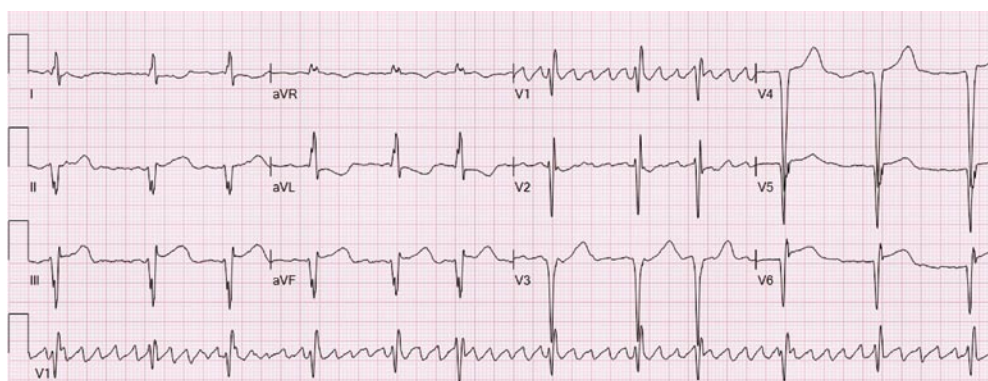

Figure 2 12-lead electrocardiogram (10 mm/mV) following direct current cardioversion. ST segment elevation is seen in the inferolateral leads.
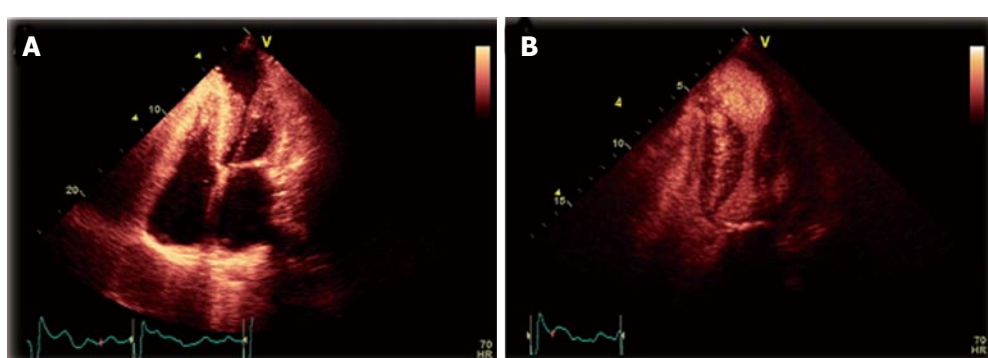

Figure 3 Transthoracic echocardiogram. A: Transthoracic echocardiogram (TTE), apical four-chamber view, demonstrating concentric left ventricular hypertrophy with mid-cavitary obliteration at end-systole, as well as a large left-ventricular apical aneurysm (LVAA); B: TTE apical two-chamber view, with ultrasound contrast demonstrating stasis within the LVAA with a circular flow pattern, as well as decreased perfusion of the apex.

appropriate ICD discharges, thromboembolic stroke, and progressive heart failure[9].

In contrast to AFD, HCM is a relatively common genetic disease and is the most common cause of sudden cardiac death in young people. Its estimated prevalence is 1 in 500. In HCM, the inheritance pattern is autosomal dominant. The mutant proteins that cause HCM are incorporated into intact filaments of the sarcomere and have been described as "poisonous peptides". Local environmental factors such as pressure, protein defect and modifier genes interact to induce the subsequent phenotype[10]. In HCM, development of ST
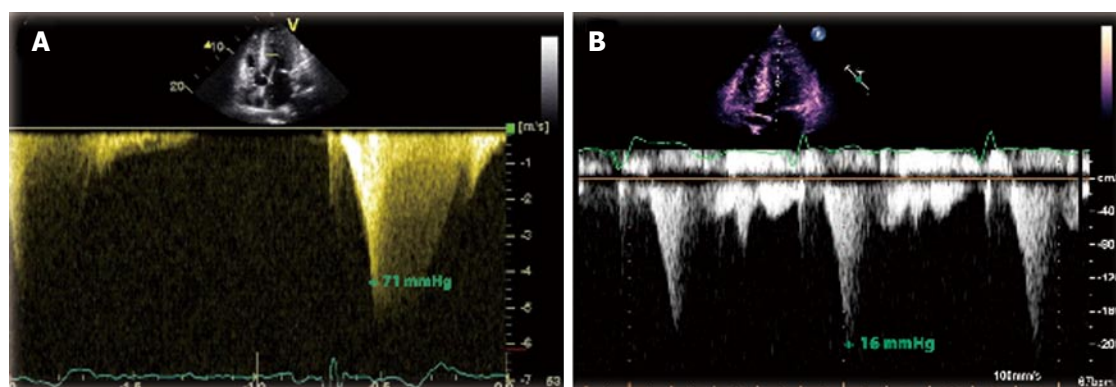
Figure 4 Transthoracic echocardiogram continuous Doppler. A: Transthoracic echocardiogram continuous Doppler flow across the left ventricle. The mid-cavitary gradient at rest from two years prior to the left-ventricular apical aneurysm (LVAA) formation (71 mmHg) is shown; B: Over time, flow across the mid-cavitary obliteration decreased and the peak pressure declined after the formation of the LVAA (16 mmHg).
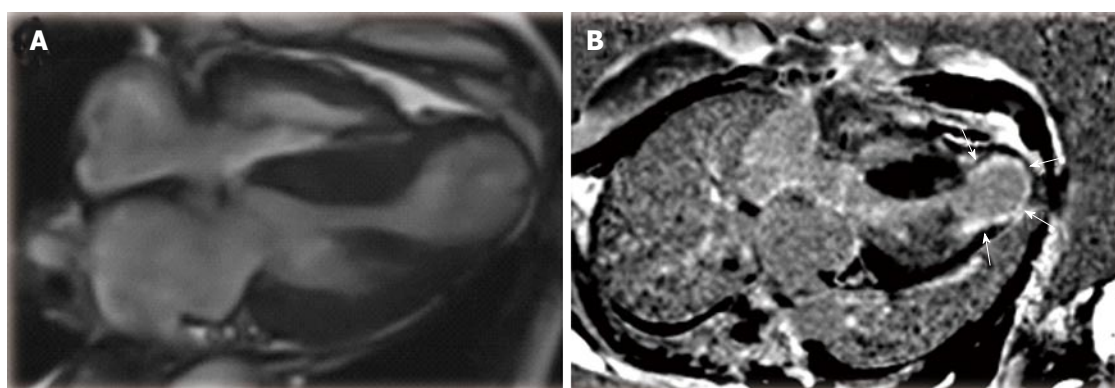

Figure 5 Contrast-enhanced cardiovascular magnetic resonance. A: Long-axis four-chamber cardiovascular magnetic resonance in systole showing concentric left ventricle hypertrophy with mid-cavitary obstruction and large apical aneurysm; B: Late gadolinium enhancement (LGE) image of the left-ventricular apical aneurysm consistent with myocardial scarring (arrows) with extension of LGE into the inferolateral segments (a pattern typically seen in Anderson-Fabry Disease).
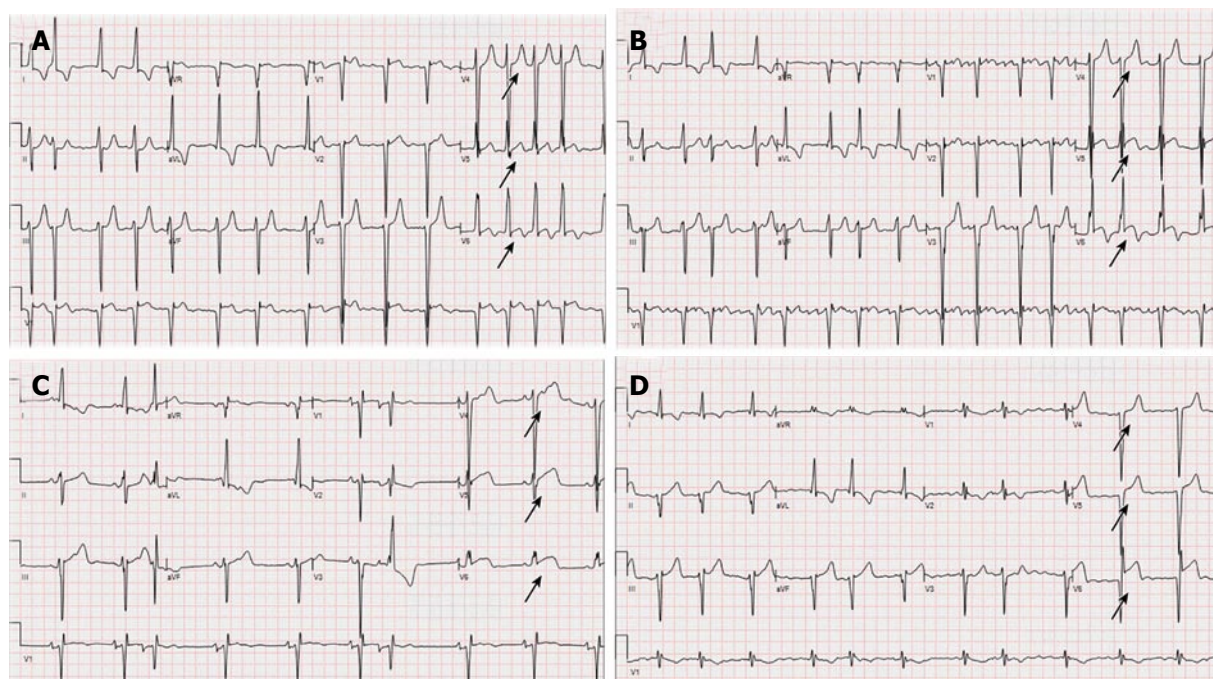

Figure 6 Serial electrocardiograms from this patient (A) 4 years prior, (B) 2 years prior, (C) 1 year prior, and (D) 3 mo prior are presented. The development of ST elevation in leads V4-V6 (arrows) can be seen, and correlates with the formation of the left ventricular apical aneurysm.
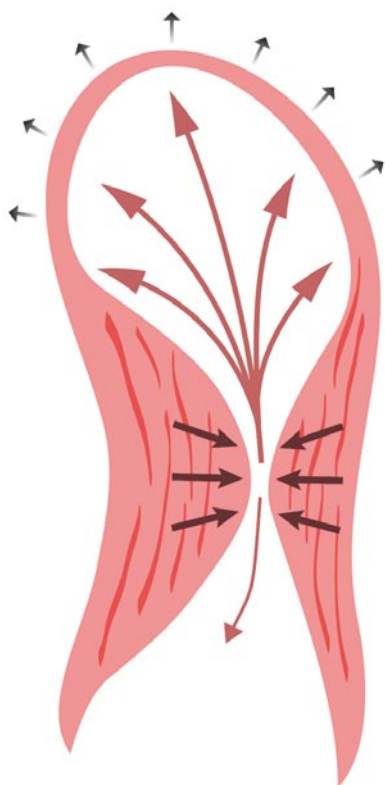
Figure 7 Illustration of blood flow direction during left ventricular systole. While some blood is ejected towards the outflow tract (single arrow), the flow is initially greater towards the apex, which is the area of least resistance (arrows from mid-cavity to the left-ventricular apical aneurysm), resulting in a lower gradient across the mid-cavitary obliteration as the aneurysm size increases.

elevation in leads V4 through V6 has been associated with LVAA formation[11]. Similar findings were seen upon reviewing our patient's serial ECGs (ranging from 4 years to 3 mo) prior to her presentation (Figure 6). To the best of the authors' knowledge, the development of LVAA has only been previously described once in AFD. In a recent report, the case of a middle-aged female diagnosed with HCM and LVAA is described. That patient was later found to have a missence mutation in the *GLA* gene (p.R118C) confirming the diagnosis of AFD[12].

The proposed mechanisms for LVAA formation in HCM are genetic predisposition and long-standing LV wall stress from elevated intra-cavitary systolic pressures as a result of mid-cavitary obstruction[8]. Both mechanisms are potential contributors in our patient, as a brother with AFD also developed a small LVAA prior to his death. We hypothesized that the formation of an apical aneurysm may be considered a hemodynamic adaptation to sustained elevation of systolic intra-cavitary LV pressure. The apex can dilate in response to the chronically elevated wall pressures during systole, with some blood flow directed towards the aneurysm, which offers less resistance than the mid-cavitary obliteration (Figure 7). Over time, this results in decreased flow across the mid-cavitary obstruction and a concordant smaller peak pressure gradient[13]. This phenomenon is exhibited in our patient by the

considerable fall in her peak intra-cavitary gradient after the LVAA developed. Of note, our patient had chronic atrial fibrillation and it could be speculated that the LVAA formation was the result of a thromboembolic event. However, this scenario seems unlikely given that she had been appropriately anticoagulated with coumadin for years and had no other evidence of (non-cerebral) systemic embolization.

The phenotypic expression of AFD in the heart is not well described and can mimic even rare forms of HCM. The findings in this case suggest a shared mechanism(s) of aneurysm formation in AFD and HCM, independent of the underlying cardiomyopathy. Screening for AFD should be strongly considered in cases of unexplained LVH, particularly in patients with the aneurysmal variant of HCM. As previously demon-strated in HCM, it is likely that LVAA formation in AFD portends a poor prognosis.

COMMENTS

Case characteristics
A middle-aged female with Anderson-Fabry disease (AFD) presented with chest pain, palpitations and dizziness for a few hours after missing two doses of her beta-blocker.

Clinical diagnosis
She was found to have sustained ventricular tachycardia originating from the left ventricular (LV) apex, and further imaging confirmed the presence of a new LV apical aneurysm (LVAA).

Differential diagnosis
The differential diagnosis included aneurysm from hypertrophic cardiomyopathy (HCM), aneurysm from prior infarct, apical diverticulum and Takotsubo cardio-myopathy.

Laboratory diagnosis
The diagnosis of AFD was established by genetic testing with the presence of R342Q missense mutation on exon 7 in the *GLA* gene.

Imaging diagnosis
A transthoracic echocardiogram revealed that her intra-cavitary gradient had significantly decreased from two years prior and identified a new LVAA, which was confirmed by a cardiovascular magnetic resonance imaging.

Pathological diagnosis
The findings in this case suggest a shared mechanism(s) of aneurysm formation in AFD and HCM: genetic predisposition and long standing LV wall stress from elevated intra-cavitary systolic pressures as a result of mid-cavitary obstruction.

Treatment
She was placed back on her beta blocker and a defibrillator was implanted prior to discharge.

Related reports
Left ventricular hypertrophy in AFD can mimic HCM, however the pattern of hypertrophy is typically symmetric in AFD as opposed to asymmetric with preferential septal involvement in HCM. Development of a LVAA is uncommon in HCM (reported in only 2% of patients) and has only been (recently) reported once in AFD.

Term explanation
Development of a LVAA is a very rare phenomenon in patients with AFD.

Experiences and lessons
The findings in this case suggest a shared mechanism(s) of aneurysm formation in AFD and HCM, independent of the underlying cardiomyopathy. Screening for AFD should be strongly considered in cases of unexplained LVH, particularly in patients with the aneurysmal variant of HCM.

Peer-review
Authors showed a case of AFD complicated by apical aneurysm and ventricular

tachycardia. This report is written and presents well.

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