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Case Report

Acute Decompensated Heart Failure After Initiation of Amiodarone in a Patient With Anderson-Fabry Disease

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ABSTRACT

A 54-year-old man with the lysosomal storage disorder Anderson-Fabry disease (AFD) and cardiac involvement was placed on amiodarone for treatment of symptomatic paroxysmal atrial fibrillation. Shortly thereafter, he developed symptoms of acute decompensated heart failure, requiring hospital admission. Endomyocardial biopsy demonstrated findings consistent with AFD and possible amiodarone toxicity. Amiodarone was discontinued, and the patient's heart failure resolved with return to baseline status. Amiodarone is known to alter lysosomal pH and enzyme activity, and this case illustrates how it should be used with considerable caution in patients with AFD.

RÉSUMÉ

Un homme de 54 ans qui a la maladie d'Anderson-Fabry (MAF), une maladie de surcharge lysosomale, et une atteinte cardiaque a dû prendre de l'amiodarone pour traiter une fibrillation auriculaire paroxystique symptomatique. Peu après, il a manifesté des symptômes d'insuffisance cardiaque aiguë décompensée, qui a exigé une admission à l'hôpital. La biopsie endomyocardique a démontré des résultats correspondant à la MAF et une toxicité possible de l'amiodarone. Le patient a retrouvé son état initial après l'arrêt de l'amiodarone qui a permis de résoudre l'insuffisance cardiaque dont il souffrait. On sait que l'amiodarone modifie le pH des lysosomes et l'activité enzymatique. Ce cas illustre comment utiliser l'amiodarone avec grande précaution chez les patients atteints de la MAF.

Case

A 54-year-old man was diagnosed with classical Anderson-Fabry disease (AFD) (galactosidase alpha [GLA] gene, c.1012G > A, E338K; undetectable levels of α-galactosidase A activity, by Dr R. J. Desnick, Icahn School of Medicine at Mount Sinai, New York, NY) and was started on enzyme replacement therapy (ERT) with agalsidase-β (Fabrazyme, Sanofi-Genzyme, Cambridge, Massachusetts). His manifestations of AFD included proteinuria, acroparesthesias, corneal verticillita, and angiokeratomas. Cardiac manifestations included increased left ventricular (LV) wall thickness and mildly reduced systolic function (LV ejection fraction [EF] 45% to 50%) and paroxysmal atrial fibrillation (AF), but no history of heart failure (HF). He developed symptomatic bradycardia and subsequent dependence upon the permanent pacemaker that was implanted. This was later upgraded to a dual-chamber implantable cardioverter-defibrillator (ICD) after a ventricular fibrillation arrest, from which he subsequently made a full recovery. Because of an agalsidase-β shortage, the dose was initially reduced from 1 mg/kg every second week to 0.5 mg/kg for a 3-month period before being switched to agalsidase-α (Replagal, Shire, Dublin, Ireland) 4 years previously. Following a period of clinical stability, and 10 years after starting ERT, he began developing worsening palpitations, accompanied by mild chest discomfort. Coronary angiography demonstrated no obstructive coronary artery lesions. Interrogation of his ICD demonstrated an increasing burden of AF despite β-blocker therapy. The patient was started on a loading dose of oral amiodarone, followed by maintenance therapy, with concurrent reduction of his beta-blocker dose. Several weeks later, the patient began experiencing symptoms of decompensated left HF—including worsening dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea—despite a reduction in palpitations and atrial fibrillation burden following repeat ICD interrogation. This was accompanied by a fall in his estimated glomerular filtration rate (eGFR) from 60 to 44 mL/min/1.73 m^2. Repeat transthoracic echocardiography demonstrated a decrease in LVEF to 35% to 40% and new

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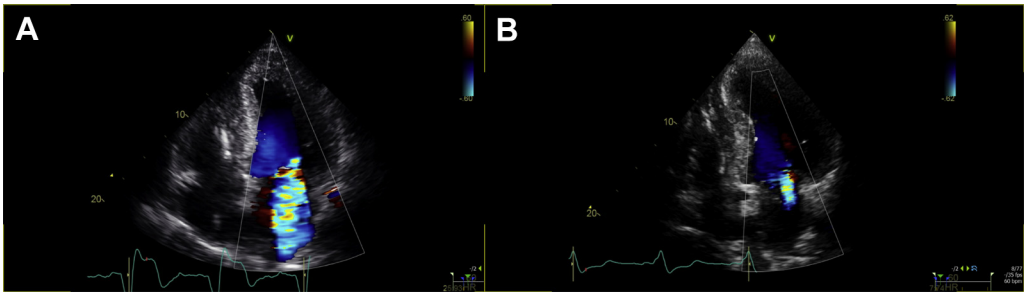

Figure 1. Transthoracic echocardiogram with colour-flow Doppler imaging demonstrating (**A**) severe mitral valve regurgitation accompanying presentation with acute decompensated heart failure after initiation of amiodarone therapy in a patient with Anderson-Fabry disease and (**B**) improvement of mitral valve regurgitation to only mild on follow-up examination with resolution of heart failure symptoms after amiodarone was discontinued.

severe mitral valve regurgitation (Fig. 1; Video 1, view video online). Urine and plasma globotriaosylceramide (GL-3), lysoGL-3 and anti-agalsidase-α antibody titre were not elevated, suggesting neither worsening AFD nor intolerance to ERT were causing the HF. The patient switched ERT agent back to agalsidase-β; however, he continued to decline clinically and subsequently required hospital admission for acute decompensated HF, requiring intravenous diuretic therapy. Because of concerns about a possible secondary myopathic process triggering his HF decompensation, he underwent right ventricular endomyocardial biopsy (Fig. 2). This demonstrated findings consistent with AFD cardiomyopathy including myocyte hypertrophy, interstitial fibrosis on Gomori trichrome staining, and intracellular lamellar layered bodies by electron microscopy. The presence of marked vacuolated cytoplasmic changes, which can be present with both AFD cardiomyopathy and amiodarone toxicity, prompted consultation between the cardiology and metabolic genetics services, and the amiodarone was discontinued. Amiodarone levels were not measured during the patient's evaluation. After stabilization of his HF, he was discharged from the hospital, and in the following weeks his symptoms steadily improved to the point at which he was requiring no maintenance oral diuretic therapy, and he returned to baseline status with no symptoms of HF. Repeat echocardiography 11 months after discharge demonstrated improved LVEF back to baseline and only mild mitral valve regurgitation

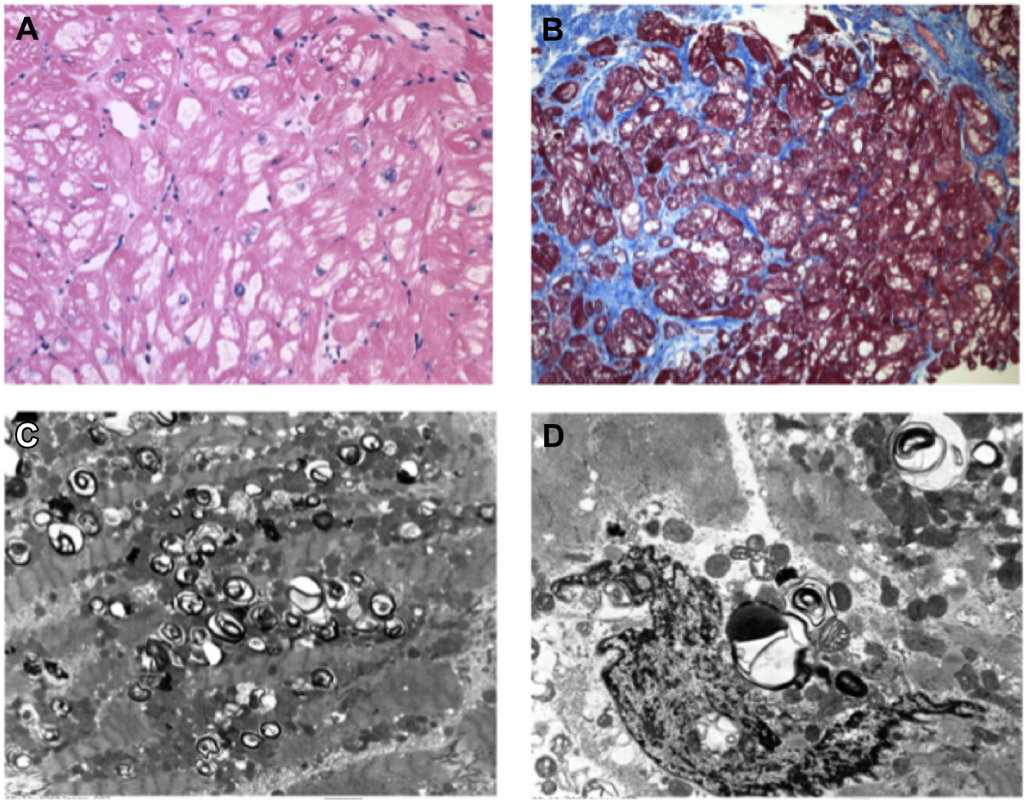

Figure 2. Endomyocardial biopsy of right ventricle. (**A**) Vacuolated and hypertrophied myocytes by Hematoxylin and Eosin stain, 20X; (**B**) interstitial fibrosis, Gomori trichrome stain, 10X; (**C**) and (**D**), lamellar bodies, electron microscopy, 2000X and 4000X, respectively.

(Fig. 1; see Video 2, view video online), and eGFR improved to 52 mL/min/1.73 m^2. The patient's beta blocker was resumed at its previous dose, and he experienced occasional episodes of atrial fibrillation that were rate controlled and well tolerated.

Discussion

AFD is an X-linked lysosomal storage disorder caused by a loss of function mutation of the GLA gene, resulting in a deficiency or absence of the α-galactosidase-A enzyme.[1] Subsequent intracellular accumulation of glycosphingolipids—specifically, GL-3—cause manifestations in multiple organ systems including cardiac, renal, neurological, dermatological, gastrointestinal, and ocular.[1,2] Cardiovascular disease is the leading cause of mortality in patients with AFD.[2] The hallmark of AFD cardiomyopathy is concentric increased LV wall thickness with preserved LVEF, leading to progressive HF in the absence of treatment.[1] Arrhythmias—including AF, bradyarrhythmia, and ventricular arrhythmia—are also common. Recombinant α-galactosidase-A ERT represents the primary approach to disease-modifying therapy and improves outcomes while slowing or even reversing progression of disease. At present, there are 2 ERT agents approved for clinical use in Canada: agalsidase-β and agalsidase-α.

To our knowledge, this is the first reported case of a patient with AFD cardiomyopathy treated with ERT who developed acute decompensated HF shortly after initiating amiodarone, with subsequent improvement following its discontinuation. Amiodarone is an organic base that has an affinity for lysosomes and decreases lysosomal pH and enzyme activity, leading to abnormal cellular morphology.[3] This not only impairs any residual enzyme activity but could also render exogenous enzyme, which relies on an acidic lysosomal pH for activity, to be less effective. Although the vacuolated cytoplasmic changes demonstrated on endomyocardial biopsy can be seen with both AFD and amiodarone toxicity, the temporal correlation of the patient's decompensated HF with amiodarone initiation resulted in a high level of suspicion that the amiodarone caused or significantly contributed to the patient's clinical decline, prompting its subsequent discontinuation. Both the Fabrazyme and Replagal product monographs recommend against concurrent administration with amiodarone. Given the high prevalence of AF that it is often difficult to control among patients with AFD, clinicians unaware of this potential interaction may be tempted to initiate amiodarone in patients with AFD and AF or other tachyarrhythmias. This case serves as an example of how amiodarone should be used with considerable caution in patients with AFD and highlights the importance of communication among physicians in the multidisciplinary care of patients with AFD.

Disclosures

Dr Fine has received speakers' honoraria and consulting fees from Sanofi-Genzyme. Dr Khan has received travel funds, speakers' honoraria, consulting fees, and research grants from Amicus Therapeutics, Avrobio Inc., Resverlogix Corp, Sanofi-Genzyme, Shire Human Genetic, and the Canadian Fabry Association related to Fabry disease; he has a revenue-sharing agreement with the University Health Network related to a gene therapy technology for Fabry disease and is a member of the International Collaborative Group on Gaucher Disease (ICGG) and the Pompe registry, which are both sponsored by Sanofi-Genzyme. Dr Khan is president of M.A.G.I.C. Clinic Ltd (Metabolics and Genetics in Calgary), which is involved in the care of patients with Fabry disease, and is president of the Rare Disease Network of Alberta Ltd, which provides educational information about Fabry disease. He is a member of the Canadian Fabry Disease Initiative (CFDI) Scientific Advisory Board and Guidelines Committee. Dr Wang has no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2018.10.004.