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CASE REPORT

Systemic Emboli and Biventricular Hypertrophy Due to Glycogen Storage Disease: Clinical, Imaging, and Pathologic Predicament

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Abstract
Glycogen storage disease cardiomyopathy is being recognized increasingly as a mimicker of hypertrophic cardiomyopathy. It is important to diagnose these diseases, as there are prognostic and treatment ramifications. This case report discusses a patient who presented with cardioembolic renal infarction and was ultimately diagnosed with glycogen storage disease XV (which is extremely rare). The diagnosis was made by pursuing multimodality imaging, endomyocardial biopsy, and genetic testing.

Background
Glycogen storage diseases are an uncommon cause of left ventricle hypertrophy (LVH) and should be on the list of differential diagnoses, especially for younger patients or those with unexplained LVH (1). It is important to diagnose, as there are prognostic ramifications and potential treatments. Multimodality imaging and genetic testing should be performed in patients with unexplained LVH (2), and endomyocardial biopsy may be considered (3).

Objectives
To become familiar with the differential diagnosis of LVH, including uncommon causes, such as glycogen storage disease cardiomyopathy. To recognize the importance of multimodality imaging, endomyocardial biopsy, and genetic testing in elucidating the cause of LVH.

Case Report
A 35-year-old man with a remote history of COVID-19 was hospitalized with right-sided flank and abdominal pain. He also reported progressive dyspnea on exertion and fatigue for the past several months that limited his career as a landscaper. Apart from COVID-19, he did not report any medical history and reported an unremarkable childhood development. Family history was notable for maternal grandfather with Huntington disease and maternal grandmother with type 2 diabetes. Vital signs were unremarkable. On examination, right costovertebral angle tenderness and right lower-quadrant tenderness were present. Laboratory test results were notable for an elevated troponin I (peak 0.003 ng/L) and mildly elevated C-reactive protein (0.23 mg/L); the remaining laboratory values were unremarkable. Electrocardiogram revealed sinus bradycardia with LVH, incomplete right bundle branch block, and left anterior fascicular block. Computed tomography of the abdomen revealed multiple wedge-shaped areas of the right kidney consistent with renal infarcts (Figure 1A). It also showed thickened and heterogeneous myocardium with hypodense, fat-like foci concerning for infiltration (Figure 1B).

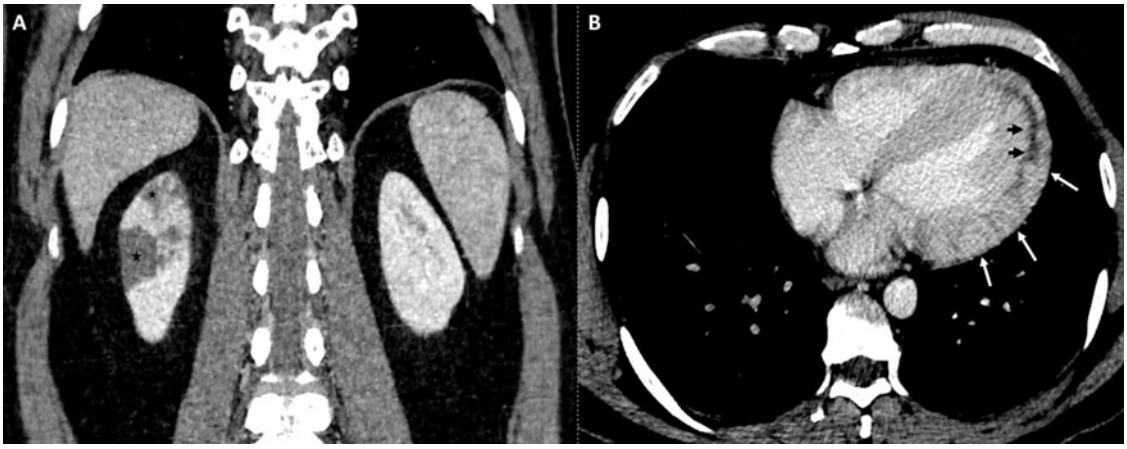

Figure 1. **Coronal contrast-enhanced CT image (A) showing multiple peripheral wedge-shaped right renal infarcts (star). Axial (B) CT image through the chest base showing septal hypertrophy with heterogeneous enhancement along the lateral wall of the left ventricle (*white arrows*). There are internal "fat-like" (–10 HU) hypodense areas (*black arrows*) within this heterogeneous area along the LV. CT = computed tomography; HU = Hounsfield unit; LV = left ventricle.**

Transthoracic echocardiogram with contrast noted moderate concentric LVH with normal chamber size. There was normal systolic function (left ventricular ejection fraction 60%) with apical akinesis but a hyperdynamic midventricle. No thrombus was noted on contrast imaging.

Cardiac magnetic resonance imaging (CMR) revealed biventricular hypertrophy with asymmetric thickening of the septum (maximal thickness 2.1 cm) and heterogeneous myocardial signal (Figure 2). There was normal biventricular systolic function with left ventricular ejection fraction of 55%. No left ventricular outflow tract obstruction or left ventricular thrombus was present. CMR parametric mapping demonstrated increased T1 and T2 time, predominantly in the basal and mid inferolateral wall (Figure 3).

Myocardial delayed enhancement (MDE) images showed patchy, nonischemic pattern mid-myocardial and subepicardial enhancement in the inferolateral and apical wall, along with the right ventricular free wall (Figure 3). Due to the hypodense foci on computed tomography, increased T2 time, and patchy heterogenous MDE, the patient was thought to have hypertrophic cardiomyopathy (HCM) with superimposed additional inflammatory or infiltrative disease. The patient had a left and right heart catheterization with endomyocardial biopsy. Coronary angiography findings were normal.

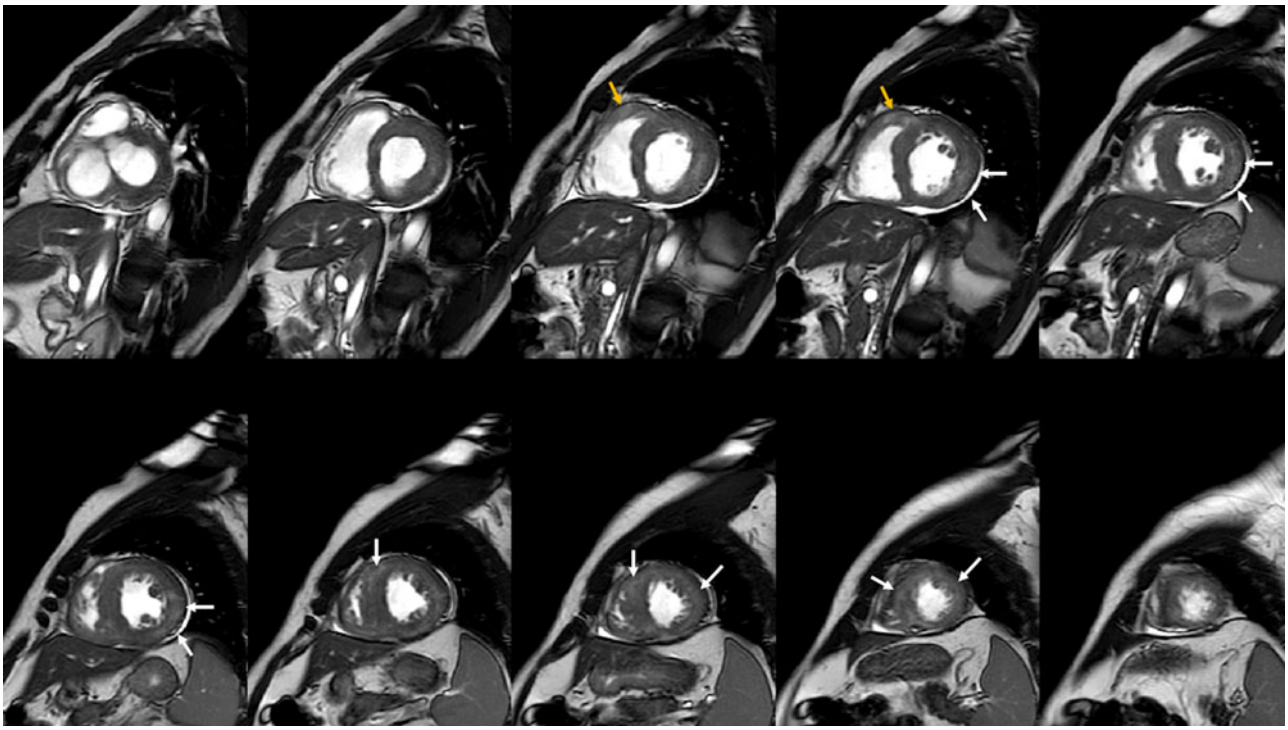

Figure 2. **Short-axis balanced steady-state free precession (SSFP) end-diastolic cardiac MRI images showing left and right ventricular hypertrophy with heterogeneous areas of high signal in the thickened RV (*yellow arrows*) and LV (*white arrows*). MRI = magnetic resonance imaging; RV = right ventricle.**

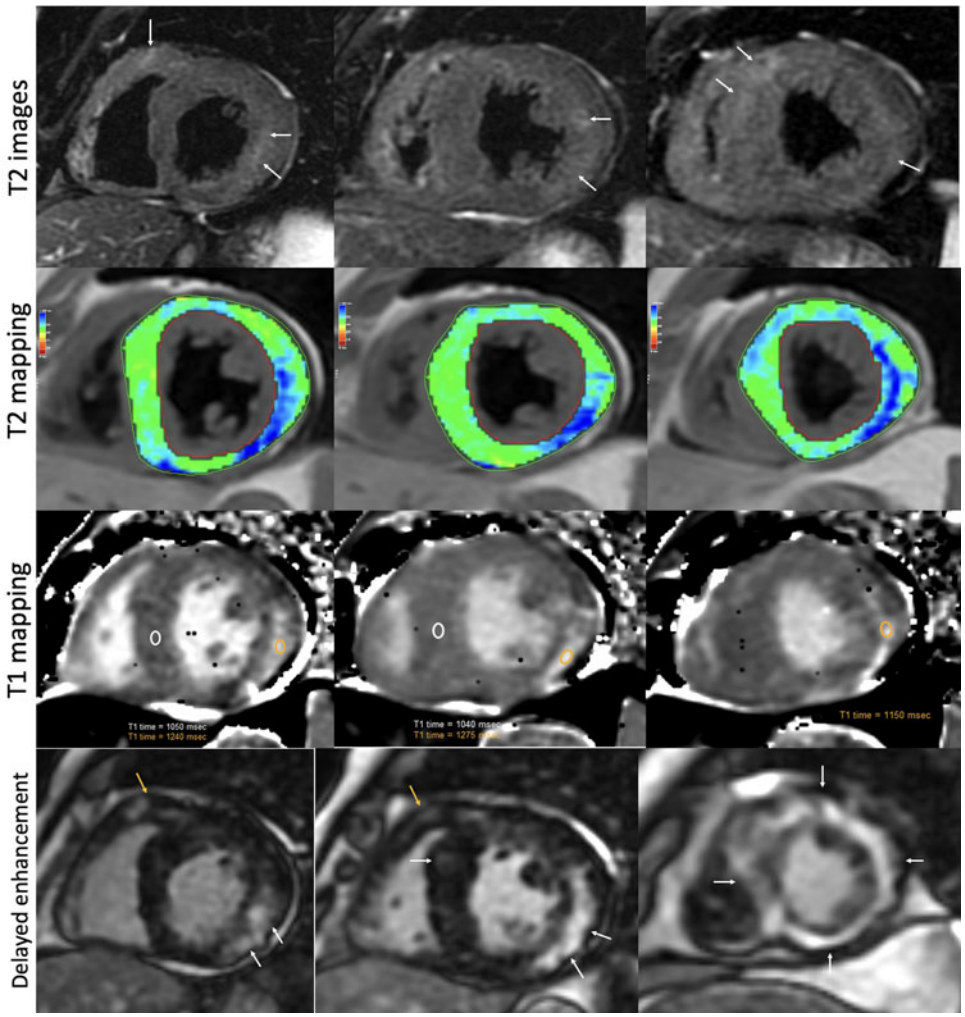

Figure 3. **Short-axis T2 weighted images (*first row*) showing areas of increased T2 signal (*white arrow*) suggesting edema or increased water content. T2-mapping (*second row*) confirms patchy areas of high T2-time (*blue*, greater than 55 milliseconds) in the left ventricle. T1-mapping (*third row*) shows diffuse increase in T1 time (>1000 milliseconds), which is most increased in the lateral wall (*orange* region of interest). Short- axis myocardial delayed enhancement (MDE) images (*fourth row*) showing extensive patchy, nonischemic, predominantly mid-myocardial enhancement in the thickened RV (*yellow arrows*) and LV (*white arrows*) myocardium. LV = left ventricle.**

Endomyocardial biopsy demonstrated prominent myocyte vacuolization with periodic acid–Schiff–positive material sensitive to diastase (Figure 4A). CD68 immunohistochemical stain was negative, suggestive of a lack of abnormal lysosome accumulation. Electron microscopy revealed marked accumulation of cytoplasmic electron dense particles compatible with glycogen (Figure 4B). The combined light and electron microscopic findings were consistent with a glycogen storage disease. The patient was discharged on apixaban for presumed cardioembolic thrombus and followed up in the heart failure clinic. Genetic testing revealed homozygous pathogenic mutation in *GYG1* (c.304G>C,p.Asp102His), consistent with glycogen storage disease XV. This specific homozygous missense mutation has been previously reported in multiple individuals with this disease (4). Because of the extreme rarity and autosomal-recessive nature of this disease, screening of his children was not recommended, but his siblings were recommended to be tested for the *GYG1* mutation and have a screening echocardiogram. At 6-month follow-up, kidney function remained normal.

Discussion

LVH is associated with various cardiac diseases, most commonly hypertension and aortic stenosis. In younger patients, clinicians should consider less-common causes of LVH, such as athlete's heart, HCM, infiltrative diseases, and inherited diseases such as lysosomal storage diseases and glycogen storage diseases (1).

Echocardiography is the preferred imaging method to initially evaluate LVH and cardiac source of embolism. CMR is the test of choice for evaluating the underlying cause of LVH, presence of thrombus, and myocardial fibrosis. CMR has a class I indication for patients with LVH in whom an alternative diagnosis to HCM is being considered (2). In our patient, CMR was ordered due to the unusual pattern of LVH with apical akinesis and the absence of thrombus on transthoracic echocardiogram with

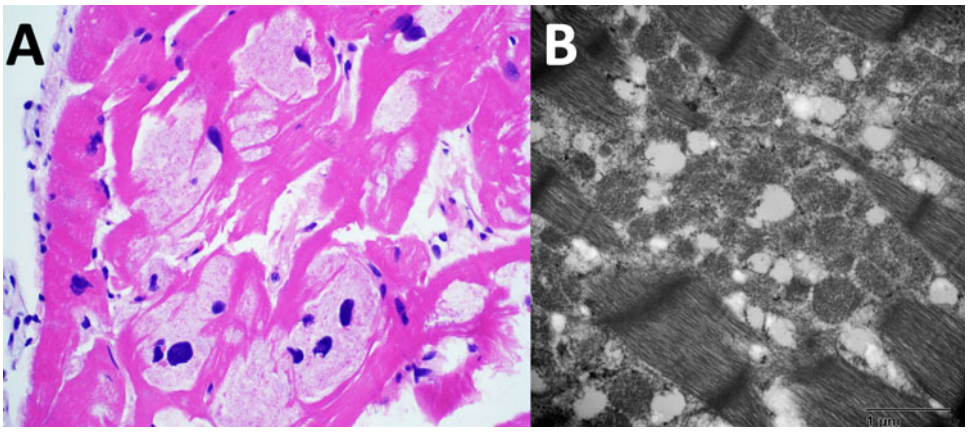

Figure 4. **Light microscopy (A) showing myocyte vacuolization with granular cytoplasmic inclusions (H&E, 200×). Electron microscopy (B) cardiac myocytes showing disruption by increased extralysosomal glycogen. H&E = hematoxylin–eosin stain.**

contrast. CMR revealed biventricular hypertrophy with some degree of asymmetric septal thickening, which overlaps with morphologic features of HCM. However, the MDE pattern was not confined to the septum or right ventricular insertion points, which favored a superimposed pathology or alternative diagnosis to HCM. Ultimately, endomyocardial biopsy and genetic testing confirmed the diagnosis of glycogen storage disease XV. Genetic testing is a class I indication for patients with HCM and unexplained LVH (2). Endomyocardial biopsy is less supported and is a class IIB recommendation for patients with heart failure and unexplained LVH (3).

In the past 20 years, phenocopies of HCM have become increasingly recognized (1, 2, 5–8). These phenocopies include lysosomal storage diseases and glycogen storage diseases, such as Fabry, Pompe, and Danon disease. It is important to differentiate the cause, as it has prognostic and treatment ramifications. Glycogen storage disease cardiomyopathies tend to have worse prognosis with fewer treatment options, although this may change in the future with developments in gene- and enzyme-replacement therapy (7, 8).

Glycogen storage diseases are caused by enzymatic defects leading to the inability to synthesize or breakdown glycogen. The presentation of these diseases can vary widely. Cardiac manifestations may include heart failure with reduced ejection fraction, atrial and ventricular arrhythmias, and conduction disease (5, 7–10). Extracardiac manifestations may include muscle weakness, hepatomegaly, and intellectual disability (5, 9, 11). Depending on the specific enzymatic defect and the penetrance, cardiomyopathy and arrhythmia may be the primary or only manifestation of the disease.

Conclusions

In summary, LVH is a manifestation of a wide variety of disease processes. It is important to consider uncommon etiologies. Although echocardiography is the initial imaging method of choice, CMR should be strongly considered, as it can help suggest the underlying cause. Endomyocardial biopsy and genetic testing may be necessary to confirm the diagnosis.

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