

The Mount Sinai Hospital Clinicopathological Conference:

A 45-Year-Old Man with Pompe's Disease and Dilated Cardiomyopathy

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Abstract

This is an unusual case of a 45-year-old man, born in Ecuador, with evidence of profound left ventricular dysfunction, dilated cardiomyopathy and marked myocardial hypertrophy. Preceding events were advanced atrioventricular block (necessitating pacemaker implantation) and atrial flutter.

The diagnosis of Pompe's disease was established by endomyocardial biopsy and appropriate staining, which indicated abnormal glycogen storage.

Key Words: Dilated cardiomyopathy, heart block, glycogen storage disease, Fabry's disease, Pompe's disease, Chagas' disease, congestive heart failure, ventricular dysfunction

Case Presentation

A 45-YEAR-OLD MAN was admitted to the hospital for progressive heart failure. The patient had felt well until he was in his early thirties. He had been able to compete in multiple triathlons and other sporting events. At the age of 31, he developed several episodes of exercise-induced syncope, and his electrocardiogram (ECG) revealed advanced atrioventricular heart block (Fig. 1). A dual-chamber pacemaker was implanted and the patient resumed his athletic activities.

Eleven years later, he was admitted to the hospital with acute onset of abdominal pain and nausea. An extensive investigation revealed a renal artery thrombus to be the cause of his symptoms. A transesophageal echocardiogram was performed to rule out a cardioembolic source. The test revealed no thrombi or vegetations within the heart or aorta. The patient's

left ventricular ejection fraction was noted to be moderately decreased, at approximately 40%. There was marked concentric left ventricular hypertrophy, with a diastolic thickness of the interventricular septum of 20 mm (normal 8–11 mm). The left ventricle and atrium were moderately dilated. A search for a hypercoagulable state (antiphospholipid antibodies, activated protein C resistance, protein C, protein S and antithrombin 3 deficiencies) revealed no abnormalities. The patient was started on warfarin therapy and discharged from the hospital.

He remained on anticoagulation therapy and felt well until the age of 44, when he experienced an episode of acute shortness of breath and palpitations. An electrocardiogram showed atrial flutter with a rapid ventricular response related to ventricular tracking (Fig. 2). Both the arrhythmia and his symptoms abated spontaneously within twenty-four hours.

Nine months later, the patient began to experience a marked decrease in his exercise tolerance and significant dyspnea on exertion, and he again experienced symptomatic atrial flutter with shortness of breath, requiring DC cardioversion, after which he reverted to regular sinus rhythm. A transesophageal echocardiogram (Fig. 3) was performed. Left ventricular ejection fraction had decreased to 9% and all four chambers of the heart were severely dilated. Also noted was a prominent fibrosed left ventricular apical endocardium. The patient was subsequently treated with digoxin, war-

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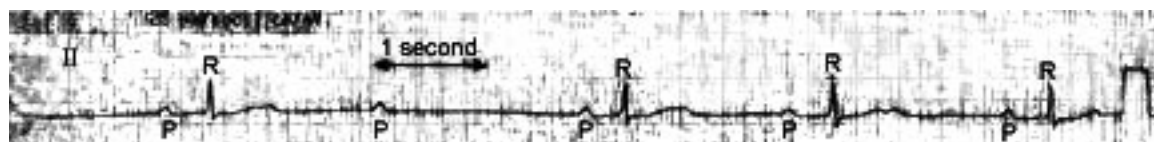


Fig. 1. Electrocardiogram of patient at age 31, showing sinus bradycardia and advanced atrioventricular block.



Fig. 2. A. Electrocardiogram of patient at age 44, showing atrial flutter with rapid ventricular response due to ventricular tracking. **B.** Atrial flutter is seen after pacemaker had been programmed at a slower rate.

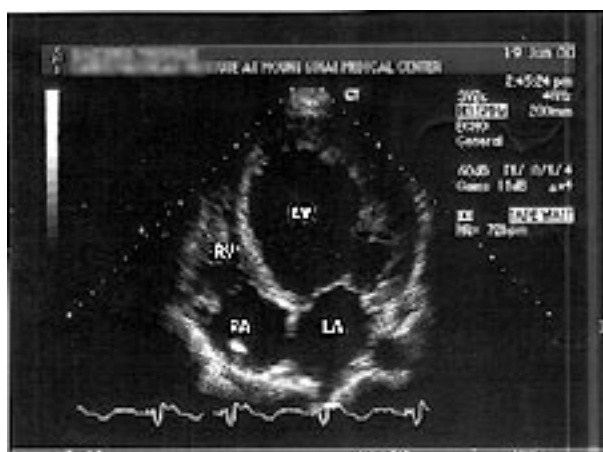


Fig. 3. Echocardiography showing severe left ventricular dilatation and fibrosed apical endocardium.

farin, an ACE inhibitor, and furosemide, and admitted to the hospital.

The patient had lived in Ecuador until he was 10 years old, at which time his family moved to the United States. He worked as a computer analyst. He drank a can of beer

every two weeks or so, and denied alcohol abuse, smoking, or use of illicit drugs. His parents were first cousins. There was no family history of cardiac disease, hypertension, diabetes, sudden death, or arrhythmias, and there were no apparent risk factors for infection with human immunodeficiency virus. He had not experienced any recent viral or flu-like illness.

On admission to the hospital at this time, physical examination demonstrated minimal crackles at the bases of the lungs, an S3 gallop, a displaced apical impulse, and trace pedal edema. The patient's blood pressure was 128/76 mm Hg, pulse 68 bpm and respiration 16/min. A chest X-ray showed an enlarged heart without pulmonary congestion. Laboratory tests on admission, including thyroid-stimulating hormone, were within normal limits. An electrocardiogram showed an atrioventricular-paced rhythm (Fig. 4). Coronary angiography revealed normal coronary arteries. Left ventricular cine-angiography revealed severely reduced global left-ventricular function. A diagnostic procedure was performed.

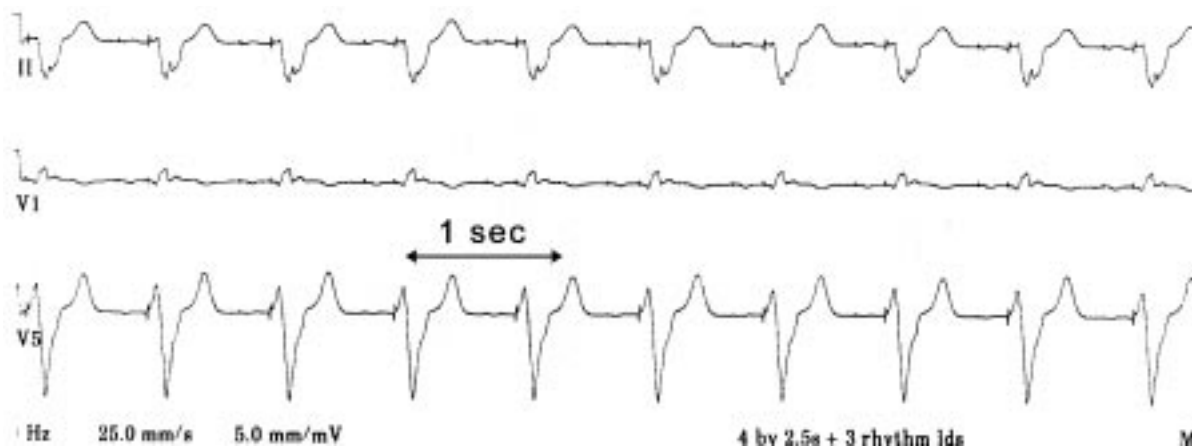


Fig. 4. Electrocardiogram showing atrioventricular-paced rhythm.

Discussion

Principal clinical features in this 45-year-old man included:

- Stokes-Adams attacks due to sinus bradycardia and advanced atrioventricular block, which became manifest at the age of 31
- A dilated cardiomyopathy, the first signs of which were detected ten years later, when he experienced a systemic thromboembolic event
- Atrial flutter
- A notable absence of primary involvement of extracardiac organ systems by a disease process

Two features set this case aside from typically presenting idiopathic dilated cardiomyopathy (DCM). One is the appearance of a complete atrioventricular block many years before the onset of cardiomyopathy. The other is the significant concentric myocardial hypertrophy noted on the first echocardiogram performed three years prior to the last admission, where an interventricular wall thickness of 20 mm with moderate left ventricular dysfunction was described. It may be tempting to attribute this finding to this patient's athletic activities. However, a vast majority of competitive athletes have a left ventricular wall thickness of 12 mm or less; only a few have a wall thickness of 12 to 16 mm. A left ventricular wall thickness of 20 mm is well within the hypertrophic cardiomyopathy range (1).

Did this patient have a hypertrophic cardiomyopathy which progressed into a dilated

one? This seems unlikely, since a late dilated phase is not part of the natural history of hypertrophic cardiomyopathy (2).

The process we are looking at is therefore one which involves the conducting system early in its course, presents with a thick but poorly contracting myocardium, and eventually progresses to a DCM. We will concentrate on the differential diagnosis of DCM while taking these other features into consideration.

DCM was defined by a World Health Organization task force in 1995 as dilatation and impaired contraction of the left ventricle or both ventricles (3). In order to identify a primary myocardial process as the cause, extrinsic forces which may cause myocardial dilatation must be ruled out. These include hypertension, coronary artery disease, valvular heart disease and congenital heart disease. For this patient, coronary angiography was normal and echocardiography showed no evidence of primary valvular disease or a cardiac shunt.

Patients with DCM most commonly present with heart failure which is typically advanced (90% are classified as New York Heart Association class III or IV). Less common modes of presentation include chest pain and asymptomatic cardiomegaly detected incidentally. Only 1.5–4% have a thromboembolic event as their first manifestation, as in this case (4).

DCM is believed to be the end result of multiple toxic, metabolic, infectious and inflammatory insults to the heart (Table). Sustained tachycardia is also an important reversible cause of DCM. This patient presented with supraventricular tachycardia, but the termination of the arrhythmia was not associated with improved left ventricular function, a feature common to all patients with tachycardia-

TABLE
Differential Diagnosis of Dilated Cardiomyopathy

Extramycocardial Disease

Hypertension, coronary artery disease, valvular heart disease, congenital heart disease, coronary artery bypass surgery

Intrinsic Myocardial Disease

Toxins/Drugs

Ethanol*, chemotherapeutic agents, cobalt*, antiretroviral agents*, phenothiazines*, carbon monoxide*, lead*, cocaine*, mercury*, radiation

Metabolic causes

Nutritional deficiency: thiamine*, selenium*, carnitine*

Endocrine: hypothyroidism*, thyrotoxicosis*, acromegaly*, Cushing's disease, pheochromocytoma*, diabetes mellitus

Electrolyte abnormalities: hypocalcemia*, hypophosphatemia*

Uncontrolled tachycardia*

Infectious causes

Viral: Coxsackie B3, CMV*, HIV

Rickettsial: Lyme disease

Bacterial: diphtheria*

Mycobacterial

Fungal

Parasitic: toxoplasmosis*, trichinosis, Chagas' disease

Collagen vascular disease

Progressive systemic sclerosis, SLE, dermatomyositis, rheumatoid arthritis, polyarteritis nodosa, Wegener's granulomatosis

Other inflammatory

Hypersensitivity myocarditis, giant cell myocarditis, peripartum myocarditis

Neuromuscular causes

Duchenne's muscular dystrophy, Becker's muscular dystrophy, facioscapulohumeral dystrophy, Erb's limb-girdle dystrophy, myotonic dystrophy, Friedreich's ataxia

Infiltrative causes

Storage diseases: hemochromatosis, Fabry's disease, glycogen storage disease

Sarcoidosis

Amyloidosis

Neoplasm

Idiopathic

Familial

* Denotes potentially reversible cause.

Abbreviations: CMV — cytomegalovirus, HIV — human immunodeficiency virus, SLE — systemic lupus erythematosus

induced cardiomyopathy (5), nor did it reverse the continuing deterioration in systolic function. Thus, the tachycardia is an unlikely cause of his cardiomyopathy. Of the many toxins and drugs implicated in DCM, alcohol is particularly common and should always be considered. Alcoholic cardiomyopathy may account for as many as one third of all DCM cases in Western countries. Mechanisms involved include a direct cardiotoxicity of alcohol, nutritional deficiency of thiamine and, in rare cases, contamination of

beverages with cardiotoxins such as cobalt. Detection may be difficult when patients deny or underestimate alcohol consumption. Evidence of alcoholic damage to the liver or nervous system is frequently absent. Concurrent alcoholic myopathy may suggest the diagnosis of alcoholic cardiomyopathy. Abstinence may reverse alcoholic cardiomyopathy, but only if instituted sufficiently early in its course (6).

Nutritional deficiencies, endocrine abnormalities and electrolyte disturbances may cause

reversible forms of cardiomyopathy. For this patient, thyroid function tests were normal and no electrolyte imbalance was noted on routine blood testing.

Of the many infectious agents that may cause DCM, enteroviral infection, particularly with Coxsackie B3, is the most commonly implicated. Myocarditis is a frequent finding in biopsy samples from patients evaluated for DCM (7), and these patients have often had a recent "viral infection." Several studies using the polymerase chain reaction to look for enteroviral genome in myocytes have failed to provide any evidence of persistent viral infection in DCM (8, 9). The role of enteroviral infection in DCM remains controversial.

HIV infection is emerging as an important contributor to DCM, both as a result of direct viral infection of myocytes and cardiotoxicity of antiretroviral medications. Cardiomyopathy is usually found in advanced HIV infection, the most important contributing factor being the inverse of the CD4 cell count (10). However, HIV cardiomyopathy is unlikely in a patient who has had progressive cardiomyopathy for more than three years with no other evidence of HIV infection.

This patient spent the first ten years of his life in Ecuador, making Chagas' disease an important consideration, since Chagas' is endemic in all Latin American countries. Five percent of immigrants from South America to the United States are seropositive for *Trypanosoma cruzi* (11). The disease is characterized by an acute illness, usually in early childhood, often mild enough to be forgotten. This is followed by an asymptomatic phase, which may last for decades. Ultimately, 10–30% of patients will develop chronic Chagas' disease, which most commonly involves the heart. Chagas' favors the cardiac apex, and the finding of an apical scar or aneurysm is suggestive of this disease. In the patient under discussion, echocardiography demonstrated extensive apical endocardial fibrosis, which may be consistent with Chagas'. The conducting system is commonly affected in Chagas', the classic combination being right bundle branch block and left anterior hemiblock. Complete atrioventricular block can also occur. However, Chagas' disease would not explain the long latency between onset of conduction block and cardiomyopathy or the myocardial hypertrophy noted in this patient.

Although a variety of collagen vascular diseases can cause DCM, the absence of any systemic involvement in this patient makes these

entities unlikely. Muscular dystrophies, another etiology of DCM, can be safely ruled out in view of this patient's exercise capacity. Of the 50% of DCM cases which continue to be defined as idiopathic (7), 20% have at least one first degree relative who has DCM, and it can now be demonstrated that more than 30% have a genetic mutation associated with DCM (12). Several of these mutations have recently been characterized. Patients are usually 20–50 years old at presentation, the familial nature of the disease often remaining unsuspected until another family member is diagnosed. In contrast to mutations causing hypertrophic cardiomyopathy, which involve components of the sarcomere, mutations causing DCM involve components of the cytoskeleton. These structures serve to anchor the sarcomere to the myocyte membrane, and their disruption uncouples sarcomeric contraction from shortening of the entire myocyte, thus impairing systolic function. Of particular relevance to this case are mutations in lamin A and C, which are components of the nuclear membrane. In the families studied by Fatkin and colleagues, 54% of affected individuals required placement of a pacemaker due to high-degree atrioventricular block (13). However, mutations in lamin A/C are inherited in an autosomal dominant manner with high penetrance, so the absence of a family history would be difficult to explain. A *de-novo* mutation is still a possibility, although it would not account for the myocardial hypertrophy seen in this patient.

Infiltrative causes of DCM merit special consideration in this case. An infiltrative process can involve the conducting system early in its course. Myocardial thickening may be caused by infiltration (so-called pseudohypertrophy), but in contrast to hypertrophic cardiomyopathy, systolic function is impaired. With continued deposition of pathologic matter and replacement of functional myocytes, DCM will ensue.

Of the storage diseases involving the heart, hemochromatosis is by far the most common. Cardiomyopathy is the presenting feature in 15% of these patients, with dilatation being more common than a restrictive pattern (13, 14). Conduction abnormalities are also common; in one study iron overload was found in 2% of 232 men requiring a pacemaker for idiopathic high-grade atrioventricular block (15).

Fabry's disease is X-linked and usually presents with angiokeratomas, corneal opacities and renal disease. However, a variant with manifestations limited to the heart may occur

when residual activity of the enzyme alpha-galactosidase A is present (16). Deposition of ceramide trihexoside may mimic hypertrophic cardiomyopathy (17). Mitral valve thickening and prolapse are also common. DCM has only rarely been described with Fabry's disease. Pre-excitation is the common conduction abnormality, and AV block is very rare (18). Taken together, these features make Fabry's an unlikely diagnosis in this case.

Glycogen storage diseases (GSD) are rare. Type II GSD (acid maltase deficiency) involves the heart and is usually fatal before the age of two years. Partial enzymatic activity is responsible for the adult onset form of this disease, but these patients have predominantly skeletal myopathy; clinically significant heart disease is uncommon (19). Few patients have been described with cardiomyopathy, conduction abnormalities and lysosomal glycogen deposits similar to type II GSD but with normal acid maltase activity (20).

Sarcoidosis is an infiltrative granulomatous disease of unknown etiology. Five percent of patients have clinically apparent cardiac involvement, which may be the only manifestation of the disease. Involvement of the conducting system is common and sudden death may be the presenting symptom (21). The cardiomyopathy of sarcoidosis may be restrictive or dilated, and pseudohypertrophy is rare.

Amyloidosis involves the heart in one third of patients with AL amyloidosis and 25% of those with familial disease. Echocardiographic features suggestive of amyloidosis include myocardial thickening (coupled with low voltage on ECG), a sparkling appearance of the myocardium, and interatrial septal thickening (22). Conduction abnormalities are common. The presence of a highly echogenic myocardium is 87% sensitive and 81% specific for this diagnosis (22), but was not described in our patient. Also, amyloidosis is a disease of the elderly and is unlikely to present at the age of thirty.

A recent publication from the Johns Hopkins cardiomyopathy service reported on 1,278 patients, the single largest series with DCM to date (7). These patients underwent a basic clinical work-up, laboratory studies (including thyroid function tests and iron studies when appropriate) and endomyocardial biopsy. After this extensive investigation, 51% were designated as having idiopathic DCM. The most frequent specific diagnosis was myocarditis (9.2%). Of the infiltrative disorders, amyloidosis was diagnosed in 3.2%, sarcoidosis in 1.3% and he-

mochromatosis in 0.7%. While clearly subject to referral bias, this report demonstrates the utility of endomyocardial biopsy in reaching a specific diagnosis in DCM.

In summary, we believe that the sequence of atrioventricular block, pseudohypertrophy and DCM is most compatible with an infiltrative cardiomyopathy. Possible etiologies include sarcoidosis, hemochromatosis, and an atypical form of GSD. The diagnostic procedure performed was probably an endomyocardial biopsy.

Pathological Findings

The hematoxylin and eosin (H&E) stain of a right endomyocardial biopsy showed severely vacuolated cytoplasm devoid of myofibrils (Fig. 5). A PAS stain revealed dark-staining, coarse, granular inclusions in the cytoplasm of the myocytes (Fig. 6), which disappeared on predigestion with diastase (Fig. 7), proving that they are glycogen. Electron microscopic examination showed lamellar and granular inclusions in the cytoplasm at nuclear poles. Similar inclusions are also seen within interstitial macrophages and capillary endothelial cells. The nature of these inclusions in macrophages is largely granular.

The microscopic and ultrastructural features are consistent with a glycogen storage disease, probably Pompe's disease. The late onset form of Pompe's disease was first recognized in 1965. This autosomal recessive disorder is characterized by deficiency of acid alpha-1, 4-glucosidase, a lysosomal enzyme that catabolizes the breakdown of glycogen, thus resulting in accumulation of glycogen in the lysosomes in the cytoplasm. In cardiac tissue, the result is hypertrophy and vacuolization of myocytes.

The only other entity to be considered in pathologic differential of this patient is Fabry's disease, a storage disease, characterized by deficiency of alpha-galactosidase. The result is an accumulation of glycosphingolipids in the hypertrophied vacuolated myocytes, with myofibrillary disorganization. The clinical findings, such as angiokeratomas, corneal opacities and nervous system disorders, together with enzyme assays in skeletal muscle biopsies, should help differentiate the two entities.

Alpha-galactosidase activity was normal in this patient. He is unwilling to undergo a skeletal muscle biopsy at this time. GSD clinically restricted to the heart and presenting in adulthood is extremely rare. In the infrequently reported cases of Pompe's disease in adults, skeletal my-

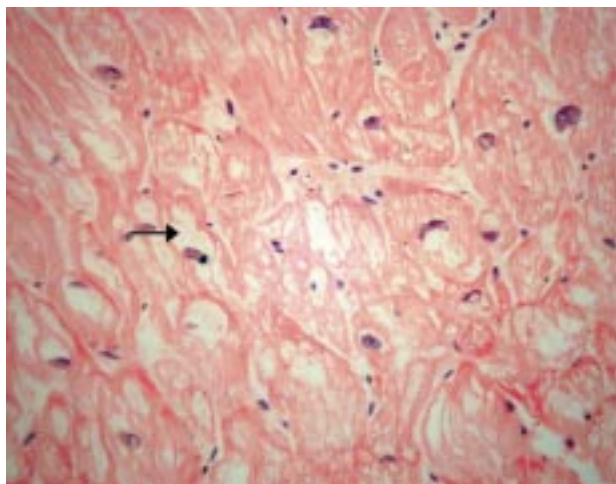


Fig. 5. Endomyocardial biopsy showing vacuolated myocytes (arrow) (H&E stain, 20x).

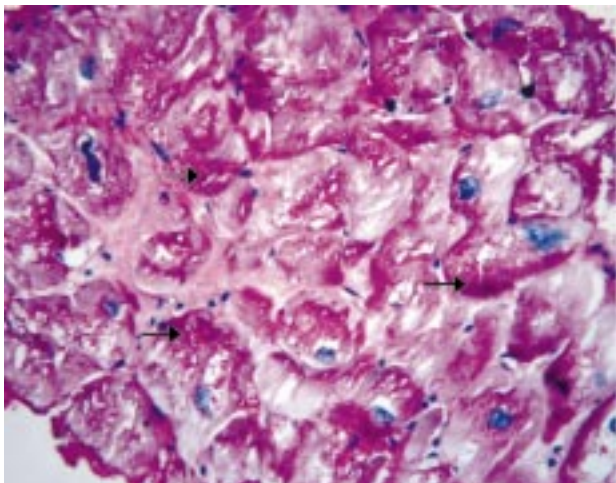


Fig. 6. Endomyocardial biopsy showing dark, coarse, granular inclusions in cytoplasm (arrows) (PAS stain, 20x).

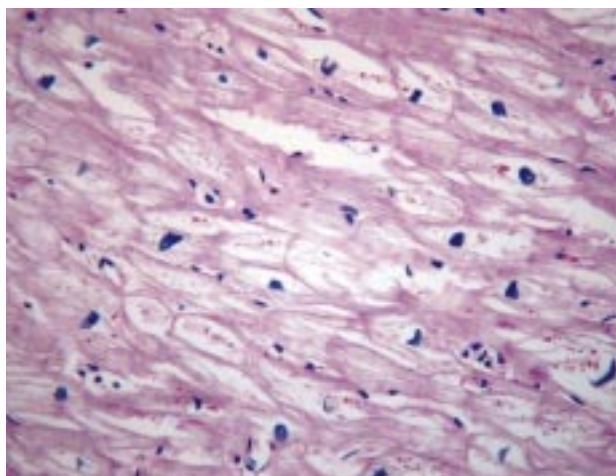


Fig. 7. After pre-digestion with diastase, cytoplasmic inclusions disappear (PAS stain, 20x).

opathy predominates. We are aware of only one similar report in the medical literature (20).

Follow-up

The patient is seen periodically. He continues to be physically active in athletic activities, including swimming and jogging. His cardiac function, however, is slowly deteriorating. His liver function tests and skeletal muscle function are normal. Thus, the metabolic defect appears to be confined to the cardiac muscle. The patient will be a candidate for cardiac transplantation in the near future if skeletal muscle and liver biopsies verify the absence of glycogen storage in these organs.

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