Surviving Malignant Hypertrophic Cardiomyopathy With all Major Complications in a Single Patient

Barry J. Maron, MD*a, Henry L. Weiner, MDb, Martin S. Maron, MDC, and William C. Roberts, MDD

The natural history and clinical course of hypertrophic cardiomyopathy (HC) is diverse, ranging from benign forms compatible with normal or extended longevity to adverse consequences requiring major interventions: surgical myectomy (or selectively alcohol septal ablation) for left ventricular (LV) outflow obstruction producing progressive heart failure; defibrillation and therapeutic hypothermia for cardiac arrest; implantable cardioverter-defibrillators (ICD) for prevention of sudden death; and heart transplant for refractory progressive heart failure in the absence of obstruction.1,2 Patients with HC may have their clinical course importantly influenced by either of these 3 major disease complications,1,2 but the occurrence of all 3 sequentially in a single patient over a 38 year period represents a notable and unusually aggressive form of HC. We present such a patient, prospectively followed and evaluated, who not only has incurred all major adverse consequences of HC but most importantly has survived due to effective treatment modalities available to patients with this disease.

Case Description

This patient was initially diagnosed with obstructive HC after a precordial murmur was detected at age 3 (Figure 1). Her father had experienced a resuscitated cardiac arrest from HC and one brother (age 40) has HC with an uneventful course. Surgical myectomy was performed at age 11 years to relieve outflow tract obstruction (gradient, 100 mm Hg) and heart failure symptoms, associated with massive ventricular septal hypertrophy (wall thickness, 35 mm). Symptomatic improvement ensued briefly, but at age 19, the patient was successfully resuscitated from an out-of-hospital cardiac arrest, and a secondary prevention implantable cardioverter-defibrillator (ICD) was placed and subsequently replaced at ages 24, 27 (with biventricular pacing), and 33 years. A lead extraction at age 26 was complicated by a tear in the superior vena cava which was repaired surgically.

Appropriate ICD interventions for sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) occurred at ages 25 (during tennis), 26, and 32 (sitting at beach) and 34 years. In addition, 25 episodes of monomorphic VT terminated by anti-tachycardia pacing were tabulated, as well as hundreds of spontaneously aborted runs of nonsustained VT evident on ICD interrogation.

At age 26, the patient developed progressive heart failure in NYHA class III associated with adverse LV remodeling: maximum LV wall thickness = 11 mm; LV end-diastolic cavity dimension = 56 mm, and ejection fraction = 20%. Advanced heart failure symptoms persisted for the next 12 years refractory to a variety of pharmacologic agents, including beta-blockers, verapamil, angiotensin-converting enzyme inhibitors, sotalol, mexiletine, digoxin and spironolactone. Despite her significant functional limitation, the patient held sedentary jobs and performed treadmill exercise and yoga.

During this time period, LV remodeling progressed with cavity dimension increasing to 68 mm, and ejection fraction decreasing to only 15%. Peak oxygen consumption ranged from 19 to 21 ml/kg/min; cardiac index was 2.1 L/min/m²; pulmonary capillary wedge pressure was 18 mm Hg; and brain natriuretic peptide was 3500 pg/ml. At age 38, the patient consented to heart transplant listing, and the operation was performed at Hospital of University of Pennsylvania. Postoperative recovery has been uneventful. Genetic testing documented a pathogenic mutation in the MYBPC3 gene (c. 2441_2443 delAGA).

The explanted heart weighed 440 g. Ventricular septum was 14 mm in thickness, and the LV free wall was 16 mm (Figure 2). The LV cavity was markedly dilated, but the right ventricle was normal-sized. Extensive areas of grossly visible scarring were present involving the ventricular septum and LV free wall. The mural endocardium of ventricular septum in apposition to the anterior mitral leaflet was severely thickened by fibrous tissue, extending distally and resulting (at least in part) from the myectomy performed 27 years earlier. The LV wall at the apex was thinned, aneurysmal, and fibrotic. The epicardial coronary arteries were free of atherosclerotic plaque, and the right and left main coronary arteries arose from the aorta in normal position.

Extensive scarring of the LV wall was confirmed histologically. In addition, many myocytes in the subendocardial regions were vacuolated and enlarged. Disorganized patterns of myocyte arrangement were present in ventricular septum, associated with numerous intramural coronary arteries, increased in size with thickened walls and luminal narrowing (Figure 3), both histopathologic hallmarks of HC.

Comments

The patient presented here illustrates the most extreme example of HC and its deleterious consequences through the first 38 years of life, but nevertheless represents an important principle for this complex genetic disease. Once regarded as a disease with uniformly grim prognosis largely without effective management strategies, this patient underscores the new paradigm in which HC has become
a treatable cardiac disease,\textsuperscript{3} with management options now available to target each adverse complication and prolong life, that is, surgical septal myectomy (or alcohol ablation) for limiting symptoms caused by LV outflow obstruction;\textsuperscript{1,4,5} external defibrillation for cardiac arrest, often with therapeutic hypothermia;\textsuperscript{6} ICD therapy to terminate potentially lethal ventricular tachyarrhythmias (VT/VF) and prevent sudden death; and ultimately heart transplant only in the event that progressive end-stage heart failure intervenes with extreme LV remodeling (and in the absence of outflow obstruction).\textsuperscript{7,8}

Implementation of these interventions permits most HC patients to achieve extended longevity with good quality of life, and for the present patient the prolongation of life.\textsuperscript{1} Notably, this patient endured NYHA class III heart failure symptoms and limitations for at least 12 years before consenting to heart transplantation. Finally, despite the fact that atrial fibrillation is common in HC (in about 20% of patients), and is also linked to end-stage heart failure, our patient showed no evidence of left atrial dilatation (or atrial fibrillation).\textsuperscript{1}

Typical of the HC end-stage there was substantial LV remodeling with striking regression from massive hypertrophy (in childhood) to virtually normal wall thickness, associated with LV chamber dilatation. The basis for the LV wall thinning was the development of extensive, diffuse and transmural myocardial scarring, presumably resulting from microvascular ischemia, and also involving the most distal LV segment where early aneurysm formation is evident.\textsuperscript{10}

Two additional issues related to the natural history of HC are underscored by the findings in this informative patient.
First, the characteristic heterogeneity of disease expression and clinical course is evident in the diverse disease pathways taken by our patient’s malignant course in comparison to that of her asymptomatic 40-year-old brother, with HC and the same pathogenic mutation and genetic substrate. Second, the mutation in the sarcomere MYBPC3 gene responsible for HC in our patient with highly aggressive HC has been previously regarded as benign. Therefore, this patient’s clinical profile is consistent with the principle that specific mutations cannot predict future outcome in individual HC patients.

Disclosures

The authors have no conflicts of interest to disclose.