

Apical Variant of Hypertrophic Cardiomyopathy and Systemic Scleroderma- A Hint for Autoimmune Mechanism?

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Abstract

We present a 75-year-old female, Ms. W, with systemic scleroderma and Hypertrophic Cardiomyopathy (HCM) who was evaluated for one-year history of swelling in her ankles and feet. Cardiac auscultation revealed a left lower sternal border ejection systolic murmur that increased with Valsalva maneuver. ECG was consistent with Left Ventricular (LV) hypertrophy whereas transthoracic echocardiogram and cardiac MRI revealed increased LV wall thickness with asymmetric involvement of the apex and circumferential pericardial effusion. Although genetic mutations of cardiomyocyte sarcomeric proteins have been implicated in HCM, screening in several HCM cohorts have failed to identify genetic mutations in a substantial proportion of cases. A predisposition for HCM with certain human leukocyte antigen subtypes has been reported. In addition, an increased prevalence of HCM has been reported in chronic hepatitis C virus infection, a disease with multiple extra-hepatic autoimmune manifestations. Thus the occurrence of HCM in patients with autoimmune diseases such as systemic scleroderma may indicate potential autoimmune mechanism. Studies testing the hypothesis that autoimmune mechanisms are involved in producing the HCM phenotype, at least in patients with no identifiable genetic mutation affecting sarcomeric proteins, are needed.

Introduction

Autoimmune diseases including scleroderma can lead to cardiovascular involvement due to chronic inflammation and fibrosis affecting the pericardium, myocardium and conduction tissue. Myocardial fibrosis is the most common form of cardiac involvement and asymptomatic pericardial effusions are frequently seen [1,2]. Other forms of involvement may include, systolic and diastolic left ventricular heart failure, right heart failure usually secondary to pulmonary arterial hypertension and dysrhythmias as a result of fibrosis or ischemia of the conduction system. Cardiac involvement of any form and pulmonary arterial hypertension are poor prognostic markers [1]. Hypertrophic Cardiomyopathy (HCM), characterized by asymmetric Left Ventricular (LV) hypertrophy out of proportion of systemic after load, is not commonly associated with scleroderma. While hundreds of mutations in genes coding sarcomeric, calcium handling and mitochondrial proteins have been described in HCM, apart from isolated case reports, there is no direct evidence that implicates chronic viral infection or immunologic mechanisms in the pathogenesis of HCM. In this case report we describe a 75-year-old female with systemic scleroderma and apical variant of HCM.

Case Report

We report a 75-year-old female, Ms. W, who presented with systemic scleroderma associated with Raynaud's disease, esophageal strictures, positive centromere antibodies and depressed complement 4 levels. Ms. W. was evaluated for one-year history of swelling in her ankles and feet. She did not have change in body weight or abdominal girth. She denied any history of palpitations, syncope, chest pain, paroxysmal nocturnal dyspnea, orthopnea or exertional shortness of breath. While she did not exercise regularly she was able to go on her daily walks for 2 miles on a level surface without any symptoms. For the last 10 years her fingers turned pale white, blue and then red in the cold weather of winter but she did not have any ulcers. She had dysphagia associated with an esophageal stricture in the upper third of her esophagus that required dilatation. She was taking amlodipine 10 mg tablets daily for hypertension. She did not have a family history

of autoimmune disease, HCM or sudden cardiac arrest. Her blood pressure was 134/76 mmHg and pulse rate was 66/minute. Physical examination revealed elevated jugular venous pressure, a grade 3/6 ejection systolic murmur best heard at the left lower sternal border that increased with standing and Valsalva maneuver (maneuvers that decrease LV preload) and decreased with squatting. Lung exam revealed good air entry throughout without evidence of pulmonary edema. She had moderate pitting edema up to her knees. There was no evidence of chronic venous stasis.

Electrocardiogram (ECG) showed sinus bradycardia (ventricular rate = 54/min), left atrial enlargement and left ventricular hypertrophy with T wave inversion in leads V1-V3 (Figure 1). 24-hour ECG-holter monitoring did not find any evidence of cardiac arrhythmia. She had an ECG exercise stress study in which she exercised for 5 minutes on the Naughton exercise protocol. There was no evidence of ischemia. She had normal heart rate and blood pressure response to exercise. Chest X-ray showed cardiomegaly. A transthoracic echocardiogram revealed increased LV wall thickness with asymmetric involvement of the apex, circumferential pericardial effusion and a LV ejection fraction of 67% (Figure 2). Estimated right ventricular systolic pressure was 46 mm Hg.

Cardiac magnetic resonance imaging showed hypertrophy of the LV most prominent at the apex with a spade-like configuration of the LV cavity consistent with the apical variant of HCM. Maximal thickness of the myocardium measured in diastole was 18 mm at the

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anterior apex. There was a moderate-sized circumferential pericardial effusion, not typically seen in HCM but nonetheless a known cardiac

manifestation of autoimmune diseases such as scleroderma and systemic lupus erythematosus (Figure 3). Subtle delayed myocardial

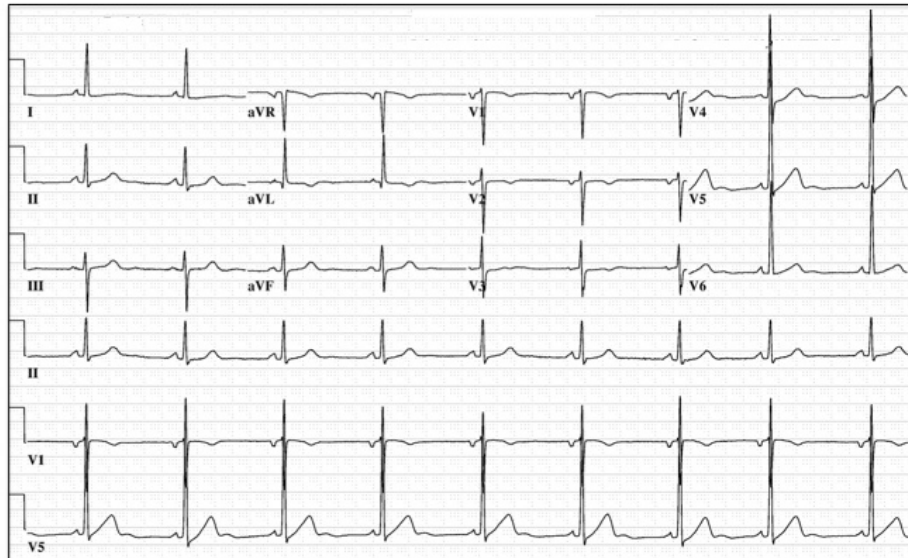


Figure 1: Electrocardiogram. Sinus bradycardia (ventricular rate = 54/min), P-wave with negative deflection >1 mV in V1 consistent with left atrial enlargement, tall R-wave in the lateral pericardial leads fulfilling voltage criteria for left ventricular hypertrophy. T-wave inversion in leads V1-V3 is also seen.

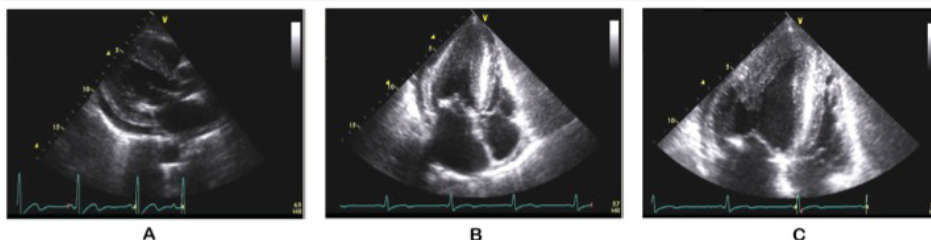


Figure 2: Transthoracic echocardiogram. A. Parasternal long axis view showing thickened septum and posterior wall of the left ventricle. B & C. Four chamber apical view showing thickened left ventricular walls with asymmetric involvement at the apex. Pericardial effusion and left atrial enlargement is also seen.

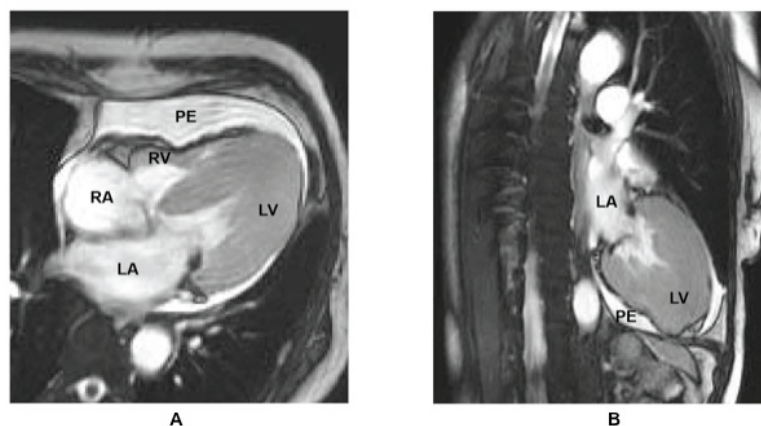


Figure 3: Cardiac MRI. A. Four chamber axial and B. two-chamber views using steady state free precession sequence are shown. There is asymmetric hypertrophy of the LV that is most prominent at the apex with a spade-like configuration of the LV cavity consistent with the apical variant of Hypertrophic Cardiomyopathy (HCM). There is also a moderate circumferential pericardial effusion. The Left Atrium (LA), Left Ventricle (LV), Pericardial Effusion (PE), Right Atrium (RA) and Right Ventricle (RV) are labeled.

enhancement with gadolinium contrast was present predominantly involving the cardiac apex, a common finding in HCM and cardiac involvement with systemic scleroderma. Following genetic counseling, Ms. W declined to undergo genetic testing to screen for known mutations associated with HCM.

Discussion

HCM is the most common cardiac genetic disorder. Although mutations in genes coding sarcomeric, calcium handling and mitochondrial proteins have been implicated in HCM, screening in several HCM cohorts have failed to identify genetic mutations in 40-75% of cases [3-7]. Lack of an identifiable genetic mutation is associated with the apical variant of HCM and lack of family history of HCM [3,5,7]. Thus, the pathogenesis of HCM in a substantial proportion of patients remains unexplained.

To date, there hasn't been direct evidence that implicates immunologic mechanisms in the pathogenesis of HCM. Similar to the case we are presenting, previous reports have described HCM in patients with systemic scleroderma, systemic lupus erythematosus, polyarteritis nodosa and mixed connective tissue disease [8-12]. Additional evidence for an autoimmune association comes from a group of 11 HCM patients with an 82% increase in serum reactivity against infant heart muscle compared to sera from patients with congestive cardiomyopathy, coronary artery disease, congenital heart disease, chronic rheumatic heart disease and normal subjects [13]. It is still unclear if the increased prevalence of "anti-heart" antibody in HCM is involved in the pathogenesis of the disease or a result from injuries to heart muscle. Organ specific anti-mitochondria (anti-M7) antibodies have been reportedly found in 33% of patients with HCM [14]. 12-13% of patients with HCM have antibodies against β 1-adrenergic receptors in their serum whereas 22% of patients have antibodies against M2-Muscarinic receptors [15].

A predisposition for HCM with certain human leukocyte antigen subtypes has been reported. The human leukocyte antigen (HLA) system consists of a group of genes on chromosome 6 that code for proteins involved in immune defenses including cell surface markers and antigen-presenting molecules. Unrecognized foreign- or self-antigens provoke an immune response following recognition by T-cell receptors on HLA molecules. In a series of 12 Italian patients with HCM, 50% of patients had HLA-DR3 antigens [16]. Among Japanese HCM patients an association was noted with the major histocompatibility antigens HLA-BW52, HLA-CW3 and HLA-CW4 [17]. In the Japanese cohort it was also noted that HLA-DRW4 was present in 73.3% of patients with hypertrophic obstructive cardiomyopathy and in 33% patients with non-obstructive cardiomyopathy. HLA-DPB1 gene has been associated with a predisposition towards the development of HCM in hepatitis C virus infection [18]. HLA-B51 and HLADR2 levels were also found to be significantly increased in HCM patients from South India [19]. In addition, an increased prevalence of HCM has been reported in chronic hepatitis C virus infection, a disease with multiple extra-hepatic autoimmune manifestations [20].

Although genetic mutations of cardiac sarcomeric proteins have been implicated in the pathophysiology of HCM, the exact nature of the defect in protein products of mutated genes is not understood. Autoimmune mechanisms may target cardiac sarcomeric proteins resulting in an HCM phenotype without identifiable mutations in genes for sarcomeric proteins. Our case report describes an interesting observation; however, this does not substitute for empiric data that can clarify whether the presentation of HCM with systemic scleroderma or

other autoimmune diseases is a coincidental or causative association. Studies testing the hypothesis that autoimmune mechanisms are involved in producing the HCM phenotype, at least in patients with no identifiable genetic mutation affecting sarcomeric proteins, are needed.

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