CASE REPORT

Hypertrophic cardiomyopathy in a lupus patient: a case of hydroxychloroquine cardiotoxicity

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Abstract

Hydroxychloroquine (HCQ) is a well-established and effective immunomodulatory therapy for systemic lupus erythematosus and other autoimmune diseases. While retinal toxicity is a well-recognized complication, cardiotoxicity is lesser known. This case consists of a 63-year-old Filipina on chronic HCQ treatment that led to severe biventricular hypertrophy, increased filling pressure, systemic and pulmonary hypertension, and elevated brain natriuretic peptide. Genetic testing ruled out lysosomal storage disorders but revealed five rare variants of uncertain significance, including one that was temporarily re-classified as likely pathogenic. Endomyocardial biopsy demonstrated myeloid bodies admixed with curvilinear bodies, most consistent with a diagnosis of HCQ toxicity. This case illustrates the importance of clinical integration of multiple causes of cardiomyopathy, recognition of HCQ cardiotoxicity, and increased uncertainty in genetic test findings among racial minorities.

Introduction

Hydroxychloroquine (HCQ), used widely for the chronic treatment of autoimmune disorders with minimal toxicity, is better known for its potential irreversible retinal toxicity and thus limited to a daily dose of 5 mg/kg and recommended for annual visual field and optical coherence tomography screening for retinal toxicity after the first 5 years of treatment by the 2016 American Academy of Ophthalmology guidelines.[1] HCQ cardiotoxicity is less recognized, and its routine screening is currently not recommended by rheumatology or cardiology society guidelines. If unrecognized, HCQ cardiotoxicity may lead to progressive and potentially irreversible heart failure, heart transplant, and death.[2]

Case report

The patient is a 63-year-old woman with a past medical history of systemic lupus erythematosus (SLE), Raynaud's

phenomenon, hypertension, and left ventricular hypertrophy who presented for genetic evaluation due to concerns of hypertrophic cardiomyopathy (HCM). Since the diagnosis of SLE at the age of 40, she has been hospitalized twice for Raynaud's phenomenon; otherwise, SLE has been stable on HCQ of 300 mg daily for more than 20 years. Hypertension has been well controlled on metoprolol and losartan with systolic pressures of 120–130 mmHg. She endorsed occasional palpitations but denied chest pain, shortness of breath, or fluid retention. She exercised by walking 2 miles 4 days a week and was able to climb up three flights of stairs limited by exertional dyspnoea. She worked 3 days per week as a nurse. Her family history was significant for her father passing away from congestive heart failure in his 90s; one of her three children had a heart murmur and a normal electrocardiogram (ECG) at age 30. No other family member has been diagnosed with HCM or sudden cardiac death. Her physical exam was notable for mild erythema of the hands and scalp line. Jugular venous pressure was elevated at 10 cmH$_2$O. Heart auscultation showed regular rate and rhythm, normal S1, S2, with no

murmurs, rubs, or gallops. Abdominal and extremity exams did not reveal any signs of distension or oedema.

Laboratory studies showed a normal comprehensive metabolic panel and a complete blood count, except for mild thrombocytopenia of $117 \times 10^3/\mu L$. BNP levels were between 800 and 1000 pg/mL. Her ECG showed sinus bradycardia, voltage criteria for left ventricular hypertrophy, and prominent anterolateral horizontal ST depression and T wave inversion (*Figure 1A*). Echocardiogram showed severe biventricular wall hypertrophy with a septal wall thickness of 2 cm and a posterior wall thickness of 1.5 cm, hyperdynamic left ventricular (LV) systolic function, and right ventricular systolic pressure of 75 mmHg. Cardiac magnetic resonance imaging showed normal LV size and systolic function (LV ejection fraction of 65%), asymmetric moderate septal and concentric apical hypertrophy with few scattered patchy enhancements in the hypertrophied septum, mildly dilated right and left atria, mild mitral and tricuspid regurgitation, and dilated pulmonary artery measuring 3.2 cm (*Figure 2*). Right heart catheterization demonstrated elevated filling pressures, systemic and pulmonary hypertension, and low cardiac output (*Table 1*). Based on the current morphology-based HCM definition of increased LV wall thickness that is not solely explained by abnormal loading conditions, she was diagnosed with HCM[3] and started on a loop diuretic.

A comprehensive cardiomyopathy genetic panel was performed that revealed five variants of uncertain significance (VUS) in *DMD*, *FLNC*, *HCN4*, *MYH7*, and *SLC22A5*, respectively, and no genetic variants in *GLA*, *LAMP2*, and *PRKAG2*. In the subsequent months, genetic test reports were re-issued upgrading the heterozygous *MYH7* c.5326A>G (p.Ser1776Gly) variant to likely pathogenic and then downgrading it to VUS again.

Due to ongoing concerns of HCQ cardiotoxicity, a repeat right heart catheterization with endomyocardial biopsy was performed, which showed improved right and left heart filling pressures, systemic and pulmonary hypertension, and continued low cardiac output (*Table 1*). Endomyocardial biopsy with haematoxylin and eosin stain showed diffusely vacuolated myocytes [*Figure 3(A)*]. Ultrastructural evaluation demonstrates numerous intra-cytoplasmic laminated inclusions characteristic of myeloid bodies (zebra bodies) admixed with curvilinear bodies in all areas of the tissue (*Figure 3B, C*). A diagnosis of HCQ cardiotoxicity was made, and HCQ was promptly discontinued in consultation with the patient's rheumatologist. In 6 months after HCQ was discontinued, BNP continued to rise from 1800 to 3500 pg/mL. She experienced an episode of heart failure exacerbation due to atrial fibrillation with a rapid ventricular response (*Figure 1B*), which stabilized after restoring sinus rhythm via direct current cardioversion. Although the patient remains clinically stable, cardiac transplantation may be on the horizon.

Figure 1 Electrocardiogram demonstrated findings consistent with left ventricular hypertrophy. Twelve-lead electrocardiograms demonstrated voltage criteria for left ventricular hypertrophy and prominent anterolateral horizontal ST depression and T wave inversion (A). One year later, the patient developed atrial fibrillation (B).
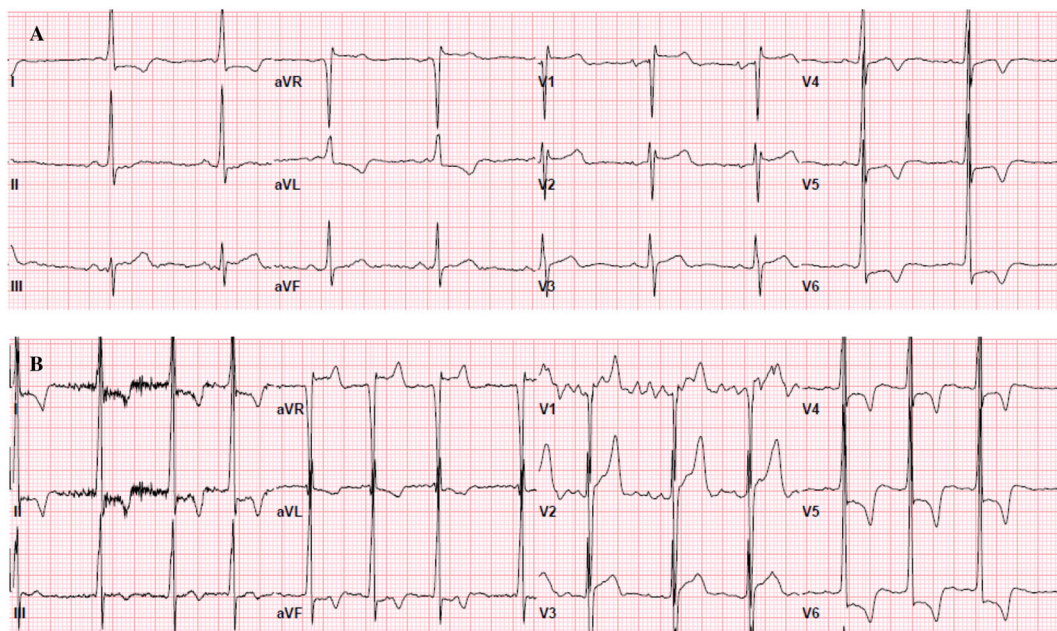
Figure 2 Cardiac magnetic resonance imaging demonstrated hypertrophic cardiomyopathy phenotype. Cardiac magnetic resonance imaging demonstrated normal left ventricular size and left ventricular hypertrophy and mildly dilated right and left atria (A) and dilated pulmonary artery measuring (B).
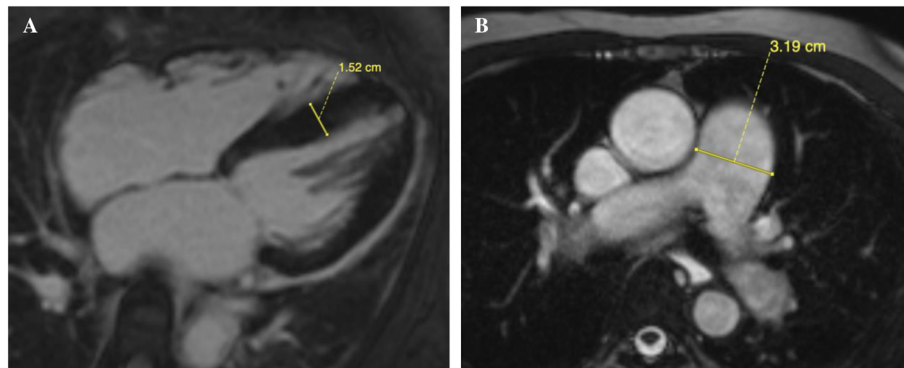
Table 1 Right heart catheterization before and after diuretic use

	Initial	Post-diuretic
HR	57 b.p.m.	55 b.p.m.
BP	197/88 (124) mmHg	125/79 mmHg
RA	13 mmHg	4 mmHg
RV	63/13 mmHg	45/4/9 mmHg
PA	63/25 mmHg	45/23 mmHg
PCW	28 mmHg (v wave to 36 mmHg)	19 mmHg
CO by thermodiluation	3.2 L/min	3.0 L/min
CO by Fick	3.3 L/min	NA

BP, blood pressure; CO, cardiac output; HR, heart rate; PA, pulmonary artery; PCW, pulmonary capillary wedge; RA, right atrium; RV, right ventricle.

Discussion

Delayed recognition of HCQ cardiotoxicity carries significant morbidity and mortality, warranting the need to raise the index of suspicion among patients who may have minimal symptoms but have high-risk features, including older age, female sex, and long duration of therapy.[4] Specifically, lifetime cumulative dosage has been shown to be important for retinal toxicity[5] and cardiotoxicity.[6] Our patient, who weighs approximately 50 kg, took 300 mg of HCQ per day for over 20 years, which exceeded the currently recommended maximal dosage of 5 mg/kg/day.[1] Moreover, her cumulative dose well exceeded the mean cumulative dose of 1843 g among patients diagnosed with HCQ cardiotoxicity.[6] HCQ cardiotoxicity commonly presents as concentric HCM with restrictive features or as conduction disorders including bundle branch block and third-degree AV block[7]; therefore, ECG and echocardiogram should be performed to monitor for HCQ cardiotoxicity especially among patients who exceed the maximal daily recommended dose or for periods greater than 5 years.[8]

Genetic predisposition for HCQ-induced cardiomyopathy was first proposed in a set of twin sisters who both suffered from SLE.[9] Chatre *et al.* described a case of a 61-year-old woman whose diagnosis of α-galactosidase A deficiency was unmasked by chronic HCQ treatment.[10] Because Fabry disease and other lysosomal storage disorders, such as Danon disease, lead to similar pathological processes and features of myelin figures and glycogen accumulation as HCQ toxicity, individuals with underlying lysosomal genetic defects may be at a higher risk for HCQ toxicity. Following HCQ treatment withdrawal, clinical response varies widely from full recovery to progressive symptoms, irreversible damage, heart transplant, or death.[7,11] A potentially reversible cause of heart failure, HCQ cardiotoxicity should be ruled out prior to consideration for heart transplant. In the case of our patient, in spite of improved filling pressures and HCQ withdrawal, BNP continued to rise from 1800 to 3500 pg/mL, suggestive of progressive and irreversible disease. In a case of a 38-year-old woman diagnosed with SLE, antiphospholipid syndrome, the *GLA* p.Pro343Leu variant, low normal range GLA activity of 39 nmol/hr/mg protein (normal range 33–134), and HCQ toxicity by endomyocardial biopsy, the patient continued to have vascular complication with a myocardial infarction and stroke, despite HCQ withdrawal and enzyme replacement therapy for Fabry disease.[12] Because HCQ, SLE, and Fabry disease lead to overlapping cardiac and renal manifestations, genetic testing to evaluate concurrent lysosomal storage disorders may provide important prognostic value, even among those with biopsy proven HCQ cardiotoxicity.

Due to the diverse aetiology of the HCM phenotype, a systemic search for its underlying cause, including genetic analysis, is recommended.[13] Current commercially available gene panel for HCM include sarcomeric genes along with lysosomal storage disorder genes, *GLA* (Fabry disease), *PRKAG2*, and *LAMP2* (Danon disease). Our patient was tested negative for notable genetic variants among lysosomal storage disease genes; rather, she was found to have multiple VUS, including p.Ser1776Gly in *MYH7*. The interpretation of genetic variants

Figure 3 Cardiac endomyocardial biopsy demonstrated histological findings consistent with hydroxychloroquine cardiotoxicity. (A) Haematoxylin and eosin stain demonstrated diffusely vacuolated myocytes, scale bar = 50 μm. Ultrastructural evaluation by electron microscopy demonstrated (B) intracellular accumulation of myeloid bodies (star) and curvilinear bodies (arrow) and vacuoles containing electron-dense autophagolysosomes (C); evaluation, original magnification ×16 000.
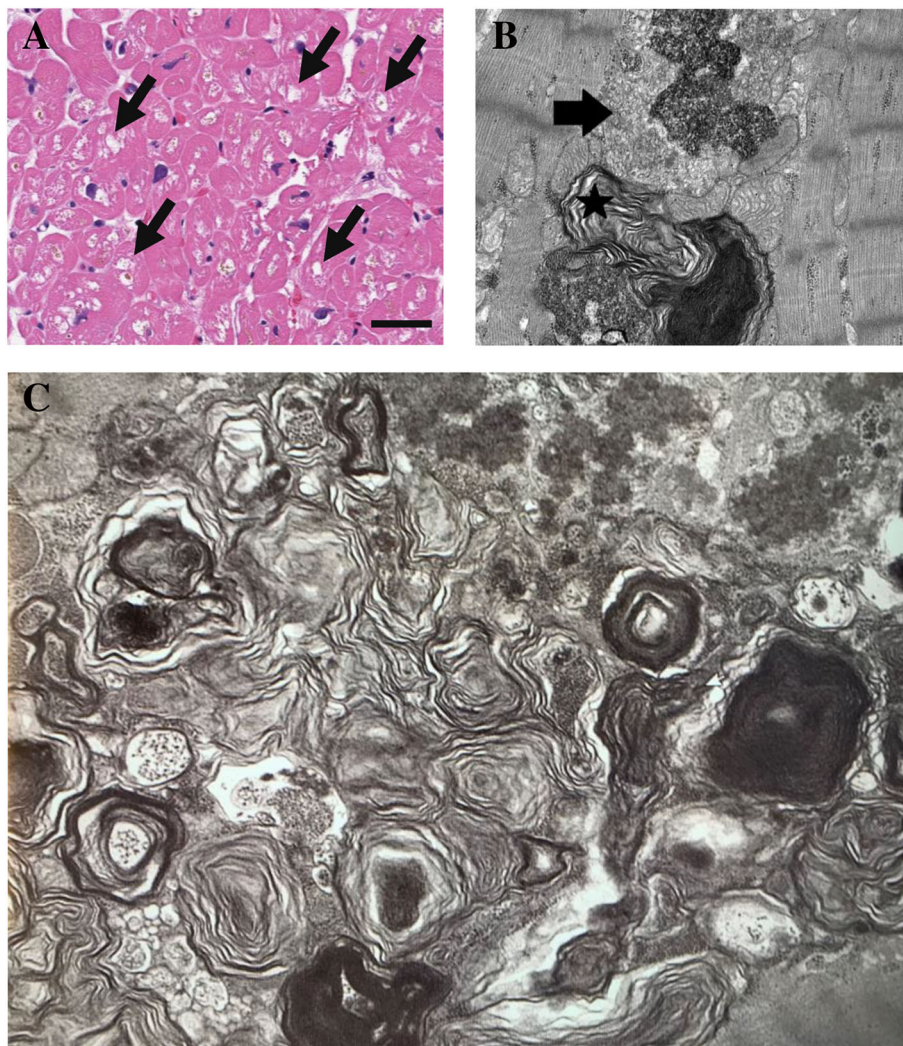
from racial groups, where there is insufficient population data, is known to be less accurate.[14] The period in which the *MYH7* variant was temporarily classified as likely pathogenic, thus suggestive of genetic HCM, could have led to unnecessary anxiety for the patient and her family members. It is currently unknown whether there is molecular interaction between sarcomeric mutations and HCQ to cause an elevated risk of HCQ toxicity.

This case illustrates that patients who report minimal symptoms may demonstrate overt signs on BNP, ECG, and echocardiogram suggestive of advanced HCQ cardiotoxicity. Although not currently recommended in rheumatology or cardiology society guidelines,[15] early recognition, screening, and diagnosis of cardiotoxicity and discontinuation of HCQ treatment may reduce unnecessary cardiac complications.

This case further illustrates the intersection of autoimmune disease, HCQ cardiotoxicity, lysosomal storage disorders, and sarcomeric molecular dynamics. Genetic testing has a role in patient diagnosed with the HCM phenotype and may provide insights among those diagnosed with HCQ toxicity with regard to underlying genetic predisposition and prognosis. Finally, this case illustrates the current clinical challenge in the interpretation of genetic variants, the need for genetic counselling, and the complexity in attributing the cause of pathology to processes that may have overlapping clinical features. We concluded that HCQ is the main driver of our patient's clinical presentation based on endomyocardial biopsy results that demonstrated clear curvilinear bodies. We ruled out lysosomal storage disorders, but it remains unclear whether a genetic predisposition, whether due to the *MYH7*

VUS or other currently unmeasured genetic risk, places that patient on a progressive course in spite of HCQ withdrawal.

Conflict of interest

None declared.

Funding

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