Double Jeopardy Cardiomyopathy Requiring Heart Transplant: Hydroxychloroquine and Rheumatoid Arthritis

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INTRODUCTION

The estimated prevalence of rheumatoid arthritis (RA) in the global population is 0.5%-1%, and there is an estimated 50% increase in the incidence of cardiovascular events and death in patients with RA.[1] Toxicities due to the long-term use of medications needed to avoid flare-ups further increase the morbidity and mortality risk in these patients. Many patients with these conditions receive long-term therapy, including chloroquine (CQ)/hydroxychloroquine (HCQ). Extensive experience using CQ/HCQ with malaria and autoimmune diseases supports a relatively good safety record, yet toxicity with long-term use, particularly cardiotoxicity and arrhythmogenicity due to blockade of repolarizing potassium (HERG/Kv11.1) channel in the heart, has been reported.[2,3] Herein, to highlight the salient feature of cardiotoxicity of this agent, we report a case of a patient with RA treated with HCQ who developed subsequent cardiomyopathy and progressive heart failure requiring heart transplantation. Maintaining high suspicion for iatrogenic cardiomyopathy in patients on CQ or HCQ with susceptibility to myocardial injury is crucial for early diagnosis and treatment.

CASE PRESENTATION

A 59-year-old Caucasian woman presented with class III dyspnea of 3 months' duration. She had a history of RA diagnosed at 36 years of age, breast cancer treated with surgery, and mild renal impairment. Her medications included HCQ, methotrexate, adalimumab, abatacept, and lansoprazole. Her HCQ dose was 600 mg daily for the past 23 years.

On presentation, her physical examination revealed an elevated jugular venous pressure (16 mm Hg), soft S1, grade 1/6 aortic regurgitation murmur and apical systolic murmur, and bibasilar rales. An electrocardiogram revealed sinus rhythm, prolonged PR interval, left-axis deviation, intraventricular conduction delay, and left ventricular (LV) hypertrophy. An echocardiogram revealed concentrically thickened ventricular walls (1.7 cm), reduced LV systolic function with apical akinesia (LV ejection fraction 30%), right ventricular hypertrophy and systolic dysfunction, moderate biatrial enlargement, an LV restrictive filling pattern, reduced global longitudinal strain of −4% (Figure 1, Video 1), and mild mitral and aortic regurgitation. N-terminal (NT)-pro hormone BNP (NT pro-BNP; 12,698 pg/mL) and troponin (2.07 ng/mL) were elevated. The constellation of these findings mimicked end-stage hypertrophic or infiltrative cardiomyopathy. Family history and a genetic testing panel for cardiomyopathies, including Fabry's and amyloidosis, were negative. Serologic and molecular tests for viruses were negative. There was no obstructive coronary artery disease on angiography, whereas cardiac magnetic resonance imaging showed delayed gadolinium enhancement in a transmural pattern at the apex and midmyocardium at the septum and anterior wall segments (Figure 2), with overall 30% myocardial enhancement. An endomyocardial biopsy was remarkable for prominent myocyte vacuolization (Figure 3A). There was no significant reactivity for periodic acid Schiff stain or evidence of lymphocytic myocarditis, amyloidosis, sarcoidosis, or other disorders. Thin-sections transmission electron microscopic evaluation was performed, revealing lamellar bodies (Figure 3B) and aggregates of curvilinear bodies (Figure 3C), specific markers for HCQ toxicity.

Adalimumab and HCQ therapy were discontinued, and carvedilol, losartan, spironolactone, and warfarin anticoagulation were started. A few months later, methotrexate was discontinued because she developed liver fibrosis. She was started on prednisone 5 mg for RA. Given no improvement in LV ejection fraction after 3 months of treatment, an implantable cardioverter-defibrillator was placed for primary prevention of sudden death. One year after the diagnosis and discontinuation of HCQ, a brief period of improvement in clinical symptoms—LV ejection fraction 44%, global longitudinal strain −10%, and regression of LV wall thickness (1.2 cm, Supplemental Figure 1)—was observed. Her NT pro-BNP decreased to 2,857 pg/mL. She deteriorated clinically 6 months later, with a decrease in LV ejection fraction (33%), global longitudinal strain −5%, moderate aortic and mitral regurgitation, and additional wall motion abnormalities. Her NT pro-BNP increased to 4,859 pg/mL. Repeat cardiac magnetic resonance imaging showed new transmural delayed enhancement pattern in the basal to mid inferolateral wall. She developed an RA flare-up, which was evidenced by increased wrist and hip pain that limited her walking ability, mild elevation of C-reactive protein and erythrocyte sedimentation rates, and an elevated Vectra DA blood test score of 55, all of which suggested high disease activity[4] necessitating higher doses of steroids, which were tapered over a month. The possibility of worsening inflammation from RA contributing to the valvular and cardiomyopathic exacerbation was entertained, and she was started on tofacitinib. However, despite medical therapy, her LV ejection fraction further decreased to 25% and her

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VIDEO HIGHLIGHTS

Video 1: LV and right ventricular hypertrophy and systolic dysfunction are seen in the subcostal view.

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symptoms worsened, subsequently requiring orthotopic heart transplantation. Pathology of her excised heart revealed persistent ventricular myocyte vacuolization, mild chronic patchy inflammation, mild nonspecific reactive changes including nuclear hypertrophy, and fibrosis. There was no evidence of acute myocarditis, viral inclusions, or granulomas. Special stains for iron and amyloid (Congo red) were negative. No significant atherosclerosis or stenosis of the coronary arteries was identified. One year post-transplantation she is doing well with normal allograft function on tacrolimus. Her RA remains in remission with prednisone 5 mg.

DISCUSSION

In patients with chronic autoimmune diseases such as RA, there is a direct link between degree of inflammation and a two- to four-fold increase in cardiovascular events compared with the general population.[5,6] In such patients, inflammatory mechanisms can affect coronary microvascular, myocardial, and endothelial function, which can contribute to the development of ischemia and cardiovascular events. As our patient had multiple regional wall motion abnormalities with transmural infarct pattern on late gadolinium enhancement by cardiac magnetic resonance and underlying pathophysiologic mechanisms such as microvascular dysfunction and thromboembolism, the coexistence of myocardial infarction with nonobstructive coronary arteries was also considered.[7]

Hydroxychloroquine has been in use for more than six decades as an immunosuppressant for RA. Although it is considered less toxic than CQ, frequent and long-term use of HCQ has been associated with extracardiac side effects involving the gastrointestinal (8.2%), mucocutaneous (2%), ocular (2.2%), and neuromuscular (0.5%) systems.[8] Cardiac toxicity has been described in case reports and systematic reviews with use in malaria prophylaxis and treatment of autoimmune disorders; the precise incidence is unknown. In a recent meta-analysis of all patients who had cardiotoxicity, the most common manifestations were conduction disturbance (85%) and nonspecific cardiac adverse effects (69%), including irreversible cardiomyopathy (12.9%).[9]

The pathophysiology of CQ/HCQ-induced cardiomyopathy is poorly understood but involves direct lysosomal dysfunction due to inhibition of lysosomal enzymes and impairment of autophagy and intracellular degradation of cellular debris leading to pathologic accumulation of metabolic products (phospholipids and glycogen) within the heart.[10,11] These appear histologically as granulovacuolar inclusions and ultrastructurally as "lamellar bodies" and "curvilinear bodies"

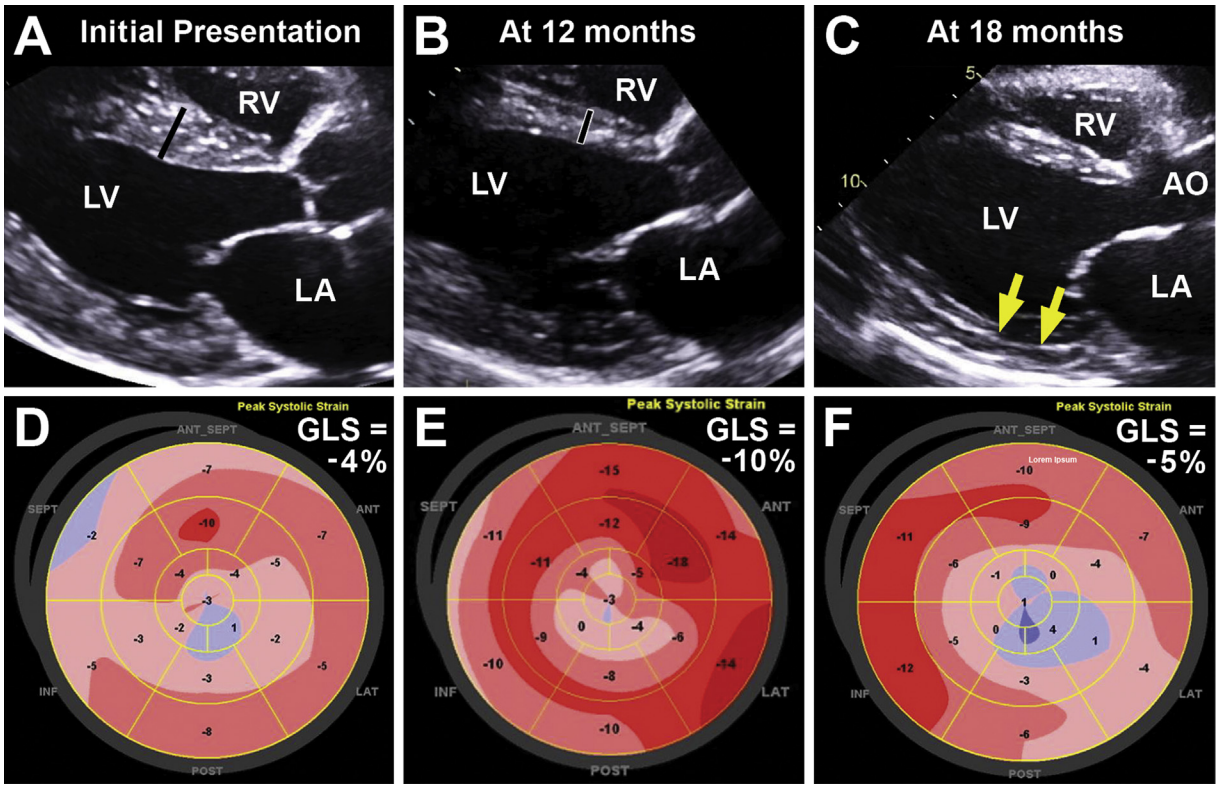

Figure 1 Echocardiography and strain analysis. **(A)** LV thickness measures 1.7 cm at the time of diagnosis. **(B)** LV thickness regressed to 1.2 cm 12 months after discontinuation of HCQ. **(C)** Development of basal to mid inferolateral akinesia (*yellow arrows*). A bull's-eye pattern of reduced global longitudinal strain shows **(D)** –4% at the time of diagnosis, **(E)** improved global longitudinal strain, –10%, 1 year after discontinuation of HCQ, and **(F)** worsening strain at 18 months. *AO*, aorta; *GLS*, global longitudinal strain; *LA*, left atrium; *LV*, left ventricle; *RV*, right ventricle.

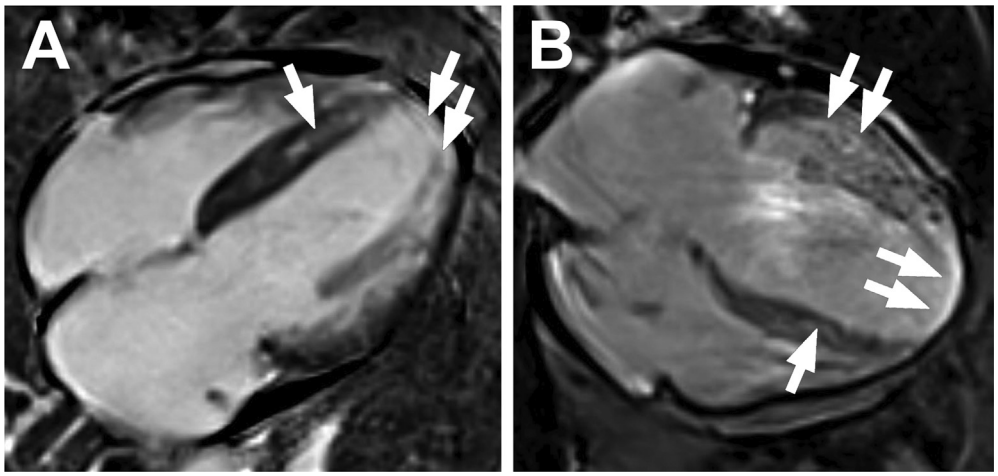

Figure 2 Cardiac magnetic resonance imaging. **(A)** Delayed gadolinium enhancement, apical transmural, midmyocardial septal delayed enhancement (*arrows*), and a trivial pericardial effusion are seen at diagnosis. **(B)** Additional basal to mid inferolateral wall transmural enhancement is seen at 18 months.

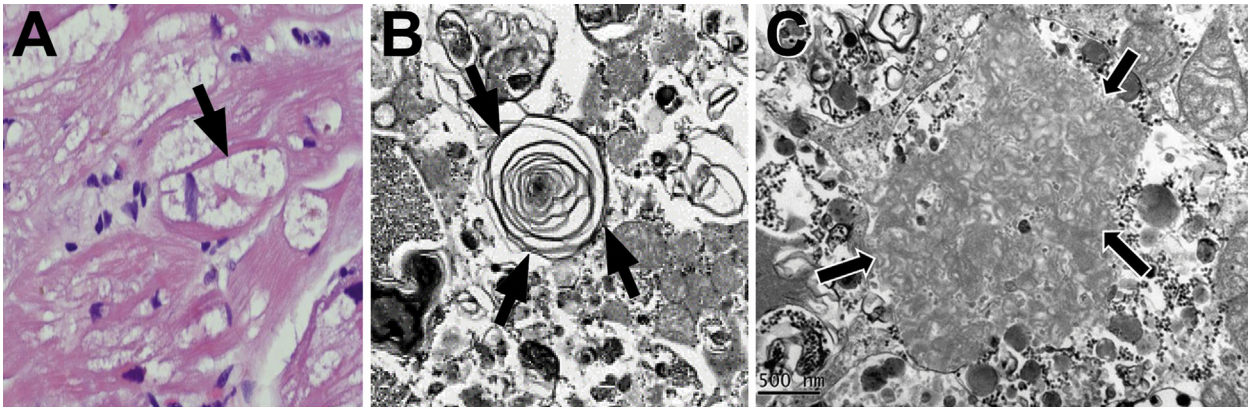

Figure 3 Endomyocardial biopsy. Light microscopy demonstrates **(A)** prominent myocyte vacuoles, and electron microscopy reveals **(B)** lamellar bodies and **(C)** curvilinear bodies.

within cytoplasm.[2] The changes result in progressive cardiac conduction defects, restrictive physiology, and systolic impairment, and about 45% of patients demonstrate improvement if the offending agent is discontinued earlier.[9] Our patient's historical course was consistent with this clinical presentation with a notable initial improvement in systolic function after discontinuation of HCQ; however, she subsequently experienced worsening of heart failure and valvular regurgitation with rheumatologic flares and ultimately required heart transplantation. Recent studies have indicated that CQ and HCQ can be used as antiviral agents with the ability to block viral attachment of coronavirus and entry to host cells by interfering with the binding of viral particles to the cellular surface (ACE2) receptor as well as the ability to disrupt postentry viral envelope maturation by impairment of pH-dependent enzymes in the endoplasmic network. Based on in vitro results and preliminary clinical studies, HCQ is being promoted as a therapeutic and prophylactic agent for the ongoing pandemic of coronavirus disease (COVID-19).[12,13] This case report illustrates the potential for harm with the long-term use of HCQ, but when used in patients with COVID-19, caution should be exercised, as acute toxicity has been reported in experimental models.[3,14] In a patient who is at high risk for myocardial injury because of COVID-19, concomitant use of a drug such as CQ or HCQ that inhibits autophagy could potentially result in significant harm that needs to be investigated with due cardiac vigilance.[15]

CONCLUSION

Given the significant morbidity and mortality associated with CQ/HCQ-induced cardiomyopathy and a lack of proven therapies for such toxicity, it is imperative to closely monitor these patients not only for QT prolongation effect of these drugs but also for early recognition of CQ/HCQ-induced cardiotoxicity. Maintaining a high index of suspicion and low threshold for imaging and histologic assessment is crucial in the evaluation of CQ/HCQ-induced cardiomyopathy.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2020.06.001.

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