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. Her HCQ dose was 600 mg daily for the past 23 years.

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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. 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.

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. 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%).

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. These appear histologically as granulovacuolar inclusions and ultrastructurally as “lamellar bodies” and “curvilinear bodies”

![Figure 1](https://example.com/figure1.png)  
**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.
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. 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). This case report illustrates the potential for harm with the long-term use of HCQ, 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.

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 http://doi.org/10.1016/j.case.2020.06.001.

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