CASE REPORT

Chloroquine-induced cardiomyopathy: a reversible cause of heart failure

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Abstract

Chloroquine (CQ) and hydroxychloroquine (HCQ) are anti-rheumatic medications frequently used in the treatment of connective tissue disorders. We present the case of a 45-year-old woman with CQ-induced cardiomyopathy leading to severe heart failure. Electrocardiographic abnormalities included bifascicular block, while structural disease consisted of severe biventricular and biatrial hypertrophy. Appropriate diagnosis via endomyocardial biopsy led to cessation of CQ and subsequent dramatic improvement in symptoms and structural heart disease. Cardiac toxicity is an under-recognized adverse effect of CQ/HCQ leading to cardiomyopathy with concentric hypertrophy and conduction abnormalities, with the potential for significant morbidity and mortality. Predisposing factors for CQ/HCQ-induced cardiomyopathy have been proposed. CQ/HCQ cardiomyopathy is a phenocopy of Fabry disease, and α-galactosidase A polymorphism may account for some heterogeneity of disease presentation.

Introduction

Cardiotoxicity from various medical therapies remains an important cause of heart disease and includes coronary artery disease, valvular heart disease, arrhythmias, and drug-induced cardiomyopathy.[1,2] Given the low cost, widespread availability and clinical efficacy, chloroquine (CQ) and hydroxychloroquine (HCQ) are commonly used in the treatment of rheumatoid arthritis, systemic lupus erythematosus, and other connective tissue disorders. Neuromyopathic, retinal, and cardiac toxicity are known adverse effects of CQ/HCQ and are more likely with increasing cumulative dose.[3] Specifically, both CQ and HCQ can cause direct myocardial toxicity and exacerbate underlying cardiac dysfunction.[1,3] We present the case of a 45-year-old woman who developed substantial structural heart disease and subsequent heart failure as a result of undiagnosed CQ toxicity.

Case report

A 45-year-old woman with a history of palindromic rheumatism and myelofibrosis presented to the emergency department with a 3 month history of worsening pedal oedema associated with 20 kg weight gain, fatigue, orthopnea, and dyspnoea [New York Heart Association (NYHA) Class III]. She denied any paroxysmal nocturnal dyspnoea, palpitations, presyncope, or angina. There was no history of smoking, alcohol, or recreational drug use, and family history was unremarkable. She was taking CQ 250 mg by mouth daily for a duration of 20 years. Physical examination revealed elevated jugular venous pressure, a III/VI systolic murmur loudest at the left lower sternal border, a distended abdomen, and pitting oedema to the level of the sacrum. Bloodwork demonstrated renal failure (estimated glomerular filtration rate = 28 mL/min/1.73 m^2) and elevated B-type natriuretic peptide (1511 pg/mL). Electrocardiogram showed bifascicular block and signs of biventricular hypertrophy (*Figure 1*). Severe biventricular hypertrophy, moderate-to-severe tricuspid regurgitation, mild mitral regurgitation, and biatrial dilatation were documented on transthoracic echocardiogram; an echocardiogram 6 years prior was completely normal. Cardiac magnetic resonance imaging (MRI) demonstrated restrictive cardiomyopathy with biatrial enlargement and concentric hypertrophy, along with left ventricular ejection fraction of 67% and right ventricular ejection fraction of 60%. (*Figure 2A,*

Figure 1 Electrocardiogram on initial admission demonstrating conduction abnormalities (bifascicular block) with signs of biventricular hypertrophy.
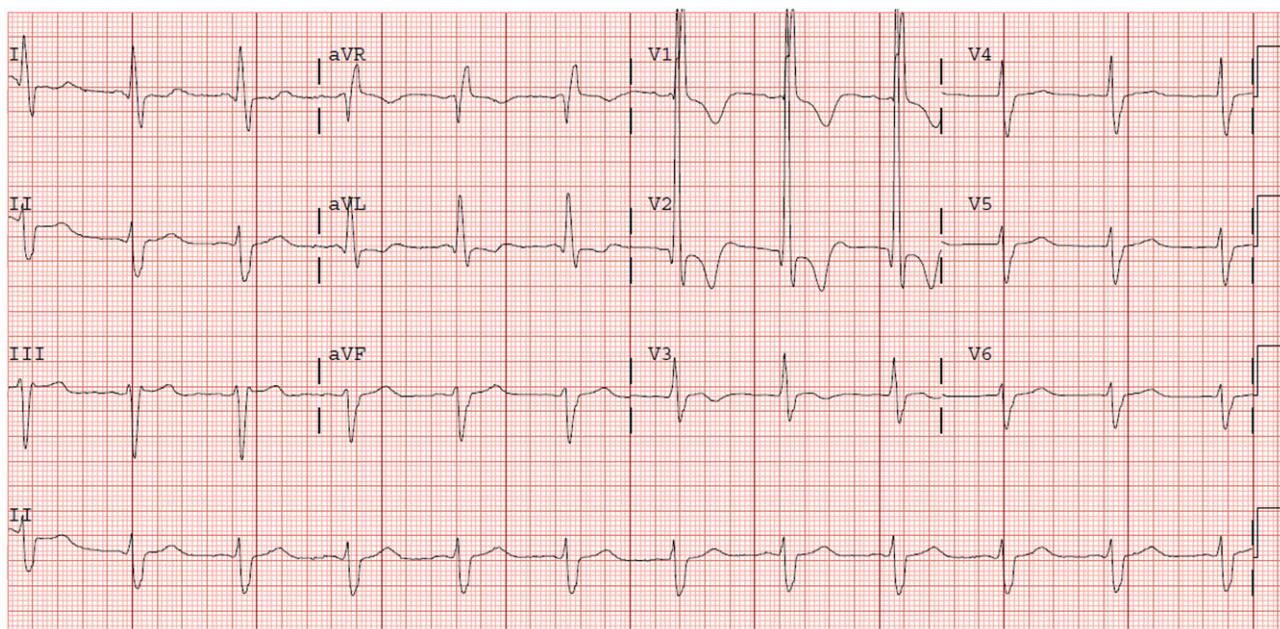
Figure 2 Cardiac magnetic resonance imaging prior to discontinuation of chloroquine (A), with biventricular hypertrophy and biatrial dilatation shown on two-chamber (A1), three-chamber (A2), four-chamber (A3), and short-axis (A4) views. Cardiac magnetic resonance imaging was performed after cessation of chloroquine (B), demonstrating significant resolution of structural abnormalities shown on two-chamber (B1), three-chamber (B2), four-chamber (B3), and short-axis (B4) views.
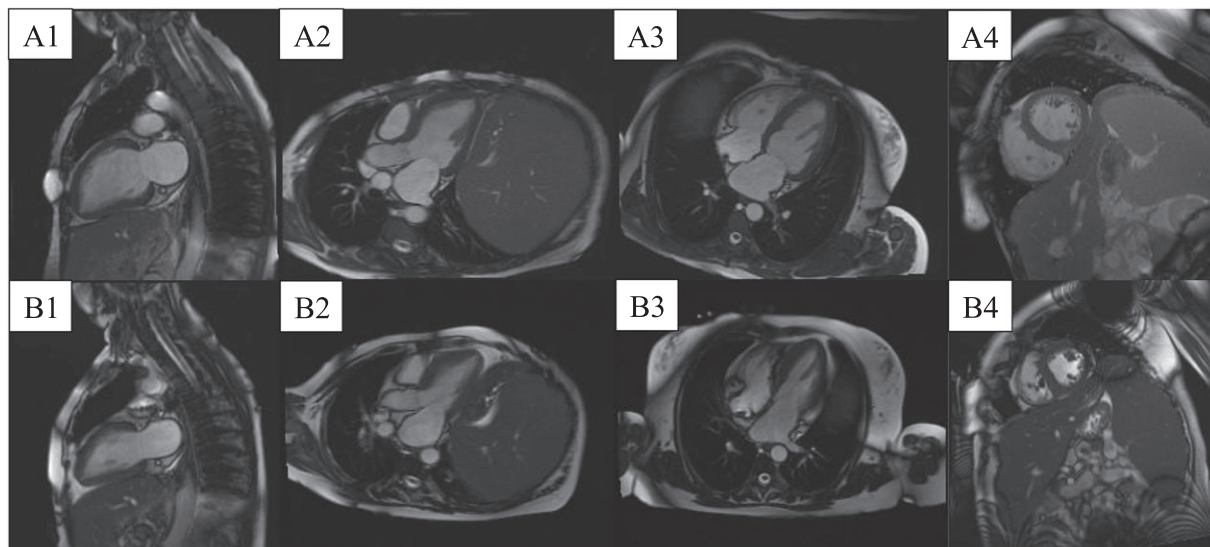
Supporting Information *Figure S1*, and Supporting Information, *Videos S1* and *S2*). Euvolemia was achieved, and the patient was discharged home on bisoprolol 2.5 mg orally daily and furosemide 40 mg orally twice daily. An angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, as well as mineralocorticoid receptor antagonist, was not initiated because of renal failure.

The patient was seen in follow-up 2 months later with significant worsening of dyspnoea (NYHA Class IV) and was admitted to the cardiology ward. Her admission was complicated by symptomatic bradycardia necessitating permanent pacemaker implantation and acute kidney injury secondary to venous congestion requiring haemodialysis. Angiogram demonstrated clear coronary arteries, and endomyocardial biopsy revealed

vacuolization consistent with CQ-induced cardiomyopathy (*Figure 3*). CQ was permanently discontinued. During subsequent follow-up 12 months after cessation of CQ, haemodialysis was ceased, and her symptoms of heart failure markedly improved (NYHA Class I). Importantly, repeat cardiac MRI, performed 12 months after cessation of CQ and the prior MRI, demonstrated normal biventricular structure and function with a moderately enlarged left atrium and only mild tricuspid regurgitation (*Figure 2B* and Supporting Information, *Videos S3* and *S4*).

Discussion

Despite increasing recognition, CQ/HCQ cardiotoxicity remains a preventable and under-recognized problem.[3] The pathophysiology of CQ/HCQ-induced cardiomyopathy is poorly understood but likely involves direct lysosomal dysfunction via inhibition of lysosomal enzymes.[1,3] Pathological accumulation of metabolic products within the heart leads to significant cardiac manifestations including cardiomyopathy with concentric hypertrophy and conduction disorders, and subsequent heart failure.[3] Biatrial dilatation is a feature of CQ/HCQ-induced cardiomyopathy and is likely reflective of the degree and duration of diastolic dysfunction and elevated filling pressures in the setting of heart failure with preserved ejection fraction (HFpEF). Given the significant morbidity and mortality associated with HFpEF and the lack of proven therapies, and the widespread use of CQ/HCQ, recognition of iatrogenic CQ/HCQ-induced cardiotoxicity is especially critical.[4]

If diagnosed early, as in this case, withdrawal of the offending drug potentially results in partial or complete reversal of cardiomyopathy,[5] with potential cessation of medical therapy for heart failure. We demonstrated clinical and structural evidence of significant reversal of CQ-induced cardiomyopathy following withdrawal of CQ. The likelihood of

patients with chronic heart failure to recover from NYHA Class IV to I, in the absence of transplantation, is exceedingly rare, making CQ/HCQ cardiomyopathy an especially important diagnosis to make. Additionally, the corresponding dramatic improvement in structural disease, demonstrated in our case using cardiac imaging, is also remarkable and further signifies the risk that missed diagnosis of CQ/HCQ cardiomyopathy presents. In patients where presentation and/or diagnosis is delayed, ongoing heart failure and/or irreversible consequences such as conduction disturbances may occur. In these cases, permanent pacemaker implantation may be required.[3] In addition, 5 year mortality rates for HFpEF are as high as 55–74%.[6] Accordingly, early diagnosis and treatment is paramount in order to avoid potential morbidity and mortality in these patients.

Patients who are prescribed CQ/HCQ often have underlying connective tissue disease and are therefore at increased risk of cardiac disease because of decreased exercise, systemic inflammation,[7] and/or cyclooxygenase inhibition via use of nonsteroidal anti-inflammatory medications. In these patients, the presentation may be obfuscated by concomitant coronary artery disease, in which case significant heart failure may be falsely attributed to vascular disease alone, leading to failed recognition of CQ/HCQ cardiomyopathy. Accordingly, in the absence of a clear clinical history, endomyocardial biopsy (EMB), with electron microscopy, is indicated.[1,8] Although EMB is an invasive procedure, it is the gold standard for diagnosis of CQ/HCQ cardiomyopathy. In addition, it can be useful for excluding other causes of unexplained cardiomyopathy, such as the aforementioned cardiac manifestations of connective tissue disease.[1,8] An acceptable alternative in patients who are unable to undergo EMB is skeletal muscle biopsy, as CQ/HCQ myopathy can sometimes be identified outside the heart.[9] Following diagnosis, immediate cessation of CQ/HCQ and replacement with a non-cardiotoxic disease-modifying anti-rheumatic drug are warranted.[5]

Figure 3 Pathology images of endomyocardial biopsy specimen. Light microscopy using haematoxylin and eosin stain demonstrates vacuolization of cardiomyocytes at ×200 magnification (A); light microscopy using periodic acid–Schiff stain at ×400 magnification shows that the vacuoles are periodic acid–Schiff-negative (B); electron microscopy at ×25 500 magnification demonstrates myeloid and curvilinear myeloid bodies, as well as vacuolated cytoplasm characteristic of chloroquine-associated cardiomyocyte damage (C).
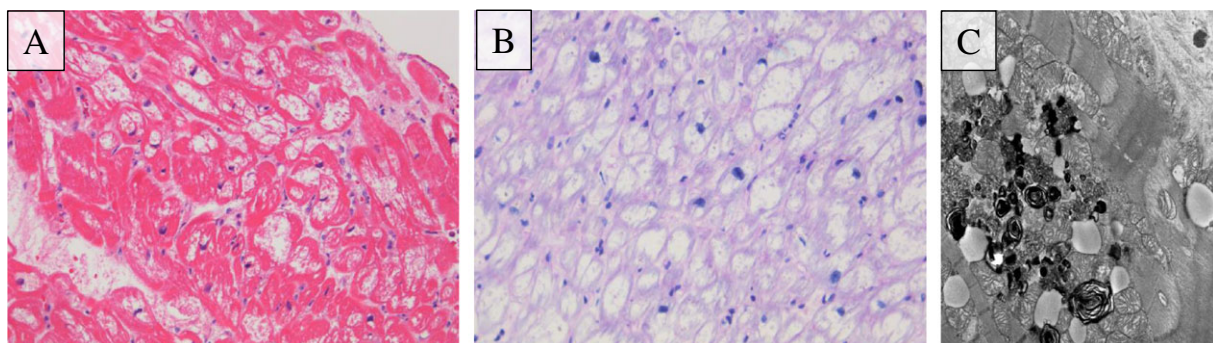
Many patients are treated with CQ/HCQ; it is unclear why only certain patients experience adverse events. Long-term exposure, higher doses, and the use of CQ instead of HCQ are proposed risk factors; however, there is significant heterogeneity in the presentation of patients with CQ/HCQ-induced cardiomyopathy.[1,3] It is possible that some patients may possess a genetic predisposition such as α-galactosidase A polymorphism, the genetic basis for Fabry disease, with varying degrees of severity. CQ cardiomyopathy represents a phenocopy of Fabry disease as they are clinically and histologically similar.[3] In the absence of curvilinear bodies, it can be difficult to differentiate between the two conditions.[10] Indeed, unrecognized Fabry disease has been diagnosed in patients with HCQ-induced cardiomyopathy.[11] Further studies are needed to elucidate other potential predisposing factors for CQ/HCQ-induced cardiomyopathy.

Acknowledgements

Conflict of interest

None declared.

Funding

Supporting information

Additional Supporting Information may be found online in the supporting information tab for this article.

Figure S1. Gadolinium-enhanced cardiac magnetic resonance imaging prior to discontinuation of chloroquine (A), with biventricular hypertrophy, biatrial dilatation, and late gadolinium enhancement shown on 2-chamber (A1), 3-chamber (A2), 4-chamber (A3), and short-axis (A4) views.
Video S1. Cine video of cardiac magnetic resonance imaging prior to discontinuation of chloroquine, demonstrating left ventricular hypertrophy and left atrial dilatation in 2-chamber view.
Video S2. Cine video of cardiac magnetic resonance imaging prior to discontinuation of chloroquine, demonstrating biventricular hypertrophy in short-axis view.
Video S3. Cine video of cardiac magnetic resonance imaging following discontinuation of chloroquine, demonstrating left ventricular hypertrophy and left atrial dilatation in 2-chamber view.
Video S4. Cine video of cardiac magnetic resonance imaging following discontinuation of chloroquine, demonstrating biventricular hypertrophy in short-axis view.

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