

## Hydroxychloroquine induced cardiotoxicity: A case series

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### Abstract

Hydroxychloroquine (HCQ) induced cardiotoxicity is a rare diagnosis and is often associated with chronic use of the medication. It has been shown that chronic HCQ use is associated with a drug-induced cardiomyopathy mainly driven by acquired lysosomal storage defects leading to hypertrophy and conduction abnormalities. As the only proven treatment is the discontinuation of the offending agent, prompt recognition is required to avoid further exposure to the drug and potential progression of disease. History, physical examination and advanced imaging modalities are useful diagnostic tools, but more invasive testing with an endomyocardial biopsy is required for definitive diagnosis. We present a descriptive case series of ten patients that were diagnosed with biopsy proven HCQ cardiotoxicity.

**Key Words:** Hydroxychloroquine, drug toxicity, cardiomyopathy, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome.

### INTRODUCTION

Hydroxychloroquine (HCQ), an amino-quinolone derivative traditionally known for its anti-malarial properties, is widely used for a multitude of rheumatologic diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome and Antiphospholipid Syndrome as it has helped improve clinical symptoms and long-term outcomes (1). During the COVID-19 pandemic, HCQ has gained popularity in the media as a proposed treatment modality for COVID-19. This has significantly increased its use amongst the general population in the United States, even in the absence of proven efficacy (2). HCQ's cardiovascular safety profile is limited and mainly based on observational studies and case reports. HCQ induced cardiotoxicity is a rare diagnosis and is often associated with chronic use of the medication. It has been shown that chronic hydroxychloroquine use is associated with a drug-induced cardiomyopathy mainly driven by acquired lysosomal storage defects leading to hypertrophy and conduction abnormalities (3). We present a descriptive case series outlining the clinical and pathologic findings in patients diagnosed with hydroxychloroquine cardiotoxicity.

### MATERIALS AND METHODS

A search of the electronic medical record over the last 10 years at a single enterprise comprised of three major teaching hospitals in three different geographic areas was performed to identify patients with HCQ induced cardiotoxicity. Our database included 226 records of patients that received HCQ as part of their management. We identified 16 patients that were diagnosed with HCQ induced cardiotoxicity. Only patients with endomyocardial biopsy proven HCQ toxicity were included, which resulted in 10 subjects meeting the eligibility requirements. Demographics, presenting symptoms, medical and pharmacological history, laboratory results, cumulative HCQ dose, electrocardiogram (ECG) findings, echocardiogram findings, Magnetic Resonance Imaging (MRI) findings, endomyocardial biopsy findings were recorded.

### RESULTS

Of the ten patients with biopsy proven HCQ toxicity, nine were female, seven identified as

white, one as native American, one as African American and one as other. The mean age of the patients was approximately 65 years and ranged from 42 to 77. Hypertension followed by heart failure and diabetes mellitus were the most common identified comorbidities. SLE was the most common rheumatologic disease identified, occurring in half of our cohort, followed by Sjogren's and RA which were each identified in two individuals. Only half of the patients underwent rheumatologic work-up at initial presentation and the most commonly identified antibodies were ANA and SSA followed by SSB. A majority of our cohort was found to have at least stage IIIa chronic kidney

disease (CKD). Dyspnea was the most common presenting symptoms, followed by fatigue, chest pain, edema, cough and palpitations. Baseline Characteristics, pertinent comorbidities, HCQ dosing, and outcomes are summarized in table 1. Biopsy as well as MRI findings are summarized in table 2.

No statistical difference was seen when comparing total dose per kilogram ( $p=0.33$ ), cumulative dose ( $p=0.34$ ) and survival in months ( $p=0.27$ ) between patients with CKD and those without. Overall, the average cumulative dose of HCQ was 1371.9 g with an average dose of 24.8 g/kg. Average survival after discontinuation of HCQ was 111 months.

Table 1

Baseline Characteristics, pertinent comorbidities, HCQ dosing within our cohort of 10 patients treated with HCQ

| Patient | Sex | Age | Race             | CKD      | Autoimmune Disease              | Antibodies | Comorbidities                | HCQ Dose     | Cummulative HCQ Dose | Outcome | Interval since HCQ discontinuation and last follow up |
|---------|-----|-----|------------------|----------|---------------------------------|------------|------------------------------|--------------|----------------------|---------|-------------------------------------------------------|
| 1       | F   | 62  | Native American  | CKD IIIb | SLE                             | ANA        | HTN                          | 400 mg daily | 560.6 g              | Alive   | 89 months                                             |
| 2       | F   | 73  | White            | No CKD   | Sjogren                         |            | HTN                          | 400 mg daily | 3916.4 g             | Alive   | 337 months                                            |
| 3       | F   | 60  | Other            | CKD IIIa | RA                              |            | HTN, Heart Failure           | 400 mg daily | 387.6 g              | Alive   | 38 months                                             |
| 4       | F   | 72  | White            | No CKD   | SLE                             | ANA, SSA   |                              | 400 mg daily | 428.6 g              | Alive   | 102 months                                            |
| 5       | M   | 69  | White            | CKD IIIa | RA                              |            | HTN, Heart Failure, Diabetes | 400 mg daily | 1569.6 g             | Alive   | 149 months                                            |
| 6       | F   | 77  | White            | CKD IIIb | SLE                             |            | HTN, Heart Failure, Diabetes | 400 mg daily | 1516.8 g             | Dead    | 142 months                                            |
| 7       | F   | 42  | White            | No CKD   | SLE                             |            | Heart Failure                | 400 mg daily | 767.2 g              | Dead    | 45 months                                             |
| 8       | F   | 63  | White            | No CKD   | SLE                             | SSB        |                              | 400 mg daily | 2558 g               | Alive   | 121 months                                            |
| 9       | F   | 57  | African American | CKD V    | Mixed connective tissue disease |            | HTN                          | 400 mg daily | 1238 g               | Dead    | 5 months                                              |
| 10      | F   | 76  | White            | CKD IIIa | Sjogren                         | SSA        | Heart Failure                | 400 mg daily | 776.4 g              | Alive   | 79 months                                             |

Table 2

MRI and cardiac biopsy findings. (Legend: LV=left ventricle, RWMA=regional wall motion abnormalities)

| Patient | MRI | MRI findings                                                                   | MRI tissue characterization                                                            | Biopsy | Biopsy findings                                                                             |
|---------|-----|--------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|--------|---------------------------------------------------------------------------------------------|
| 1       | Yes | Abnormal LV thickness, RWMA, Akinesis/Hypokinesis, Abnormal LV volume/function | Apical late enhancement pattern suggestive of "burned out" hypertrophic cardiomyopathy | Yes    | Severe myocyte hypertrophy, mild interstitial fibrosis, and extensive myocyte vacuolization |
| 2       | Yes | Abnormal LV thickness                                                          | Atypical variant hypertrophic cardiomyopathy                                           | Yes    | Atypical variant hypertrophic cardiomyopathy                                                |
| 3       | Yes | Abnormal LV thickness                                                          | Mild basal and apical hypertrophy, extensive late gadolinium enhancement               | Yes    | Extensive myocyte vacuolization, interstitial fibrosis and associated myocyte hypertrophy   |

Table 2 (continued)

| Patient | MRI | MRI findings                                                     | MRI tissue characterization                                                                                                                                                            | Biopsy | Biopsy findings                                                                                                                           |
|---------|-----|------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 4       | Yes | Abnormal LV thickness                                            | Mild concentric basal left ventricular hypertrophy without obstructive features, favoring hypertension or drug toxicity as underlying etiology rather than hypertrophic cardiomyopathy | Yes    | Mild sarcoplasmic vacuolization with occasional myelinoid bodies                                                                          |
| 5       | Yes | Akinesis/Hypokinesis                                             | Nonspecific pattern                                                                                                                                                                    | Yes    | Focal myocyte vacuolization and scattered myeloid bodies in the absence of curvilinear bodies suspicious for HCQ-mediated cardiotoxicity. |
| 6       | No  |                                                                  |                                                                                                                                                                                        | Yes    | Extensive myocyte vacuolization                                                                                                           |
| 7       | Yes | Akinesis/Hypokinesis, Abnormal LV volume, Valvular abnormalities | Nonspecific pattern                                                                                                                                                                    | Yes    | Extensive myocyte vacuolization                                                                                                           |
| 8       | No  |                                                                  |                                                                                                                                                                                        | Yes    | Extensive myocyte vacuolization                                                                                                           |
| 9       | No  |                                                                  |                                                                                                                                                                                        | Yes    | Extensive myocyte vacuolization and hypertrophic changes                                                                                  |
| 10      | No  |                                                                  |                                                                                                                                                                                        | Yes    | Extensive myocyte vacuolization                                                                                                           |

## DISCUSSION

HCQ is thought to be a well-tolerated disease-modifying antirheumatic drug (DMARD) for the treatment of several rheumatologic diseases (4). Although their clinical safety profile is reassuring, the drug is associated with a multitude of adverse effects including gastrointestinal symptoms, such as nausea and vomiting, retinopathy, and skeletal muscle toxicity (5,6). Furthermore, it has been proposed that patients receiving HCQ for the treatment of RA are at a three times higher risk of developing heart failure compared to unexposed individuals when exposed for longer than fourteen years (7). The drugs pharmacokinetic properties suggest a slow accumulation over time with a variable therapeutic response after initial dosing based on interindividual differences. HCQ has a large volume of distribution reported to be several thousands of liters and renal clearance accounts for up to 25% of its total clearance (8).

Chronic exposure to HCQ has been associated with ventricular wall thickening as well as microscopic changes leading to cardiomyopathy. The changes observed on a microscopic level include the vacuolization and enlargement of cardiac myocytes along with the deposition of myeloid and curvilinear bodies within these cells. Patients exposed to HCQ over long periods of time may have echocardiogram findings consistent with diffuse hypokinesia and overall decreased ejection fraction (9). One of the proposed mechanisms of cardiotoxicity is based on HCQ's innate ability to inhibit autophagy by inhibiting autophagosome

fusion and the prevention of endosomal acidifications on a cellular level, leading to the accumulation of several metabolic by-products within the cells. This accumulation leads to a more acidic pH within the cell, affecting the beneficial functions of proteins, mainly lysosomal enzymes. Long term use causes an accumulation of these effects and can lead to cell damage, increased apoptosis, myocyte necrosis and ultimately cell death. Additionally, it has also been proposed that HCQ's hydrophobic properties may lead to a disruption and structural change of the cell's membrane, ultimately leading to necrosis and cell death (7,9). The inhibition of autophagy appears to be the main mechanism driving cardiotoxicity associated with HCQ and its deleterious effects have been described in biopsy findings of both smooth and skeletal muscles (10).

In the more acute setting, HCQ can lead to cardiotoxicity and death through its properties as a "quinidine-like" pharmacologic agent. HCQ's ability to block several electrolyte channels in cardiac myocytes leads to a widening of the QRS complex and increased risk of arrhythmias, a result of sodium channel blockade, as well as delayed ventricular repolarization and widening of the QT interval leading to increased risks of torsades de pointes, an effect of potassium channel blockade (11). Patients with inherent prolongation of their QT interval, renal disease and presence of structural heart disease prior to initiation of HCQ have been found to be at a greater risk of developing acute toxicities (12). While acute toxicities can be observed early after initiation of

HCQ, the disruption of autophagy described in chronic exposure to the drug takes several years to show effect and its rhythm abnormalities are mainly driven by direct damage of the cardiovascular conduction system (5).

Endomyocardial biopsy aids in the diagnostic work-up of HCQ cardiotoxicity as it provides accurate visualization of the intracellular processes involved and allows to differentiate this drug induced toxicity from other disease processes, including amyloidosis, sarcoidosis, and myocarditis. Pathologic findings of HCQ cardiotoxicity associated with chronic use include enlargement and vacuolization of cells visualized on light microscopy. Furthermore, transmission electron microscopy has identified myelinoid and curvilinear bodies in the cardiac tissues of these patients, features suggestive of dysfunctional lysosomes. The presence of curvilinear bodies is most specific to HCQ induced cardiotoxicity as these findings are not seen with other toxic or infiltrative processes such as Fabry's disease (13).

Discontinuation of the drug after the diagnosis of cardiotoxicity is made has been associated with improvement of clinical symptoms as well as restoration of normal ventricular ejection fraction. Several case reports have described a reduction and oftentimes elimination of the intracellular pathologic findings after six months of HCQ discontinuation (13,14).

Our cohort consisted of mostly female patients with a majority of them carrying cardiovascular and renal comorbidities. Most of our patients received HCQ for treatment of SLE and were exposed to a large cumulative dose of 1371.9g, suggesting an average exposure of less than ten years (9 years 5 months). The prevalence of renal disease within our cohort was high, with 60% of patients having been diagnosed with advanced renal disease. Although nonspecific, MRI can serve as a useful test in the early work-up of these individuals and may show late gadolinium enhancement as well as cardiac myocyte hypertrophy different from the hypertrophy seen in hypertrophic cardiomyopathy. Given the fact that several of our patients were previously diagnosed with hypertension, this is a valuable differentiation as they could have easily been misdiagnosed with hypertrophic cardiomyopathy in the setting of hypertensive cardiovascular disease. Cardiac biopsy was the mainstay of diagnosis within our cohort, and the histologic findings ultimately lead to the discontinuation of HCQ. Interestingly, a review of the literature suggests that the histological findings

associated with HCQ toxicity are observed in both skeletal and smooth muscles, suggesting that a skeletal muscle biopsy could potentially be sufficient to make a diagnosis in patients in whom cardiac biopsy is contraindicated (13).

Given the increased use of HCQ during the COVID-19 pandemic and rising concern for cardiotoxicity, Fram *et al.* performed a systematic literature review of cardiac complications attributed to HCQ prior to the COVID-19 pandemic in 2021 where 58 case reports and 11 case series were identified. Studies reporting cardiac complications from HCQ use were included. Studies describing systemic toxicities other than cardiac manifestations as well as studies where HCQ was used to treat autoimmune conditions with potential cardiac manifestations were excluded. 84% of patients were female with a median age of 49.2 years. The most commonly treated rheumatological disease was SLE, consisting of 52% of the patients. When focusing on the patients who experienced toxicities after long-term use, the median duration of HCQ exposure until onset of symptoms was 10.5 years with a median lifetime cumulative dose of 1493.8 g (range: 16 – 3212.0 g). The most common reported cardiac manifestation was left sided heart failure (15). Dey *et al.* stress the importance of early diagnosis in their review article and point out that high cumulative doses of HCQ over several years, female sex and older age are some of the high-risk features of patients that develop HCQ cardiotoxicity (1).

Review of the aforementioned study as well as a search of the PubMed, Medline, Cochrane, Embase and Google Scholar databases revealed that our study appears to be the second largest case series to date that specifically focuses on the chronic cardiac manifestations associated with HCQ. Both the cumulative lifetime dose as well as onset of symptoms reported by Fram *et al.* are consistent with the findings in our cohort. The common light and electron microscopic findings on endomyocardial biopsy in patients with HCQ-induced cardiomyopathy were outlined by Nadeem *et al.* and our case series further adds to our understanding of the disease process by discussing the MRI findings and utility of advanced imaging modalities in the diagnostic work-up (7).

Even in the absence of statistical significance between our CKD and non-CKD cohorts when it comes to dosing and survival, one cannot exclude the possibility that CKD poses a higher risk of developing chronic HCQ cardiotoxicity given its

pharmacokinetics as well as its high prevalence within our cohort. Furthermore, the fact that renal disease is associated with acute HCQ toxicity may hint at a potential involvement in chronic toxicity as well. However, further research needs to be conducted in order to prove this assumption (8,12).

Clinicians need to be aware of the potentially life-threatening cardiac manifestations of both short- and long-term exposure to HCQ and its prevalence amongst patients with both cardiac and renal comorbidities. Although history and physical examination are important in the early work-up, more invasive testing is often required to make a definitive diagnosis. Endomyocardial biopsy is not without risk with reported complication rates as high as 6% (16,17). Of the six patients undergoing MRI as part of their work-up, all six had abnormal findings including abnormal ventricular wall thickness and volume, abnormal ventricular function, regional wall motion abnormalities, hypokinesis, akinesis as well as valvular abnormalities. As discontinuation of the drug is currently the only available treatment, we propose obtaining an MRI in symptomatic individuals and immediately discontinuing HCQ if abnormal findings are present. Patient should

subsequently be referred to Cardiology for symptomatic management and consideration of endomyocardial biopsy.

## CONCLUSION

In conclusion, this article presents several patients with HCQ cardiotoxicity and highlights the importance of maintaining a high clinical index of suspicion in patients presenting with vague symptoms in order to make the diagnosis. The data analysis of our case series suggests that HCQ toxicity more commonly presents in females, patients suffering from CKD, and those who have been exposed to large cumulative doses of HCQ. We propose prompt discontinuation of HCQ in patients who have been exposed to large cumulative doses over long periods of time. Imaging modalities, such as MRI, can aid in the diagnosis of HCQ toxicity, but more invasive testing with endomyocardial biopsy is often required to make a definitive diagnosis. HCQ cardiotoxicity remains a rare diagnosis and prompt recognition is required to avoid further exposure to the drug and potential progression of disease.

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*Cardiotoxicitatea indusă de hidroxichlorochină (HCQ) este un diagnostic rar și este adesea asociată cu utilizarea cronică a medicamentului. S-a demonstrat că utilizarea cronică a HCQ este asociată cu o cardiomiopatie indusă medicamentos determinată în principal de defecte dobândite de stocare lizosomală care conduc la hipertrofie și anomalii de conducere. Deoarece singurul tratament dovedit este întreruperea agentului incriminat, este necesară recunoașterea promptă pentru a evita expunerea ulterioară la medicament și potențiala progresie a bolii. Anamneza, examenul fizic și modalitățile avansate de imagistică sunt instrumente de diagnosticare utile, dar pentru diagnosticul definitiv sunt necesare teste invazive cum ar fi biopsie endomiocardică. Prezentăm o serie de cazuri descriptive de zece pacienți care au fost diagnosticați cu cardiotoxicitate HCQ dovedită prin biopsie.*

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**Declaration of interest:** The authors declare no conflict of interest.

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