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Review Article

Hydroxychloroquine and Chloroquine Induced Cardiomyopathy: A Concise Review

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Abstract: Hydroxychloroquine and Chloroquine are commonly used for the treatment of malaria and autoimmune conditions. Most recently, hydroxychloroquine has been implicated in the treatment armamentarium of Severe acute respiratory syndrome (SARS) caused by SARS-associated coronavirus-2. A rare, underreported side effect of hydroxychloroquine and chloroquine is cardiotoxicity. The cardiomyopathy occurs as a result of inhibition of lysosomal enzymes causing lysosomal dysfunction and intra-cellular accumulation of metabolic byproducts in the myocardium, leading to hypertrophy with or without restrictive physiology and resultant conduction abnormalities. Based on our review of 57 reported cases of hydroxychloroquine or chloroquine induced cardiomyopathy, dyspnea was the most common associated symptom. The most common rhythms seen on EKG were as follows: complete heart block (18.75%), right bundle branch block (RBBB) (18.75%). The most common findings on echocardiography were left ventricular hypertrophy (LVH) (54%), systolic dysfunction (48%) and diastolic dysfunction (32%). A definitive diagnosis is established by endomyocardial biopsy which demonstrates the presence of curvilinear inclusion bodies. The outcome following cessation of the offending agent ranges from complete reversal in 45% of the cases to continued progression with need for cardiac transplantation or even death in 17.5% of the cases.

Keywords: Drug-induced Cardiomyopathy, Hydroxychloroquine, Chloroquine, Biventricular Hypertrophy, Non-ischemic Cardiomyopathy, Complete Heart Block, Inclusion Bodies

1. Introduction

The anti-malarial agents chloroquine and hydroxychloroquine belong to a class of drugs known as 4-amnioquinolines [1]. Given their immunomodulatory effects, their use has extended to include treatment of systemic lupus erythematous (SLE), rheumatoid arthritis (RA), antiphospholipid syndrome (APS), primary Sjögren syndrome [2-6]. Most recently, hydroxychloroquine has been reported to have a role in the treatment of COVID-19 (Coronavirus Disease) caused by SARS-CoV (Severe Acute Respiratory Syndrome associated Coronavirus) [2-6]. When used in these rheumatological conditions, they may lower cardiovascular risk by way of inhibiting atherosclerosis and reducing hyperglycemia and hyperlipidemia [7, 8]. Interestingly, there have been case reports and case series documenting conduction system abnormalities and

cardiomyopathy caused by these two drugs. The mechanism of this pathology is still not clearly elucidated and there remains a paucity of data about this iatrogenic cardiotoxicity. We present a review of the literature of chloroquine and hydroxychloroquine induced cardiomyopathy in rheumatologic conditions.

2. Methods

On January 13, 2020, a systematic search was conducted using PubMed and Google Scholar. Studies listing the keywords "cardiomyopathy, hydroxychloroquine, chloroquine" were used to identify cases of hydroxychloroquine and chloroquine induced cardiomyopathy. The reference list of each report was reviewed for potential additional cases. All cases were reviewed in detail. Data reviewed included demographic data, cardiovascular risk factors, electrocardiography (ECG) findings, associated trigger factors, transthoracic echocardiography, coronary angiography and management of hydroxychloroquine and chloroquine induced cardiomyopathy when available.

3. Results

A total of 57 cases (Table 1) of hydroxychloroquine or chloroquine induced cardiomyopathy have previously been reported, with the first of these reports occurring in 1987. Of these cases, 14.3% (8) were described in males and 86% (49) were in females. The age was reported in 56 of the patients, the mean age was 57.232 years (standard deviation [SD] 11.59, 25th percentile 45.642 years, 75th percentile 68.822 years). Prevalent historical cardiovascular (CV) risk factors were as follows: heart failure with reduced ejection fraction (HFrEF) 54.38%, hypertension (HTN) 24.56%, heart failure with preserved ejection fraction (HFpEF) 22.80%, hyperlipidemia (HLD) 10.52%, coronary artery disease (CAD) 10.52%, smoking 7.01%, diabetes mellitus (DM) 3.5%. In 34 (60.0%) of the cases, the patients received hydroxychloroquine only. Eighteen (31.2) of the cases received chloroquine only. Four patients (7.02%) received a combination of both hydroxychloroquine and chloroquine. One patient (1.75%) was changed from hydroxychloroquine to chloroquine. Treatment duration was measured in 47 of the cases, the average duration of treatment was 14.01 years (SD 11.089, 25th percentile 6 years, 75th percentile 20 years, confidence interval 3.256). Cumulative dosing of chloroquine was documented in 17 of the cases, the mean cumulative dosing was 1440.11 g (SD 901.98, 25th percentile 885g, 75th percentile 2115g, CI 463.755). Cumulative dosing of hydroxychloroquine was documented in 28 cases, the mean cumulative dosing was 1288.72 (SD of 1040.73, 25th percentile 202g, 75th percentile 1813g, CI 432.512).

In our review, the indication for treatment with hydroxychloroquine or chloroquine was documented in all 57 cases. They are as follows: SLE alone: 56.14%, RA alone: 26.31%, SLE and Sjögren syndrome: 1.75%, RA and SLE: 1.75%, RA and Sjögren syndrome: 1.75%, malaria prophylaxis: 1.75%, psoriasis: 1.75%, mixed connective tissue disease: 1.75%, Sjögren syndrome: 1.75% and palindromic rheumatism: 1.75%.

Symptoms at presentation were reported in all of the cases (57). The most common chief complaints were dyspnea on exertion (47.6%), chest pain (14.03%), peripheral edema (14.03%), fatigue (12.28%), weakness (7.01%), shortness of breath (5.26%), palpitations (3.5%), orthopnea (3.5%) and weight gain (3.5%).

Electrocardiogram (EKG) was performed in 48 of the 57 cases. The most common rhythms seen were as follows: complete heart block (18.75%), right bundle branch block (RBBB) (18.75%), paced rhythm (12.5%), normal EKG (8.3%), sinus bradycardia (8.3%), left bundle branch block (LBBB) (8.3%) and incomplete RBBB (6.25%). Transthoracic echocardiograms (TTE) were performed in 50 out of 57 cases. The most common findings were left ventricular hypertrophy (LVH) (54%), systolic dysfunction (48%), diastolic dysfunction (32%), left atrial enlargement (24%), right ventricular hypertrophy (RVH) 20%, right atrial enlargement (16%), septal wall hypertrophy (16%), mitral regurgitation (12%), hypokinesis (12%), left ventricular dilation (8%), tricuspid regurgitation (8%), pulmonary hypertension (8%) and restrictive cardiomyopathy (4%). Right ventricular failure was seen in 8 cases (14.0%). Ejection fraction (EF) was measured in 36 patients. Mean initial ejection fraction was 40.33% (SD 15.06, median 38%, 25th percentile 27%, 75th percentile 50%). Follow up EF was measured in 6 cases; mean EF was 50.5% (SD 13.99%, median 50.0%, 25th Percentile 38%, 75th percentile 56%). Coronary angiography was done in 34 of the cases, the most common findings were: non-obstructive coronary arteries (79.41%), pulmonary hypertension (11.4%), depressed EF (8.8%), elevated right sided pressures (5.8%), elevated LV diastolic pressure (5.8%) and restrictive cardiomyopathy (5.8%). Endomyocardial biopsy with electron microscopy was done for 43 cases. The most common finding was curvilinear bodies (65%), cytoplasmic vacuolization (16.27%), myeloid bodies (9.3%), myelinoid inclusion bodies (4.6%). Cardiomyopathy was present in all 57 cases and was distributed as follows: 31 (54.38%) had unspecified cardiomyopathy, 12 (21%) had restrictive cardiomyopathy, 9 (15.7%) had dilated cardiomyopathy, 3 (5.26%) had hypertrophic cardiomyopathy, 1 (1.75%) had takosubo cardiomyopathy, 1 (1.75%) had biventricular cardiomyopathy.

In terms of outcomes, reversibility of cardiomyopathy was seen in 26 patients (45.6%), 11 (19.3%) patients were evaluated for or underwent left ventricular assist devices (LVAD) placement, 13 (22.8%) were evaluated for or underwent cardiac transplantation. Mortality was observed in 10 cases (17.5%).

Table 1. *Case Reports and Case Series Describing Hydroxychloroquine and Chloroquine Induced Cardiomyopathy.*

	Paper	Number of cases
1	Ratliff NB, et al. [9]	2
2	Iglesias Cubero G, et al. [10]	1
3	Walsh DS, et al [11]	2
4	C August, et al [12]	1
5	Baguet JP, et al [13]	1
6	Cervera A, et al [14]	1
7	Roos JM, et al [15]	3
8	Teixiera RA, et al [16]	1
9	Freihage JH, et al [17]	1
10	Nord JE, et al [18]	2
11	Keating RJ, et al [19]	1
12	Naqvi TZ, et al [20]	1
13	Reffelmann T, et al [21]	1
14	Costedoat-Chalumeau N, et al [22]	1
15	Soong TR, et al [23]	2
16	Cotroneo J, et al [24]	1
17	Fragasso G, et al [25]	1
18	Manohar VA, et al [26]	1
19	Magnussen, I, et al [27]	1
20	Lee JH, et al [28]	1
21	Muthukrishnan P, et al [29]	1
22	Hartmann, M., et al [30]	1
23	Bae SM, et al [31]	1
24	Azimian M, et al [32]	2
25	Champion S, et al [33]	1
26	Tönnesmann E, et al [34]	1
27	Frustaci A, et al [35]	1
28	Joyce E, et al [36]	1
29	Vereckei A, et al [37]	1
30	Yogasundaram H, et al [38]	1
31	Lopez-Ruiz N, et al [39]	1
32	Abdin A, et al [40]	1
33	Tselios K, et al [41]	1
34	Sabato LA, et al [42]	1
35	Chatre C, et al [43]	1
36	Pavsic N, et al [44]	1
37	Di Girolamo F, et al [45]	3
38	Yogasundaram H, et al [46]	1
39	Dogar MU, et al [47]	1
40	Tselios K, et al [48]	7
42	Zhao H, et al (REF- 49)	2

4. Discussion

The bark of the Cinchona trees was known for centuries as a remedy for fever and chills by the indigenous people of Peru. In 1633, it was introduced in Europe and used as a treatment for malaria. In 1820, quinine was isolated from the cinchona bark and became the standard of treatment for malaria. Given the limited supply, the cinchona bark was hard to come by and in an effort to develop a synthetic analogue, chloroquine was discovered by Hans Andersag who named it "Resochin" [49]. However, it was deemed too toxic for human consumption. During World War II, the US government sponsored clinical trials for anti-malarial drug development. These trials were instrumental in proving chloroquine's efficacy as a potent anti-malarial. Today it is listed on the World Health Organization's list of Essential Medicines. Hydroxychloroquine was approved for use in the US in 1955. In 2017, it was the 128th most prescribed medication in the country with more than 5.6 million prescriptions [50].

The hydroxychloroquine molecule is identical to the chloroquine molecule except for the additional hydroxyl group at the end of its side chain [51]. They have similar pharmacokinetics and pharmacodynamics and have long half-lives extending 30-60 days. Hydroxychloroquine is used more preferentially due to its increased tolerability and enhanced safety profile [52]. They inhibit toll like receptor-9 and T-helper 17 cytokines thereby exerting an immunomodulatory effect utilized in the treatment of several rheumatological conditions including SLE, RA, APS and primary Sjögren syndrome [53]. Known adverse effects include retinopathy and neuromyopathy [54-56]. There exist scattered data about their cardiotoxic effects and this remains an under-recognized and under-diagnosed yet preventable iatrogenic clinical entity.

The pathophysiology of chloroquine and hydroxychloroquine induced cardiomyopathy remains poorly understood. Further, it is unclear why only certain patients develop cardiotoxicity whereas the majority do not. The reported cases were mostly in females which is likely due to the increased predilection for autoimmune disorders. The most predominant symptom is reported to be dyspnea. Long-term exposure, renal dysfunction, higher doses and the use of chloroquine over hydroxychloroquine have been identified as potential risk factors [46]. Per our review, the average duration of treatment in this subset of patients was 14 years, it can therefore be reiterated that prolonged exposure and cumulative dosing likely plays a key role.

The cardiomyopathy is hypothesized to be a result of inhibition of lysosomal enzymes causing lysosomal dysfunction and intra-cellular accumulation similar to Fabry's disease [46, 57]. The hallmark of chloroquine and hydroxychloroquine induced cardiomyopathy is the accumulation of "curvilinear inclusion bodies" (the remnants of incompletely digested membranes) on electron microscopy which narrows down the differential diagnosis to either neuronal ceroid lipofuscinosis (NCL) or chloroquine and hydroxychloroquine induced cardiomyopathy and rules out Fabry's disease [43]. NCL encompasses a group of hereditary neurodegenerative disorders seen in children and can be excluded based on the patient's history and presentation [57-79]. Pathological accumulation of metabolic byproducts within the myocardium leads to concentric hypertrophy with or without restrictive physiology and conduction abnormalities. Resting electrocardiograms may reveal ST-segment depression, T wave inversions and QT interval prolongation at therapeutic doses [60]. Third degree AV block may precede symptoms of congestive heart failure by years [61-64]. The predominant EKG rhythms identifiers in our review are noted to be complete heart block and right bundle branch block. Bi-atrial enlargement may be seen on echocardiography reflecting diastolic dysfunction with elevated filling pressures. If diagnosed early in the course of the disease with cessation of the offending agent, there have been reports of reversal of the cardiomyopathy [41]. More commonly, the chronic heart failure is progressive and irreversible. Rarely this may warrant cardiac allograft

transplantation [17, 22]. Per our review, almost half of the patients had recovery of their ejection fraction following discontinuation of the offending agent. However, a notable proportion had significant morbidity requiring LVAD and evaluation for cardiac transplantation.

The diagnosis of chloroquine and hydroxychloroquine induced cardiomyopathy is often challenging. SLE and RA themselves may involve the cardiovascular system and no particular symptom differentiate these from chloroquine and hydroxychloroquine induced cardiomyopathy [65, 66]. The most common finding on echocardiogram is biventricular hypertrophy which may provide a clue to the diagnosis [10, 13, 19, 20, 26]. Based on our findings, echo findings suggestive of LVH, systolic and diastolic dysfunction in a symptomatic patient on chloroquine or hydroxychloroquine should prompt consideration of cardiomyopathy related to drug.

Cardiac MRI may confirm left ventricular hypertrophy and show late gadolinium enhancement in a non-coronary distribution [34]. Histology plays a crucial role in the diagnosis and MRI-guided endomyocardial biopsy to overcome sampling bias may employed when available. Light microscopy reveals vacuolar myopathy. Vacuolar myopathy may also be seen in connective tissue diseases like SLE and in steroid induced myopathy [69]. Thus, electron microscopy is vital. Ultrastructural findings of chloroquine and hydroxychloroquine induced cardiomyopathy include lamellar and curvilinear inclusion bodies. Lamellar inclusion bodies also known as myeloid bodies are non-specific and may be seen in amiodarone toxicity and storage diseases such as Fabry's disease [15]. Curvilinear inclusion bodies are comma-shaped and specific to chloroquine and hydroxychloroquine induced cardiomyopathy and NCL as mentioned above [23]. Curvilinear inclusion bodies may also be seen in the retina and peripheral nerves of patients on these agents [45, 68, 69].

Given the rarity of this diagnosis, no guidelines exist about surveillance and management of patients diagnosed with chloroquine and hydroxychloroquine induced cardiomyopathy. If cardiotoxicity is suspected, the offending agent should be stopped immediately, and the patient should receive close monitoring to avoid development of more serious adverse effects [70].

5. Conclusions

In conclusion, chloroquine and hydroxychloroquine induced cardiomyopathy remains an under-diagnosed yet preventable cause of heart failure. Increased awareness and routine surveillance for signs and symptoms of cardiomyopathy may aid in earlier detection. If suspected, the offending agent should be stopped immediately. Endomyocardial biopsy with electron microscopy remains the gold standard for diagnosis. Further trials to elucidate the mechanisms of injury are required to enhance our understanding and develop treatment strategies for its management.

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