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-aminoquinolines [1]. Given their immunomodulatory effects, their use has extended to include treatment of systemic lupus erythematosus (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 cases, the mean age was 57.232 years (standard deviation 11.59, 25th percentile 27%, 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 (HFrEF) 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%), hypokinesia (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%), decompensated LV dysfunction (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%), myeloid 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%).
The bark and became the standard of treatment for malaria. Given the limited supply, the cinchona bark was hard to come by and was too toxic for human consumption. However, it was deemed too toxic for human consumption. In 1820, quinine was isolated from the cinchona tree and used as a treatment for fever and chills by the indigenous people of Peru. 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.

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 was too toxic for human consumption. However, it was deemed too toxic for human consumption. In 1820, quinine was isolated from the cinchona tree and used as a treatment for fever and chills by the indigenous people of Peru. 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.

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

| Paper | Number of cases |
|-------|----------------|
| 1 | Ratliff, NB, et al. | 2 |
| 2 | Iglesias Cubero, G, et al. | 1 |
| 3 | Walsh, DS, et al. | 2 |
| 4 | C. August, et al. | 1 |
| 5 | Baguet, JP, et al. | 1 |
| 6 | Cervera, A, et al. | 1 |
| 7 | Roos, JM, et al. | 3 |
| 8 | Teixiera, RA, et al. | 1 |
| 9 | Freihage, JH, et al. | 1 |
| 10 | Nord, JE, et al. | 2 |
| 11 | Keating, RJ, et al. | 1 |
| 12 | Naqvi, TZ, et al. | 1 |
| 13 | Reffelmann, T, et al. | 1 |
| 14 | Costedoat-Chalumeau, N, et al. | 1 |
| 15 | Soong, TR, et al. | 2 |
| 16 | Cotonone, J, et al. | 1 |
| 17 | Fragasso, G, et al. | 1 |
| 18 | Manohar, VA, et al. | 1 |
| 19 | Magnusson, I, et al. | 1 |
| 20 | Lee, JH, et al. | 1 |
| 21 | Muthukrishnan, P, et al. | 1 |
| 22 | Hartmann, M., et al. | 1 |
| 23 | Bae, SM, et al. | 1 |
| 24 | Azimian, M, et al. | 2 |
| 25 | Champion, S, et al. | 1 |
| 26 | Tönnesmann, E, et al. | 1 |
| 27 | Frustaci, A, et al. | 1 |
| 28 | Joyce, E, et al. | 1 |
| 29 | Verecke, A, et al. | 1 |
| 30 | Yogasundaram, H, et al. | 1 |
| 31 | Lopez-Ruiz, N, et al. | 1 |
| 32 | Abdin, A, et al. | 1 |
| 33 | Tselios, K, et al. | 1 |
| 34 | Sabato, LA, et al. | 1 |
| 35 | Chatre, C, et al. | 1 |
| 36 | Pavisic, N, et al. | 1 |
| 37 | Di Girolamo, F, et al. | 1 |
| 38 | Yogasundaram, H, et al. | 1 |
| 39 | Dogar, MU, et al. | 1 |
| 40 | Tselios, K, et al. | 7 |
| 41 | Zhao, H, et al. (REF: 49) | 2 |
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 those 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 [33]. 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. Vacular myopathy may also be seen in connective tissue diseases like SLE and in steroid induced myopathy [67]. 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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