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CASE REPORT

Favorable Outcome in a Primigravida with Hydroxychloroquine (Hcq) Induced (Most Likely) Cardiomyopathy: a case report and literature review

Short title: *Outcome in a Primigravida with Hcq-Induced Cardiomyopathy.*

Nighat **Fatima** [1,*], Lama Khalid **Hamza** [1], Arif Abdullatif Abdulrahman **Almulla** [2], Ayesha **Salman** [1]

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[1] Department of Obstetrics and Gynaecology, Dubai Hospital, Dubai Health Authority, Dubai, UAE.

[2] Department of Cardiology, Dubai Hospital, Dubai Health Authority, Dubai, UAE.

*** Corresponding author:** Nighat **Fatima**, Department of Obstetrics and Gynaecology, Dubai Hospital, Dubai Health Authority, Dubai, UAE. Email: nighatdxb79@gmail.com. ORCIDs: 0000-0001-6436-8902

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ABSTRACT

Background. HCQ-induced cardiomyopathy occurs due to prolonged therapy with HCQ. For favorable outcome prompt diagnosis, immediate discontinuation of HCQ, and use of suitable alternatives is necessary for comprehensive management.

Case presentation. Here we report a case of cardiomyopathy most likely due to prolonged HCQ therapy in a 29-years-old primigravida with well-controlled discoid lupus and hypertension and no other known cardiac illness. The patient was successfully managed with standard drugs used for heart failure. She was treated by a multidisciplinary team involving obstetricians and cardiologists. Repeat echocardiogram and ultrasonography was used to assess the wellbeing of mother and fetus. Elective caesarean section at 34 weeks of gestation was opted by the team.

Conclusions. Both the mother and baby had favorable outcomes and discharged on 3rd postoperative day. Follow up after two weeks revealed well compensated cardiac status.

Keywords

Cardiomyopathy; heart failure; pregnancy; ultrasonography

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Introduction

Around 1-4% women suffer from cardiovascular diseases in the antenatal period, considered to be a common non-obstetric cause of maternal death around the world [1]. In the United Kingdom alone, cardiovascular diseases contributed to 2.4/100000 maternal deaths between 2013 and 2015 [1]. Hydroxychloroquine, which is frequently prescribed chronically for management of a number connective tissue disorder including discoid lupus, is known to cause a number of adverse effects including cardiomyopathy [2].

In recent years, improved maternal care has led to better outcome for both mother and fetus in many complicated cases [3]. Multidisciplinary approaches constituting obstetricians, cardiologists, anesthesiologists and neonatologists are recommended for effective management of such pregnancies. Many complications can be prevented taking precautionary measures. A major predictive factor to analyze stillbirths is to understand the pulsatility index of uterine arteries in second trimester and its correlation with histopathology such as maternal vascular malperfusion (MVM) [4]. It has also been reported that there are differing outcomes of the relationships between assisted reproductive technologies (ART) and developing infantile cerebral palsy (CP). These outcomes depend on various factors such as preterm birth and multiple pregnancies [5].

Case Presentation

A 28-years-old primigravida female patient with a past history of discoid lupus, essential hypertension with proteinuria since 2014, was on follow up at the rheumatology outpatient department (OPD). The patient was stable on alternative doses of 200 mg and 400 mg of hydroxychloroquine per day and Amlodipine/Valsartan of 5 mg/160 mg once daily.

The patient attended the EPAU (Early pregnancy Assessment Unit) clinic at 8 weeks of gestation and was advised to take methyldopa (250 mg/BD). She was referred to both obstetrics and rheumatology clinics. At 12 weeks of gestation, she visited a private hospital with complaints of acute onset shortness of breath and was diagnosed with acute heart failure, confirmed by chest X-ray showing pulmonary edema. She was started on beta-blockers and loop diuretics. She did not have any past history of orthopnea, dyspnea or previous cardiac events. Echocardiogram revealed severe global hypokinesia with left ventricular ejection fraction reported to be 15-20%. Subsequently, the patient visited emergency of Dubai Hospital with shortness of breath and was admitted in the cardiology ward for evaluation and management. Repeat echocardiogram revealed a left ventricular end diastolic dimension (LVEDD) of 6.2 cm (upper limit of normal is 5.2 cm) and body surface area corrected of 3.7 cm/m^2 (upper limit of normal is 3.1 cm/m^2) with severe eccentric left ventricular hypertrophy. The overall left ventricular systolic function was severely impaired with 20% left ventricular ejection fraction (LVEF). She had restrictive left ventricular filling pattern (E velocity of 1.45 m/s, A velocity of 0.35 m/s, deceleration time of 108 ms, E/e'18). There was evidence of moderate-to-severe secondary central mitral (MR) and mild tricuspid regurgitation. Her pulmonary artery systolic pressure was 40 mmHg and mean pulmonary artery pressure was 28 mmHg, assuming a right atrial pressure of 10 mmHg. Global Longitudinal Strain (GLS) was -9.8%. Bed side ultrasound examination by the Fetal Maternal Medicine unit revealed single viable fetus with crown-rump length (CRL) of 71.2 mm corresponding to the gestational age and posterior placenta. Ultrasound scan also revealed normal nuchal translucency (2.3 mm) with prominent nasal bone, single umbilical artery, and bilateral uterine artery notching with the pulsatility index (PI) at 95 percentile. She underwent blood investigations to rule out other causes of cardiomyopathies, all of which came back negative. She had no family history of heart disease or cardiomyopathies. A multidisciplinary team meeting involving cardiologists, rheumatologists and obstetricians was conducted. The team counseled the patient regarding the life risks associated with continuation of pregnancy and the chances of further deterioration of cardiac function as the pregnancy continues. The patient requested for discharge against medical advice (DAMA) to seek second opinion regarding the cardiac risks associated with continuation of pregnancy. She was

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discharged with the advice of taking azathioprine 75 mg once daily, bisoprolol 5mg twice daily, hydralazine 50 mg three times daily, furosemide 20 mg once daily and aspirin 75 mg once daily. She was also advised to immediately discontinue hydroxychloroquine.

On the next visit, the couple decided to continue the pregnancy with complete understanding of all the associated risks of progressive heart failure, need for termination of pregnancy if her condition deteriorates, and the risk of preterm delivery. Hence the patient was categorized as high-risk pregnancy and advised to follow up with cardiology outpatient department (OPD) monthly with repeat echocardiograms to monitor cardiac chamber size, LVEF, filling pressures, and degree of MR. The patient was also advised to consult with the antenatal clinic (ANC) and rheumatology OPD at an interval of 2 weeks. In addition, the patient was advised to attend the emergency immediately if shortness of breath, fatigue, and difficulty in walking occurred. Detailed anomaly scan scheduled at 20 weeks were within normal limits with umbilical cord with 3 vessels. Glucose tolerance test (GTT) results were within normal limits. Non-invasive prenatal test (NIPT) revealed low risk for trisomies. Although the patient was advised to take prophylactic enoxaparin sodium injection, she refused. Patient's heart failure medications were further optimized by increasing her hydralazine to 75 mg three times daily. Repeat echocardiogram after 2 months revealed improvement in LVEF to 30-35%, LVEDD indexed to 3.0 cm/m^2, reduction in MR to mild, normalization of LV filling pressures with normal pulmonary pressures. During routine follow up visit at rheumatology OPD at 32 weeks of gestation, abnormal Doppler was noted (with 13.5 percentile), normal amniotic fluid and intermittently absent umbilical artery Doppler. Ductus venosus a wave was present. Umbilical artery Doppler study showed high resistant pulsatile index (PI) measured above 95 percentile. Middle cerebral artery (MCA) PI was measured to be below 5th percentile and cerebroplacental ratio was measured to be less than 1 (0.981).

The multidisciplinary team meeting was held to decide the timing of elective delivery considering her impaired cardiac performance and underlying cardiomyopathy. While deciding the date of elective caesarean section, the team considered the risk-benefit ratio and decided re-evaluate cardiac condition. The patient was admitted to receive steroid (to facilitate fetal lung maturity) and echocardiogram was repeated which revealed stable LVEF between 30-35%, LVEDD index of 3.0 cm/m^2, normal LV filling pressures, trace MR, no TR with no evidence of pulmonary hypertension, and GLS of -13.4%. The patient was categorized to have well compensated cardiac status that was showing progressive improvement rather than deterioration. The team decided to perform elective caesarean section under spinal anesthesia at 33 weeks of gestation. A male baby weight 1.55 kg with Apgar score of 10 was delivered. The patient was shifted to critical care unit (CCU) and discharged in stable condition on the 3rd postoperative day. Follow up visit after 2 weeks revealed well compensated cardiac status without any cardiac symptoms and breast feeding.

The patient was advised for repeat echocardiogram after 3 months to further evaluate reverse remodeling of her left ventricle. She was advised to stop breastfeeding after 6 months and visit postnatal clinic to discuss contraception. Her echocardiogram done after 3 months post-delivery showed LVEF of 35-40%, LVEDD of 5.3 cm and LVEDD indexed of 2.9 cm/m^2, normal LV geometry and mass, normal LV filling pressures, trivial MR, trivial TR with no evidence for pulmonary hypertension, and GLS of -13.7%. After 6 months of breastfeeding, she was planned to be switched from hydralazine to Entresto (Valsartan/Sacubitril) to maximize the LV reverse remodeling.

Discussion

Drug-induced cardiotoxicity is a critical challenge for physicians [6,7]. Although the cardiotoxic side-effects of chemotherapy are well-documented, the toxic effects of several drugs on the cardiac system have not been studied in-depth. Hydroxychloroquine (HCQ) is a common antimalarial drug, also used for treatment of connective tissue disorders like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and discoid lupus erythematosus (DLE) [8].

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However, long-term HCQ therapy has several side-effects such as retinopathy, neuropathy, and cardiotoxicity [8]. Furthermore, HCQ can accumulate in tissues where it can remain for a long time and suppress lysosomal function. Lysosomal storage disorders are well-known to contribute to cardiovascular disease.

Long term exposure of HCQ is an important factor associated with cardiotoxicity. The duration of HCQ therapy can vary from several months to more two decades, with a potential risk to the environmental and genetic aspects of an individual. Large volume of distribution and long half-life of HCQ results in increased risk of damage to vital organs. In addition, HCQ is a cationic molecule with a potential to traverse cell membranes and bind to phospholipids. This can directly suppress the activity of phospholipases and lysosomal hydrolase enzymes. Consequently, vesicle fusion and exocytosis are suppressed leading to lysosomal storage diseases. Pathological accumulation of metabolites in the cardiac myocytes and the conduction system can lead to cardiomyopathy and conduction defects [8-10]. Interestingly, HCQ has been reported to benefit in maternal, fetal, and neonatal complications arising due to antiphospholipid syndrome (APS) in women [11]. APS is characterized by presence of antiphospholipid antibodies and causes pregnancy losses in about 10-15% of APS patients [12]. Due to its reported safety in pregnancy, HCQ is used extensively in pregnant patients for treatment of APS associated with SLE and/or other autoimmune diseases [13].

Herein we report a case of acute decompensated cardiac failure in an antenatal mother without any past history of adverse cardiac events. Echocardiogram suggested decompensated cardiac function with eccentric left ventricular hypertrophy. The burden of HCQ cardiomyopathy remains to be underdiagnosed and challenging but preventable health issue.

In a case report documented by Yogasundaram and his colleagues, a 59-years-old women suffering from rheumatoid arthritis was taking 200 mg of HCQ for 14 years [10]. Besides hypertension and atonic seizures, the patient presented to the emergency department with symptoms of heart failure. Echocardiogram revealed diastolic dysfunction, biatrial enlargement and left ventricular severe concentric hypertrophy. Endomyocardial biopsy was performed to identify the underlying cause of heart failure. It identified prolonged HCQ exposure as the underlying cause. Although HCQ was stopped immediately, the patient passed away.

In another case report by Nadeem, a case of prolonged HCQ-induced cardiomyopathy has been documented. The patient was under prolonged HCQ therapy for scleroderma for around 20 years [14]. Following a history of myocardial infarction (managed successfully), the patient was diagnosed with heart failure with preserved ejection fraction. Endomyocardial biopsy revealed findings (myeloid and curvilinear bodies) which confirmed HCQ-induced cardiomyopathy. The patient received cardiac transplant and was doing well till the publication of the said case report.

In another similar case report by Zhao et al, HCQ-induced cardiomyopathy was reported in twin sisters both suffering from SLE [15]. Endomyocardial biopsy was used for diagnosis confirmation in the first sister who presented to the emergency department with heart failure. She was successfully managed medically with angiotensin inhibitors, and milrinone following immediate discontinuation of HCQ. The second sister, who already had multivessel coronary artery disease and chronic stable angina, presented with new onset symptoms of heart failure. Biopsy revealed HCQ-induced cardiomyopathy in the second sister too. Despite immediate discontinuation of HCQ and medical management of heart failure, she died due to sudden cardiac arrest.

This is one of the first articles to suspect and report HCQ-induced cardiomyopathy in a pregnant woman under long-term HCQ therapy for management of connective tissue disorder (DLE). However, unlike other reports, endomyocardial biopsy was not performed to confirm the diagnosis in our case.

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Strength of the study: This is one of the first cases to report HCQ-induced cardiomyopathy in a pregnant woman who was under long-term HCQ treatment for DLE.

Limitations of the study: Endomyocardial biopsy was not performed to confirm the diagnosis of HCQ-induced cardiomyopathy.

Conclusion

HCQ-induced cardiomyopathy can be managed successfully if diagnosed and managed early and appropriately. Physicians should remain vigilant about symptoms of heart failure in patients with prolonged history of taking HCQ.

Compliance with Ethical Standards

Authors contribution:

N.F.: Conception and design, acquisition of data or analysis and interpretation of data, drafting and revising the article; L.K.H.: Validation; A.A.: Supervision and Writing – review & editing ; A.S.: Validation.

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