No histologic evidence of foetal cardiotoxicity following exposure to maternal hydroxychloroquine

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ABSTRACT

It is currently recommended that hydroxychloroquine (HCQ) be maintained during pregnancy in patients with systemic lupus erythematosus. Recent data suggest that this Toll-like receptor inhibitor may also reduce the recurrence rate of anti-SSA/Ro associated congenital heart block (CHB). This case report describes a unique situation in which a CHB-afflicted, HCQ-exposed pregnancy was electively terminated. The heart did not reveal any characteristic features of cardiotoxicity, providing further evidence supporting the safety of foetal exposure to HCQ.

Case report

Congenital heart block (CHB), a manifestation of neonatal lupus, affects 1–2% of foetuses exposed to maternal autoantibodies to Ro/SSA- La/SSB ribonucleoproteins (1). Clinical disease is usually identified at 18–24 weeks of gestation. The recurrence rate in subsequent pregnancies is 17–20% (2, 3). The mortality rate approaches 20%, and >70% of survivors require a pacemaker (4). Based on autopsy, it is hypothesised that there is an initial and transient period of antibody deposition in the foetal heart, with inflammation rapidly followed by a fibrosing cascade resulting in irreversible scarring of the AV node (5). Third degree block is irreversible, suggesting the need for a preventative approach. HCQ is an attractive candidate given *in vitro* data supporting its inhibition of macrophage Toll-like receptor signalling and subsequent release of inflammatory and fibrosing cytokines (6). HCQ has significantly reduced the rate of CHB in SLE mothers (7) and has been shown to reduce the risk of recurrence (8).

HCQ is considered safe in pregnancy (9, 10). However, long-term treatment with HCQ can cause a rare but potentially fatal cardiac toxicity in humans (11). Cardiac complications may manifest as congestive heart failure (CHF), hypertrophic and/or restrictive cardiomyopathy, and conduction disorders such as bundle-branch block and complete heart block (11, 12). HCQ-induced cardiomyopathy based on light microscopy includes vacuolar myopathy and degeneration of myocytes. On electron microscopy, myelin figures (myeloid bodies), curvilinear bodies, abundant secondary lysosomes, and megamitochondria have been reported (13, 14). Although unlikely, cardiotoxicity in foetuses exposed to HCQ might be a concern given its now widespread use in pregnancies of mothers with SLE to manage disease activity and prevent flares and, more recently, to reduce the recurrence rate of CHB (8).

A 31-year-old, clinically asymptomatic pregnant woman with anti-Ro52 and Ro60 had a previous pregnancy complicated by CHB. She had not taken HCQ during that pregnancy. Prior to the current pregnancy she was maintained on HCQ 200mg daily. At 6 weeks gestation, the dose was increased to 400 mg daily. Serum HCQ levels were monitored and at 13 weeks were 1522 ng/ml and at 19 weeks 2036 ng/ml.

The initial foetal echocardiogram performed at 18 weeks gestation was normal without evidence of AV block, valvulopathy, EFE, or effusion. At 19 weeks the echocardiogram demonstrated sinus rhythm at 120 bpm with type I 2nd degree block (Wenckebach) and periods of 3rd degree block. Other notable findings included increased echogenicity of the atrial septum and AV junction, left ventricular endocardial fibroelastosis (EFE), mild tricuspid insufficiency, and a small pericardial effusion. Dexamethasone 8 mg and IVIG 400 1g/kg were administered the same day. Repeat echocardiogram two days later demonstrated complete block with a rate of 40 bpm. Given rapid and refractory progression, the family elected to terminate the pregnancy.

The foetal heart was obtained for postmortem testing with permission of the family. Multiple sections were taken of the foetal heart for histopathological analysis. Areas outside the conducting system of the heart were unremarkable, demonstrating glycogen-filled myocytes without evidence of hypertrophy and rare mitoses. The conducting system demonstrated extensive histopathology. The area of the AV node was extensively calcified with a marked increase in inflammatory cells (primarily macrophages and lymphocytes). It

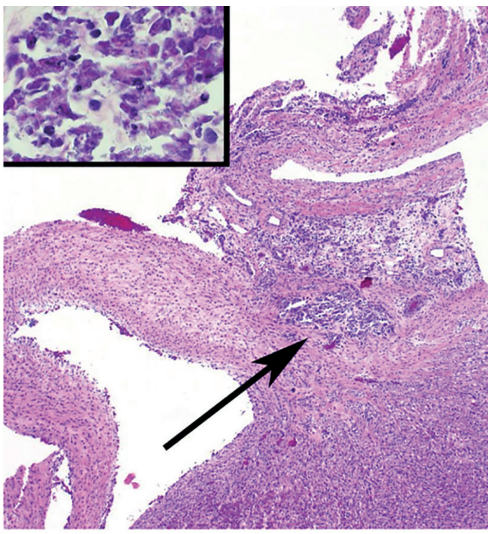
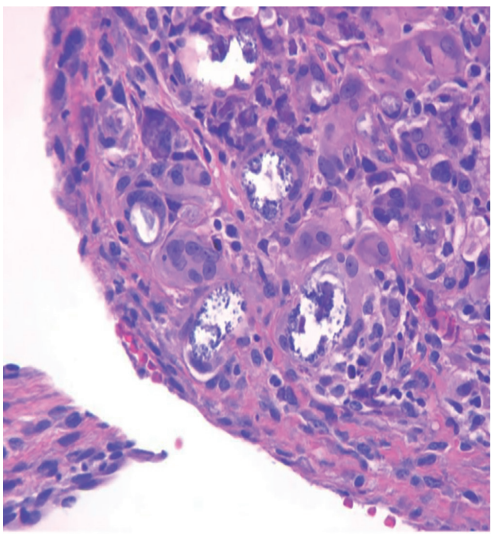
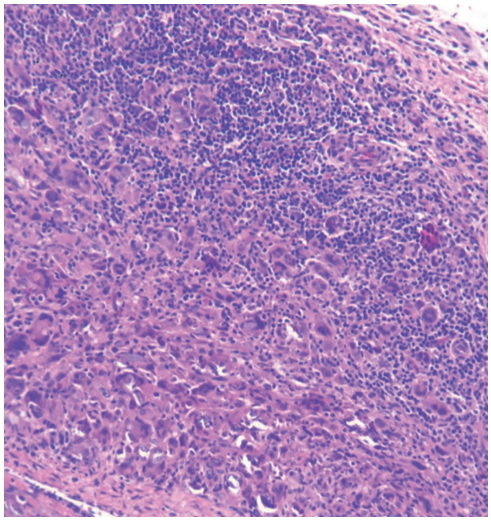


Fig. 1A. Image of the AV nodal area of the heart. A black arrow points to residual AV nodal tissue demonstrating extensive metastatic calcification of the myocytes (inset) (Haematoxylin & Eosin, original magnification 20x, 400x inset).



1B. Area of conducting system injury demonstrating vacuolated cells with stippled pattern of calcification being enveloped by multinucleated giant cells. Numerous giant cells are seen in this image (H&E, original magnification 400x).



1C. Zonal infiltration and destruction of the AV nodal region. A predominately lymphocytic infiltrate is seen in the top half to right side of the image while a more giant cell and macrophage rich infiltrate is seen on the bottom left area. (H&E, original magnification 100x).

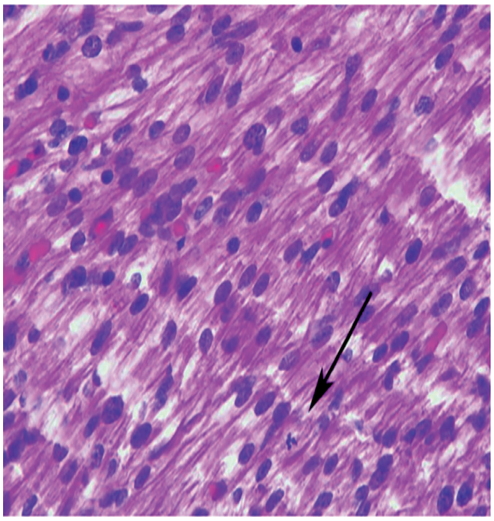


Fig. 2. Area of uninvolved myocardium. A mitosis is noted (arrow), but no reddish-brown granules typical of HCQ cardiomyopathy are present (H&E, original magnification 400x).

appeared that the conducting cardiomyocytes themselves were metastatically calcified in place (Fig. 1A). This has been reported in other cardiac diseases, often with electrolyte imbalance (15). While most cells were fully calcified, rare cells had a stippled pattern of calcification (Fig. 1B). There was an extensive and zonal polymorphous inflammatory cell infiltration comprised of macrophages, lymphocytes and rare plasma cells (Fig. 1C). Multinucleated giant cells were a prominent feature in some areas of the infiltrate (Fig. 1B-C). Areas of myocyte loss, loose fibrosis, and inflammation were noted in the AV node proper and along the conduction system in the base of the heart.

HCQ cardiotoxicity was considered. HCQ is known to rarely cause the development of myelin figures in non-dividing adult cardiac myocytes, usually after an extended duration of therapy achieving a cumulative dose >200 grams (13). Consistent with the short duration of treatment and the proliferative nature of the cardiomyocytes, reassuringly, there was no evidence of myelin figures, which would be noted on light microscopy as reddish-brown granules (Fig. 2) (14). The cumulative dose <45 grams, the absence of HCQ histopathologic findings, and the extensive inflammatory destruction/calcification of the AV node strongly suggest HCQ cardiotoxicity had no role in the foetal demise.

Discussion

This case illustrates that HCQ does not invariably prevent CHB and is consistent with the clinical observation that this approach will not be effective in all anti-SSA/Ro exposed foetuses (7, 8). As in other diseases, preventive measures are not always absolute. While the correlation of efficacy and maternal HCQ levels remains unknown, the maternal levels of HCQ in this case were well within those supportive of efficacy in adults, ruling out the possibility of maternal non-compliance. It may be that, in certain foetuses, environmental contributions overwhelm efficacy, the threshold effect on macrophage TLR signalling is not reached *in vivo*, or additional factors confer cardiac toxicity not responsive to this prophylactic approach. The pathway to fibrosis of the AV node may not be uniform in each case and the contributions of foetal genetic factors conferring protection and/or risk remain unknown. As more is learned about the pathogenesis of CHB, it is hoped that identifying foetuses most likely to benefit from HCQ will become evident.

Accordingly, the absence of efficacy in this one situation should be balanced against the weight of evidence in favour of benefit. Leveraging this informative autopsy to rule out HCQ cardiotoxicity bolsters the safety of HCQ use during pregnancy not only to prevent CHB but maternal flares of SLE during pregnancy in general. Presently, we await the results of a large prospective study (ClinicalTrials.gov NCT01379573). For pregnant women with SLE taking HCQ for disease management, this case is reassuring.

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