Restrictive cardiomyopathy caused by chloroquine

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Abstract
A 59 year old white woman who had been treated with chloroquine phosphate for 25 years presented with signs of congestive heart failure and was diagnosed as having restrictive cardiomyopathy by non-invasive methods. Electron microscopy of a biopsy specimen of skeletal muscle showed lesions compatible with chloroquine myopathy. The patient died five weeks after presentation. Electron microscopy of heart tissue showed similar lesions to those of the skeletal muscle.

Chloroquine is an antimalarial agent that is often used to treat collagen and dermatological disorders. The toxic side effects in humans are retinal lesions, neuromyopathy, and cardiomyopathy.1-3 Ratliff et al reported on the diagnosis of chloroquine cardiomyopathy by right and left cardiac catheterisation followed by endomyocardial biopsy.4 We report the findings in a patient who had been treated with chloroquine phosphate for 25 years and presented with signs of congestive heart failure.

Case report
A 59 year old woman who had been treated with chloroquine phosphate (250 mg/day) for 25 years because she had discoid lupus erythematosus was admitted to our hospital with signs and symptoms of congestive heart failure. A year before admission she had had symptomatic complete heart block requiring a permanent pacemaker. Physical examination showed a dyspnoeic woman weighing 42 kg, with a raised jugular venous pressure trace showing a dip and plateau configuration, blood pressure 100/80 mm Hg, no cardiac murmurs, bibasilar pulmonary rales, and hepatomegaly with ascites and ankle oedema. The neurological examination showed weakness and atrophy in the proximal muscles of the arms and legs. The chest x ray showed cardiac enlargement with interstitial pulmonary oedema, and the electrocardiogram showed a pacemaker rhythm. The full blood count was normal and there were no markers for collagen disease. A cross sectional thoracic echocardiogram showed combined right and left ventricular wall hypertrophy, reduced cavities and fractional shortening of 42% with brighter and speckling of the left ventricle muscle. Both atria were dilated. There were no or pericardial anomalies, however (fig 1). A biopsy specimen of the crural muscle was taken while she was in hospital, and when she died 5 weeks later her family permitted postmortem examination of the heart and lungs.

The heart was pale and rigid (weight 300 g) with concentric hypertrophy, without thrombus, of both ventricles and both atria. There was no evidence of valve disease or of coronary and pericardial abnormalities. Electron microscopy in all muscle samples (both skeletal and cardiac) showed considerable disruption of normal muscle fibre architecture, with loss of z lines and myosin filaments. The most striking finding was the abundance of curvilinear bodies, lysosomes, myeloid bodies, and glycogen granules (fig 2). The curvilinear bodies were located between myofibrils and perinuclear areas. Each body was membrane bound and contained closely grouped curvilinear shapes. The myeloid bodies and lysosomes were sparse in the cytoplasm of some cells and elsewhere were contained within vacuoles together with numerous glycogen granules.

Discussion
Experimental studies in rabbits and in biopsy specimens of human endomyocardium have established the toxicity of chloroquine in cardiac muscle. In humans the clinical features
were changes in the T wave, conduction abnormalities, and restrictive cardiomyopathy.\(^4^5\) Our patient presented with symptomatic complete heart block a year before admission. This required a permanent pacemaker. She remained symptomfree for a year. Then she presented with progressive heart failure with evidence of a restrictive pattern in the jugular venous pulse and in the cross sectional echocardiogram. Others have diagnosed restrictive myocardopathy on the basis of right and left cardiac catheterisation and endomyocardial biopsy, which showed curvilinear and myeloid bodies on electron microscopy examination.\(^4^5\) In our patient we diagnosed a restrictive cardiopathy by non-invasive methods because the patient’s condition did not permit haemodynamic studies. Histopathological examination of the biopsy specimens of skeletal muscle and heart muscle were similar: both contained myeloid and curvilinear bodies.

Chloroquine is regarded as an amphiphilic drug or cationic amphiphilic agent. It has been used as a model for investigating intracellular drug storage. Both in vivo and in vitro chloroquine induces the accumulation of phospholipid, mannose, and glucosyl residues in muscle cells. The lamellar and curvilinear bodies are believed to be caused by phospholipidosis.\(^6^7\)

Two principal mechanisms have been proposed for phospholipid storage by chloroquine. The first is that chloroquine is accumulated in lysosomes, causing a rise in intralysosomal pH. When the pH rises above certain limits the activities of most lysosomal hydrolases are inhibited. Subsequently phospholipid, glycogen, myeloid, and curvilinear bodies accumulate.\(^2^4^\) The second mechanism proposed is that chloroquine binds to lysosomal enzymes, resulting in reduced phospholipid degradation. Accumulations of phospholipid and mannose molecules acting as an anchor to bind protein molecules to membranes would result in the formation of myeloid and curvilinear bodies.\(^7\)

We conclude that chloroquine cardiomyopathy can be diagnosed by the combination of a restrictive pattern, established by non-invasive methods, together with the results of skeletal muscle biopsy.

We thank Mr D Wallace for his help in writing the paper in English and Mrs Patri González for secretarial assistance and the Electron Microscopy Unit of Oviedo University.

This work was supported by Grant SAL 91-0634 from CICYT.

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