Cardiac Damage from Chronic Use of Chloroquine. A Case Report and Review of the Literature

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Chloroquine has been widely used in rheumatological treatment, but potential severe side effects require careful follow-up. Cardiac damage is not a common consequence, but its clinical relevance has not yet been described.

We report the case of a 58-year-old woman with rheumatoid arthritis, in whom chronic chloroquine use resulted in major irreversible cardiac damage. She presented with syncopal episodes due to complete atrioventricular block confirmed by electrophysiological study whose changes were concluded to be irreversible and a permanent pacemaker was indicated. Endomyocardial biopsy was also performed to search for histopathological and ultrastructural cardiac damage. We also reviewed the 22 cases of chloroquine-induced cardiopathy described to date as well as its pathophysiology.

The antimalarial agent chloroquine has been widely used in rheumatological treatment, mainly in rheumatoid arthritis, not only due to its antiinflammatory properties, but especially because of favorable interference in natural disease evolution. However, we must consider that severe side effects such as retinopathy and neuromyopathy might occur, requiring careful follow-up [1].

Cardiac damage, such as cardiomyopathy and conduction system disturbances, are regarded as uncommon consequences of chloroquines´s toxicity [2]. Nevertheless, the clinical relevance of these findings has not yet been described.

We present a case in which chloroquine used as chronic therapy for rheumatoid arthritis therapy resulted in major cardiac damage.

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Clinical and therapeutic approaches that involved prophylactic procedures for sudden cardiac death are the main contribution of this report.

Case Report

We report the case of a 58-year-old woman with rheumatoid arthritis, diagnosed 13 years ago. She had been on chloroquine diphosphate (250mg/day) for the last 9 years. She was admitted to the emergency room at the Heart Institute of the School of Medicine of São Paulo University (InCor) with several episodes of presyncope and syncope within a 15-day period. No other previous cardiovascular symptoms were reported, and, except for the 31-bpm cardiac rate, her physical examination was normal on admission. The electrocardiogram showed complete atrioventricular block, with right bundle-branch block QRS morphology and a QT interval = 700 ms. (fig. 1) Temporary pacemaker implantation was undertaken with no complications.

An additional examination with electrocardiography showed AV conduction recovery with intraventricular conduction alternance (right and left bundle-branch blocks) and QT interval normalization (fig. 2 - A, B, and C). The temporary pacemaker was kept with a 40-ppm rate demand until full evaluation was performed.

Blood electrolyte dosages (calcium, phosphorus, magnesium, sodium, and potassium) were normal. Antinuclear antibody search was negative and rheumatic activity blood tests were abnormal (rheumatoid factor 320UI/mL, blood sedimentation rate 55mm), although no clinical signs existed of rheumatic disease activity.

The echocardiogram revealed normal cardiac function and cavity dimensions with a redundant interatrial septum.

Twenty-four-hour Holter analysis performed 2 weeks after admission showed sinus rhythm with rare premature ventricular and atrial beats. Cardiac rate ranged between 30 to 60 bpm with a PR interval of around 200 ms and alternate right and left bundle-branch blocks (RBBB and LBBB).

Electrophysiological study performed in sinus rhythm

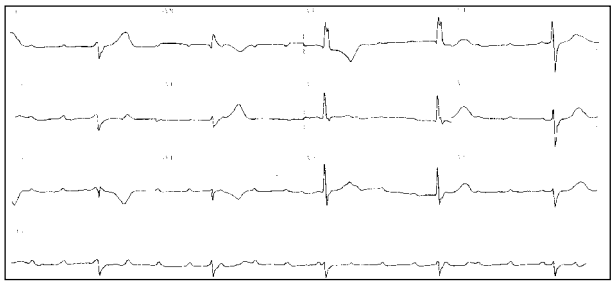

Fig. 1 - Electrocardiogram at admission: complete atrioventricular block with right bundle branch block morfology.

with first degree AV block and RBBB showed a 75 ms AH interval and a 69 ms HV interval varying up to 100 ms after procainamide infusion (infra-His block) (fig. 3). Arrhythmias were not induced.

Coronariography was normal. Endomyocardial biopsy was performed for histopathological analysis. The cardiomyocytes were enlarged and some of them had marked irregular cytoplasmic vacuoles. Electron microscopy showed numerous round lamellar bodies with concentric lamellar

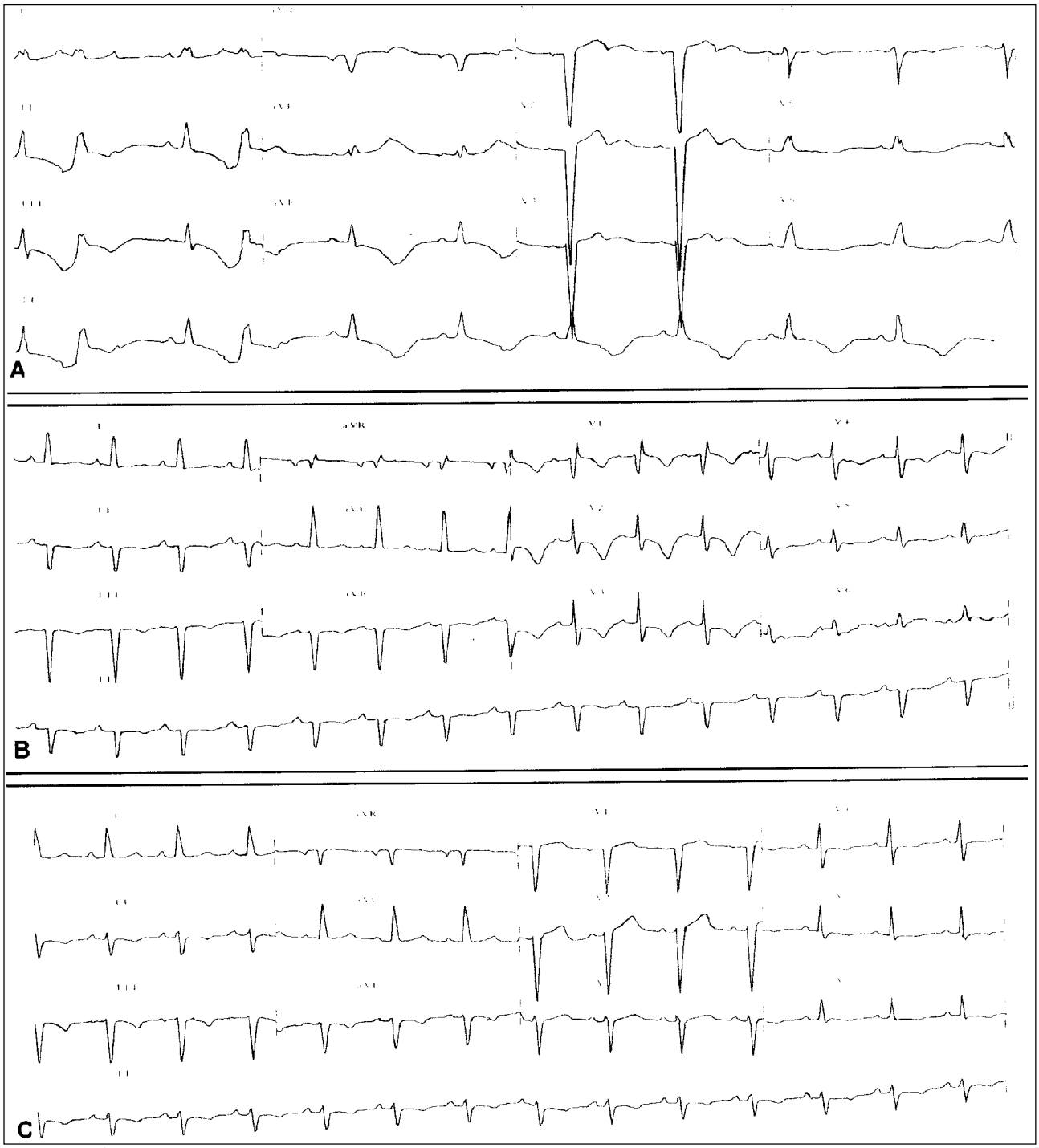

Fig. 2 - Periods of intraventricular conduction alternance - LBBB (A), RBBB (B) and no branch block (C).

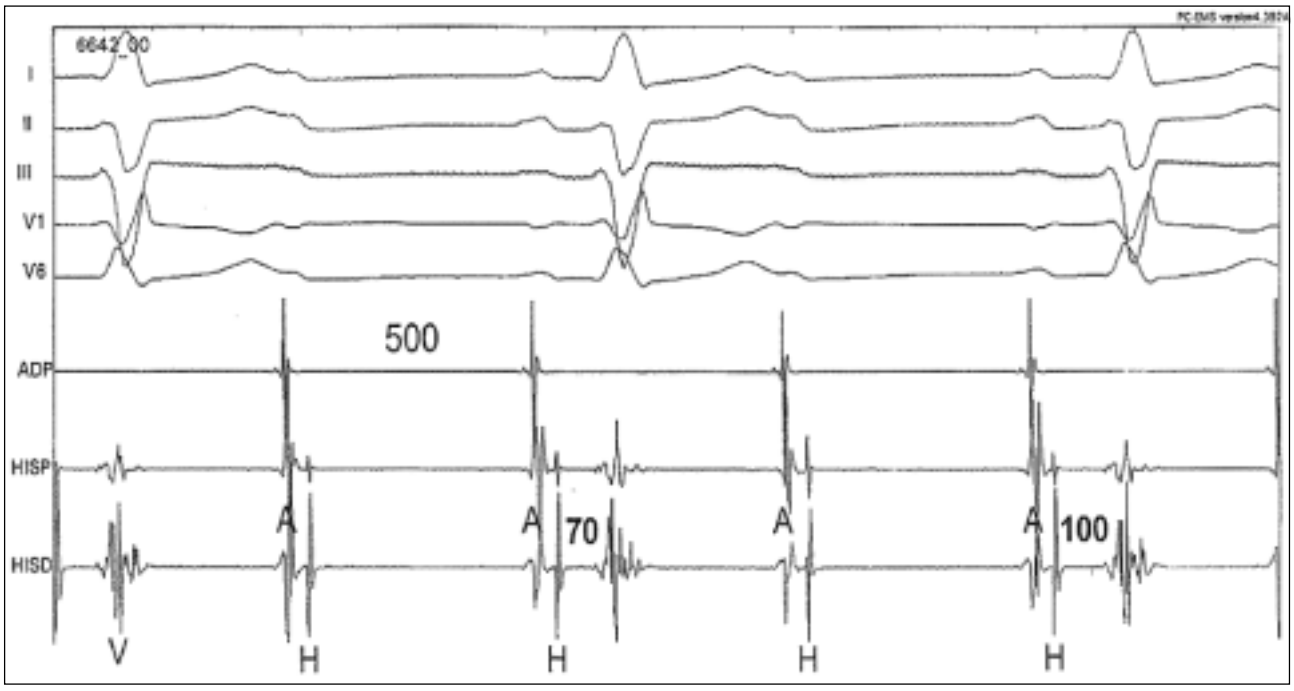

Fig. 3 - Electrophysiological study showing infra-His block.

disposition, similar to myelin bodies, and curvilinear bodies in the cytoplasm of some cardiomyocytes (fig. 4).

The alteration in the conduction system was concluded to be irreversible and secondary to the chloroquine's toxicity. Due to the high risk of sudden death as defined by the electrophysiologic study, a permanent atrioventricular pacemaker was indicated.

Discussion

The long-term use of chloroquine may induce restrictive hypertrophic (biventricular) or dilated cardiomyopathy. Atrioventricular nodal or His system malfunction has been described since the 1970s [3-15].

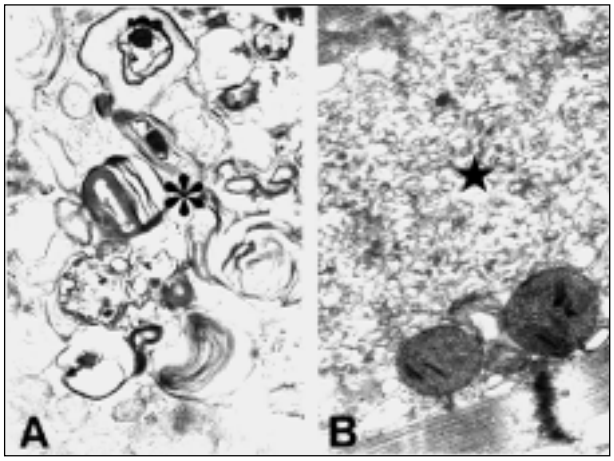

Fig. 4 - Transmission electron microscopy. Numerous round lamellar bodies are present in the cytoplasm of the cardiomyocytes (A, asterisc). Some cardiomyocytes also have curvilinear bodies in the cytoplasm (B, star). A, x 15.000; B, x 31.000.

Chloroquine, like amiodarone and chlorpromazine, inhibits phospholipase activity and induces cytoplasmic inclusion body formation. Both chloroquine and hydroxychloroquine are accumulated in lysosomes, directly inhibiting enzymatic activity, increasing lysosomal pH and causing protein inactivity [16,17].

Because of its properties, drug-induced arrhythmias and also atrial and ventricular antiarrhythmic effects have been described [16-25].

Major arrhythmias caused by chronic use of chloroquine have been related to a significant reduction in the cardiac ascent rate, increases in the potential length duration, and Purkinje fibers refractory period [17, 23-25].

The dosage and administration period have not been related to the side effects caused by chloroquine. Genetic alterations predisposing to cardiac toxicity have not been reported either [11,13]. Thus, the limits between reversible and irreversible pathological alterations are not known, although cardiac failure functional class improvement after drug withdrawal has already been described [17].

The most usual electrocardiographic alteration is fascicular block, which can lead to advanced types of atrioventricular block, generally associated with syncope [13]. Among 279 rheumatoid arthritis patients on chloroquine therapy, Jurik and Moller [26] have found only 4 first-degree AV-blocks.

Dense wall areas, especially in the septum, are the typical echocardiographic pattern [12].

The diagnosis of chloroquine cardiotoxicity is determined by endomyocardial biopsy. Electron transmission microscopy reveals numerous large secondary lysosomes containing a dense material with a lamellar structure, myelin figures, and curvilinear bodies in the cytoplasm of the car-

diomyocytes, with disorganization of the myofibrils [12,13,16]. Myocyte necrosis occurs especially in the interventricular septum, which explains the risk of atrioventricular block [10]. The pathological lesions can also be present in the skeletal muscles.

Only 22 chloroquine-induced cardiopathy cases have been described to date. Only one was male, and the average age at diagnosis was 55.8 years of age (range 27 to 81). Exclusive myocardiopathy with heart failure was present in 5 cases, 3 of them with hypertrophic cardiopathy and 2 with restrictive disease. Exclusive conduction system damage was reported in 5 cases, syncope being the most common clinical presentation. Eight patients underwent histopathological study by in vivo endomyocardial biopsy. Definitive pacemaker implantation was performed in 7 patients. Ihenacho et al [27] have described 12 AV-block cases among 30 patients with no other potential cause for conduction disease, and chronic chloroquine use resulting in cardiac disorders has also been described [2,10-15,28-35].

Our reported patient has shown many indications of chloroquine cardiotoxicity. However, diagnostic procedures have been performed under specific clinical conditions. The 24-hour cardiac monitoring (Holter), which pointed to a major cardiac limitation (bilateral intraventricular block), demonstrated clinical importance and indicated electrophysiologic study, which confirmed infra-His damage, leading to definitive pacemaker implantation.

The clinical-electrophysiological correlation has not been previously described. For the importance of the reported findings and the major AV conduction disturbances that have been observed, careful routine cardiac investigation and specific follow-up of antimalarial users are definitely indicated for the prevention of major cardiovascular events.

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