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CASE REPORT

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Cardiotoxicity after low-dose chloroquine antimalarial therapy

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Abstract Previous reports on antimalarial toxicity have only been related to long-term continuous treatments for nonmalarial indications, which require prolonged use of large doses, up to 1000 g or more every year. We describe a patient with recurrent malaria, prophylactically treated with low-dose chloroquine, who developed heart failure due to biventricular cardiac dysfunction. The right ventricle endomyocardial biopsy was suggestive of chloroquine toxicity. The heart failure improved after drug withdrawal. As a consequence, the potential for reversibility and the severity in undiagnosed cases of these toxic cardiomyopathies emphasize the importance of recognizing early signs of toxicity in order to withdraw antimalarials before the occurrence of life-threatening cardiac toxicity.

Key words Chloroquine · Cardiomyopathy · Heart failure · Toxicity · Endomyocardial biopsy

Introduction

Antimalarial agents, chloroquine (CQ), and hydroxychloroquine (HCQ), are used in long-term treatment of connective tissue diseases and dermatological disorders. The long-term use of these agents has been associated with toxicity including skin hyperpigmentation, blood dyscrasias, corneal deposits, retinopathy, encephalopathy, neuropathy, myopathy, and impairment of auditory function.[1] Cardiac complications, such as conduction disorders, myocardial hypertrophy, and cardiomyopathy have also been reported in long-term treatment and, to date, 32 cases have been reported in the literature.[2–27] However, previous reports on antimalarial toxicity have only been related to long-term continuous treatments for non-malarial indications, which require prolonged use of large doses, up to 1000 g or more every year. We describe a patient with recurrent malaria, who had been prophylactically treated with low-dose chloroquine and developed heart failure due to biventricular cardiac dysfunction. The right ventricle endomyocardial biopsy was suggestive of chloroquine toxicity. The heart failure improved after drug withdrawal.

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Case report

A 64-year-old Catholic missionary priest had a first malaria episode (*Plasmodium falciparum*) in 1997. At that time he was sojourning in Mozambique. Since then, when visiting malaria endemic regions, he was prophylactically treated with oral chloroquine (total dose 7.5 g). Notwithstanding, he suffered five relapses, the last of which was in December 2006 while he was again in Mozambique. On that occasion he was treated with chloroquine (total dose 1.5 g). The estimated total dose for prevention and therapy of acute attacks in 10 years was 15 g. In February 2007 the patient was admitted to our hospital owing to biventricular cardiac failure. Past medical history included diet-controlled glucose intolerance and grade 1 arterial hypertension, which had been treated with nifedipine. There were no other risk factors for coronary disease. Physical examination showed moderate peripheral edema. Biochemistry was normal except for mild sideropenic anemia. Normal results were obtained for ferritin and viral hepatic serological tests. Plasma concentration of N-terminal pro-brain natriuretic peptide (pro-BNP) was 1820 pg/ml. A 12-lead ECG showed right bundle branch block. Clinical conditions improved after treatment with enalapril, i.v. diuretics and, finally, carvedilol and trimetazidine.[28] A transthoracic echocardiogram showed a moderate biventricular dysfunction, with a

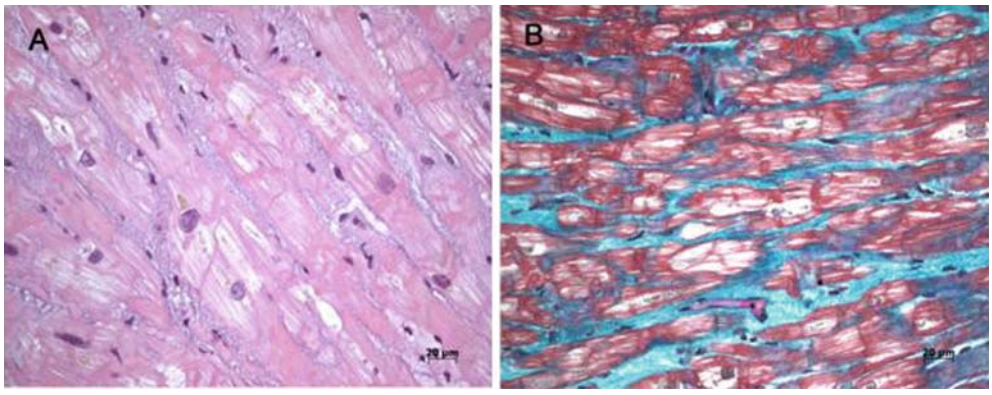

Fig. 1. Hematoxylin–eosin (**A**) and Masson's trichrome (**B**) stained sections of endomyocardial tissue show mild cellular enlargement with mild cytoplasmic vacuolization and focal interstitial fibrosis. *Bars*: 20 μm

left ventricular ejection fraction of 36%, tricuspid annular plane systolic excursion (TAPSE) of 13 mm, dilatation of the left atrium, mild mitral insufficiency, severe tricuspid insufficiency, with a derived systolic pulmonary pressure of 56 mmHg and Tei-index of 0.72. Dipyridamole myocardial perfusion scintigraphy did not show significant defects. Right ventricular endomyocardial biopsy showed cellular enlargement associated with mild perinuclear cytoplasmic vacuolization within some myocytes and moderate fibrosis (Fig. 1A,B). Although the light microscopic findings are nonspecific, and this degree of vacuolization can be seen in cases of idiopathic dilated cardiomyopathy of diverse causes, these pathological features associated with clinical findings and the patient's drug history strongly support the relation with chloroquine toxicity. Chloroquine was discontinued and the patient was advised to avoid malaria endemic regions. Subsequently, the patient was discharged, and since then he has been doing well and is asymptomatic. At a 9-month follow-up he showed an ejection fraction of 56%; TAPSE 24 mm, and derived pulmonary artery pressure of 30 mmHg. Plasma concentration of pro-BNP was 137 pg/ml. The echocardiographic Tei-index decreased to 0.42, yet it did not normalize, indicating a residual subclinical myocardial performance impairment,[29] which could however be relative to patient's age and history of arterial hypertension. The previously prescribed medical therapy was confirmed.

Discussion

To our knowledge, this is the first case of a patient, prophylactically treated with low-dose chloroquine for recurrent malaria, who developed heart failure due to biventricular cardiac dysfunction. Long-term chloroquine treatment can produce cardiac complications, such as cardiomyopathy, both restrictive and hypertrophic, and atrioventricular blocks or other conduction disorders due to lysosomal storage alteration. In fact, chloroquine toxicity seems to be restricted to patients receiving high doses or long-term treatment,[30] and it has been reported for treatments ranging from 7 months[14] to 25 years.[9] In pathological examinations[16,17] hypertrophy of myocardiocytes with heavily vacuolated cytoplasm and disorganization of the myofibrillar architecture has been found. Therefore, specific evidence of chloroquine cardiotoxicity would require electron microscopy, by showing dense residual bodies with folded membranous aggregates and curvilinear bodies. These changes are preferentially found in the cardiac septum,[31] and this might explain the possible involvement of the conduction system. In our patient, according to the results of endomyocardial biopsy, the cause of biventricular cardiac failure was likely due to chloroquine-induced cardiomyopathy. In fact, he had been only mildly hypertensive and the pathologic findings are consistent with previous well-documented descriptions from similar cases. Histopathologic examination also enabled exclusion of lipofuscinosis, secondary amyloidosis, myocarditis, and active vasculitis – differential diagnoses that may mimic this condition.[8,15,17,32] Despite the introduction of optimal medical therapy perhaps being a sufficient reason for left ventricular function and heart failure improvement, the subsequent chloroquine withdrawal, resulting in complete resolution of symptoms and left ventricular dysfunction, and normalization of pro-BNP levels,[33] further supports the hypothesis of chloroquine toxicity.

The diagnosis of chloroquine-toxicity cardiomyopathy is often delayed since the toxicity of the drug might be misattributed to other factors in these patients. The endomyocardial biopsy, or in some cases the muscle biopsy, are essential to confirm antimalarials toxicity[8] and exclude acute myocarditis.[34] Echocardiography should be used to look for cardiac hypertrophy and a biopsy specimen examined to confirm the toxicity of treatment.[24,25] Recently, magnetic resonance imaging has been proposed as a useful tool,[35] but the interpretation of images appears controversial.[36]

Chloroquine treatment should be stopped on establishment of the diagnosis. Stopping the treatment had a favorable outcome with improvement in left ventricular ejection fraction in our case, confirming previous reports. Nevertheless, other studies have shown persistence of clinical signs and histological lesions up to several years after stopping treatment.[14,23,27] In some cases the lack of improvement may have been explained by the severity of the cardiomyopathy at diagnosis. As a consequence, the potential for reversibility and the severity in undiagnosed cases of these toxic cardiomyopathies emphasize the importance of recognizing

early signs of toxicity in order to withdraw antimalarials before the occurrence of life-threatening cardiac toxicity. However, since the absolute proof of the association between low-dose chloroquine administration and cardiotoxicity would require ultrastructural examination, electron microscopy examination of the sample should be performed in order to corroborate the diagnosis.

References

1. Ochsendorf FR, Runne U (1991) Chloroquine and hydroxychloroquine: side effect profile of important therapeutic drugs. Hautarzt 42:140–146
2. Whisnant JP, Espinosa RE, Kierland RR, Lambert EH (1963) Chloroquine neuromyopathy. Proc Staff Meet Mayo Clin 38:501–513
3. Magnussen I, de Fine Olivarius B (1977) Cardiomyopathy after chloroquine treatment. Acta Med Scand 202:429–431
4. Hughes JT, Esiri M, Oxbury JM, Whitty CW (1971) Chloroquine myopathy. Q J Med 40:85–93
5. Oli JM, Ihenacho HN, Talwar RS (1980) Chronic chloroquine toxicity and heart block: a report of two cases. East Afr Med J 57:505–507
6. Piette JC, Guillevin L, Chapelon C, Wechsler B, Bletry O, Godeau P (1987) Chloroquine cardiotoxicity. N Engl J Med 317:710–711
7. McAllister HA Jr, Ferrans VJ, Hall RJ, Strickman NE, Bossart MI (1987) Chloroquine-induced cardiomyopathy. Arch Pathol Lab Med 111:953–956
8. Ratliff NB, Estes ML, Myles JL, Shirey EK, McMahon JT (1987) Diagnosis of chloroquine cardiomyopathy by endomyocardial biopsy. N Engl J Med 316:191–193
9. Estes ML, Ewing-Wilson D, Chou SM, Mitsumoto H, Hanson M, Shirey E, Ratliff NB (1987) Chloroquine neuromyotoxicity. Clinical and pathological perspective. Am J Med 82:447–455
10. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises (1988) Case 38–1988. A 58-year-old woman with fever, sweats, congestive heart failure, and lymphadenopathy after treatment for a diagnosis of systemic lupus erythematosus. N Engl J Med 319:768–781
11. Ogola ES, Muita AK, Adala H (1992) Chloroquine related complete heart block with blindness: case report. East Afr Med J 69:50–52
12. Fellahi JL, Dumazer P, Delayance S, Vernier I, Conte JJ (1993) Cardiomyopathy under treatment with hydroxychloroquine disclosed by complete auriculoventricular block. Rev Med Intern 14:275–276
13. Verny C, De-Gennes C, Sebastien P, Le Thi Houng Du, Chapelon C, Piette JC, Chomette G, Godeau P (1992) Heart conduction disorders in long-term treatment with chloroquine. Two new cases. Presse Med 21:800–804
14. Iglesias Cubero G, Rodriguez Reguero JJ, Rojo Ortega JM (1993) Restrictive cardiomyopathy caused by chloroquine. Br Heart J 69:451–452
15. August C, Holzhausen HJ, Schmoldt A, Pompecki R, Schröder S (1995) Histological and ultrastructural findings in chloroquine-induced cardiomyopathy.. J Mol Med 73:73–77
16. Veinot JP, Mai KT, Zarychanski R (1998) Chloroquine related cardiac toxicity. J Rheumatol 25:1221–1225
17. Baguet JP, Tremel F, Fabre M (1999) Chloroquine cardiomyopathy with conduction disorders. Heart 81:221–223
18. Cervera A, Espinosa G, Font J, Ingelmo M (2001) Cardiac toxicity secondary to long-term treatment with chloroquine. Ann Rheum Dis 60:301.
19. Nord JE, Shah PK, Rinaldi RZ, Weisman MH (2004) Hydroxychloroquine cardiotoxicity in systemic lupus erythematosus: a report of 2 cases and review of the literature. Semin Arthritis Rheum 33:336–351
20. Charlier P, Cochand-Priollet B, Polivka M, Goldgran-Toledano D, Leenhardt A (2002) Chloroquine cardiomyopathy revealed by complete atrio-ventricular block. A case report. Arch Mal Coeur Vaiss 95:833–837
21. Roos JM, Aubry MC, Edwards WD (2002) Chloroquine cardiotoxicity: clinicopathologic features in three patients and comparison with three patients with Fabry disease. Cardiovasc Pathol 11:277–283
22. Teixeira RA, Martinelli Filho M, Benvenuti LA, Costa R, Pedrosa AA, Nishioka SA (2002) Cardiac damage from chronic use of chloroquine: a case report and review of the literature. Arq Bras Cardiol 79:85–88
23. Freihage JH, Patel NC, Jacobs WR, Picken M, Fresco R, Malinowska K, Pisani BA, Mendez JC, Lichtenberg RC, Foy BK, Bakhos M, Mullen GM (2004) Heart transplantation in a patient with chloroquine-induced cardiomyopathy. J Heart Lung Transplant 23:252–255
24. Keating RJ, Bhatia S, Amin S, Williams A, Sinak LJ, Edwards WD (2005) Hydroxychloroquine-induced cardiotoxicity in a 39-year-old woman with systemic lupus erythematosus and systolic dysfunction. J Am Soc Echocardiogr 18:981
25. Naqvi TZ, Luthringer D, Marchevsky A, Saouf R, Gul K, Buchbinder NA (2005) Chloroquine-induced cardiomyopathy-echocardiographic features. J Am Soc Echocardiogr 18:383–387
26. Cotroneo J, Sleik KM, Rene Rodriguez E, Klein AL (2007) Hydroxychloroquine-induced restrictive cardiomyopathy. Eur J Echocardiogr 8:247–251
27. Costedoat-Chalumeau N, Hulot JS, Amoura Z, Delcourt A, Maisonobe T, Dorent R, Bonnet N, Sablé R, Lechat P, Wechsler B, Piette JC (2007) Cardiomyopathy related to antimalarial therapy with illustrative case report. Cardiology 107:73–80
28. Fragasso G, Palloshi A, Puccetti P, Silipigni C, Rossodivita A, Pala MG, Calori G, Alfieri O, Margonato A (2006) A randomized clinical trial of trimetazidine, a partial free fatty acid oxidation inhibitor, in patients with systolic dysfunction heart failure. J Am Coll Cardiol 48:992–998
29. Senju N, Ikeda S, Koga S, Miyahara Y, Tsukasaki K, Tomonaga M, Kohno S (2007) The echocardiographic Tei-index reflects early myocardial damage induced by anthracyclines in patients with hematological malignancies. Heart Vessels 22:393–397
30. Reuss-Borst M, Berner B, Wulf G, Muller GA (1999) Complete heart block as a rare complication of treatment with chloroquine. J Rheumatol 26:1394–1395
31. Ladipo GO, Essien EE, Andy JJ (1983) Complete heart block in chronic chloroquine poisoning. Int J Cardiol 4:198–200
32. Sanmartí R, Gómez-Casanovas E, Solé M, Cañete J, Gratacós J, Carmona L, Gonzalez-Alvaro I, Muñoz-Gómez J (2004) Prevalence of silent amyloidosis in RA and its clinical significance. J Rheumatol 31:1013–1014
33. Taniguchi R, Sato Y, Nishio Y, Kimura T, Kita T (2006). Measurements of baseline and follow-up concentrations of cardiac troponin-T and brain natriuretic peptide in patients with heart failure from various etiologies. Heart Vessels 21:344–349
34. Kato S, Morimoto S, Hiramitsu S, Uemura A, Ohtsuki M, Kato Y, Miyagishima K, Mori N, Hishida H (2007) Successful high-dose intravenous immunoglobulin therapy for a patient with fulminant myocarditis. Heart Vessels 22:48–51
35. Reffelmann T, Naami A, Spuentrup E, Kühl PH (2006) Contrast-enhanced magnetic resonance imaging of a patient with chloroquine-induced cardiomyopathy confirmed by endomyocardial biopsy. Circulation 114:e357–e358
36. Pieroni M, Bellocci F, Crea F (2006) Letter regarding article, "Contrast-enhanced magnetic resonance imaging of a patient with chloroquine-induced cardiomyopathy confirmed by endomyocardial biopsy." Circulation 114:e358.