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Case Report

Malaria and the heart: Two rare case reports of *Plasmodium falciparum*-associated pericarditis

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Malaria is one of the most important parasitic diseases in the world, causing significant mortality and morbidity in the tropical regions[1]. Although symptoms can range from a mild fever to severe complicated forms, there are limited published data on cardiac involvement of malaria and only a few studies have been carried out regarding cardiac function in severe malaria[2–3]. Cardiac involvement in the course of malaria ranges from severe forms with hypatension, shock, circulatory collapse and impaired haemodynamic function, to mild disorders documented by Electrocardiogram (ECG) and echocardiography[4–6]. Pericardial involvement in malaria is a very rare event[7–8]. We report here two cases of falciparum malaria complicated with pericardial effusion.

Case 1: A 19-yr-old Nigerian female, resident of Sicily, was admitted with history of intermittent high-grade fever over three days, following her return from Nigeria, 10 days prior to the onset of the symptoms. The fever was associated with headaches as well as thoracic pain during the episodes. The patient denied neck stiffness. There was no history of diabetes, hypertension or dyslipidaemia. On examination the patient was apyretic, eupneic, blood pressure was 120/70 mmHg with a pulse rate of 105 bpm. Neck stiffness and peripheral oedema were absent and there was no active bleeding from any site. Neurological examination was normal. Hepatomegaly was absent and the spleen was palpable with a long axis of approximately 13 cm. Cardiovascular examination identified a systolic murmur and pericardial rub. White blood cells (WBCs) count was 6600/mm^3, platelet count was 54000/mm^3 indicating thrombocytopenia, haemoglobin was 8.2 g/dl, and blood glucose was 110 mg/dl; coagulation profile revealed an INR of 1.38, a D-dimer of 949 ng/dl and a fibrinogen of 502 mg/dl. Liver function tests displayed a GGT of 56 IU/L and LDH of 232 IU/L. Renal function tests showed a blood urea of 21 mg/dl and a serum creatinine of 0.8 mg/dl. C-reactive protein levels were elevated at 14.95 mg/l. Blood smear was positive for *Plasmodium falciparum* with 1.5% parasitaemia. Virological screen was negative for human immunodeficiency virus (HIV) and cytomegalovirus (CMV).

ECG showed sinus tachycardia of 106 bpm and diffuse non-specific abnormality of ST-T wave. The echocardiogram, performed to investigate the cause of the thoracic pain, revealed an anterior non-compressive pericardial effusion (6 mm behind the right atrium, 9 mm in lateral) and a congenital intra-atrial and intra-ventricular communication with left-to-right shunt. Chest X-ray was normal.

The patient was treated with a co-formulation of dihydroartemisinin (DHA)-piperaquine (PPQ) 120 mg/960 mg orally (po) *once daily* for three days. The patient also started treatment for pericarditis under the supervision of a cardiologist with colchicine 1 mg po daily and ibuprofen 600 mg every 8 h (as attack dose for a week, then every 12 h for another week).

There was a favourable evolution throughout seven days of admission, with an improvement of symptomatology. Repeat blood smear at the end of antimalaria therapy showed no evidence of malarial parasites. Patient was discharged after 16 days in good and stable clinical condition, with colchicine therapy for a total period of three months. An appropriate follow-up plan was agreed upon as recommended.

*Case 2:*A 52-yr-old Ghanese woman, residing in Sicily, was admitted with history of abdominal pain and fever over five days, following her return from Ghana, 15

days prior to the onset of the symptoms. On admission, she appeared suffering, but without altered state of consciousness. On examination the patient was febrile (body temperature 39 °C), eupneic, with blood pressure 120/60 mmHg. There were no signs of meningeal irritation, cognitive impairment or any neurological deficit. She had no hepatosplenomegaly. A cardiac examination revealed soft heart sounds, with pericardial friction rub.

Laboratory studies showed a WBC count of 24200/mm^3 (neutrophils 89.7%, lymphocytes 5.5%); haemoglobin level 8.6 g/l, platelets count 17000/mm^3, C-Reactive protein 198 mg/l, D-dimer 15.112 µg/l. Examination of a thin blood smear revealed ring trophozoites typical of *P. falciparum* including multiple infected cells with 3.7% of erythrocytes parasitized. Quanti FERON-TB-Gold test and viral serology for HIV were negative.

ECG showed sinus tachycardia of 110 bpm. Transthoracic echocardiography (TE) showed a left ventricular concentric hypertrophy with preserved global systolic function, absence of any segmental wall-motion abnormalities of the left ventricle; right sections were of normal size with preserved right ventricular function. It also showed pericardial effusion (8 mm behind the right atrium, 12 mm in lateral) without haemodynamic consequences (Fig. 1). The patient was treated for malaria infection with a co-formulation of dihydroartemisinin (DHA)-piperaquine (PPQ) 120 mg/960 mg po *once daily* for three days. In agreement with 2015 ESC guidelines[9] the patient was treated for pericarditis with ibuprofen 600 mg po every 8 h (as attack dose for a week, then every 12 h for another week) plus colchicine 1 mg po *daily*. Over four days after initiation of antimalaria therapy, the patient's clinical condition improved. Repeat blood smear at the end of antimalaria therapy showed no evidence of malarial parasites. On Day 12 of hospitalization, a control TE confirmed the presence of a minor pericardial effusion (4 mm in lateral), with no signs of haemodynamic compromise. The patient was discharged on the 14th day in good condition, with colchicine therapy for a total period of three months.

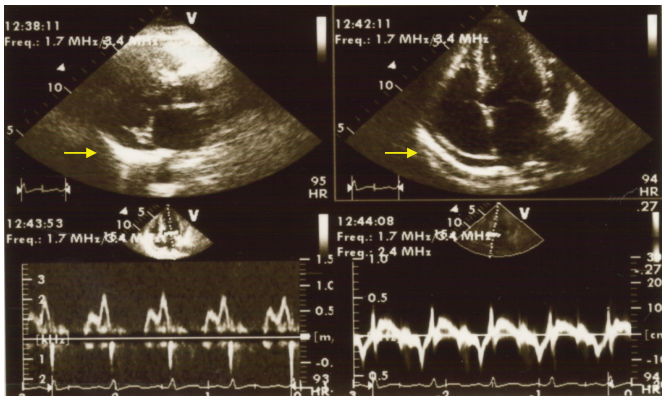

Fig. 1: Echocardiography showing a circumcardiac pericardial effusion (yellow arrow) in parasternal long axis (left) and apical 4 chamber (right).

DISCUSSION

Falciparum malaria has a wide range of symptoms, and can be complicated by acute renal insufficiency, cerebral malaria, acidosis and acute respiratory distress syndrome[4]. Cardiac involvement is rarely seen and, when present, affects predominantly the myocardium and the myoelectric system[5, 10]. Features of myocarditis, ectopic ECG changes, conduction defects, tachy-brady-arrhythmias and acute heart failure with reduced cardiac output have been observed in a few cases of imported severe falciparum malaria[10-14]. In the present cases, both the patients developed pericardial effusion. Whilst myocardial damage appears to retain a multifactorial pathogenesis, being probably the result of mechanical (microcirculatory obstruction), metabolic (systemic acidosis and related tissue hypo-oxygenation), and humoral mechanisms; the mechanism underlying the causal relationship between the parasitic infection and the development of pericardial effusion is still unclear. One possible explanation may be the locally elevated cytokine levels. Day *et al*[15] have shown that cytokines produced locally in particular tissue during malarial infection may be regulated by the degree of regional parasitic sequestration; and the documentation of parasitic antigen, by Kohli *et al*[8], in the pericardial fluid has also confirmed the association of malaria and pericardial effusion.

Plasmodium falciparum has the unique capability of causing cytoadherence, where parasitised RBCs become sequestered in capillaries. It has been shown that the production of pro-inflammatory cytokines can be regulated by the extent of cytoadherence in specific areas[16]. The pro-inflammatory state created locally alters the dynamic equilibrium between the pericardial fluid and the blood serum. Local production of inflammatory mediators can bring about the extravasation of fluid from the visceral pericardium into the virtual space between the two layers. In addition, the exudation of large molecules increases the osmotic potential inside the pericardial sheets and perpetuates the vicious cycle installed.

In the light of earlier reports, it is reasonable to conclude that pericardial effusion must be deemed a serious complication of falciparum malaria. This is crucial insight to prevent cardiac tamponade, a potentially fatal complication of what is an otherwise curable disease[8].

Conflict of interest

There are not any affiliation, financial agreement, or other involvement of any author with the companies whose products figure prominently in the submitted typescript.

Ethical statement

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor/Editor-in-Chief of this journal.

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