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CASE REPORT

Acute renal failure in *Plasmodium malariae* infection

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ABSTRACT

We report an unusual case of transfusion-transmitted malaria which remained undiagnosed for several months in an Italian woman splenectomised and polytransfused for thalassaemia major. The infecting species was *Plasmodium malariae*, and the patient developed acute renal failure, severe thrombocytopenia, and hepatic failure. Treatment with chlorochine was followed by a slow, but complete recovery of renal function.

KEYWORDS

Acute renal failure, chlorochine, malaria

INTRODUCTION

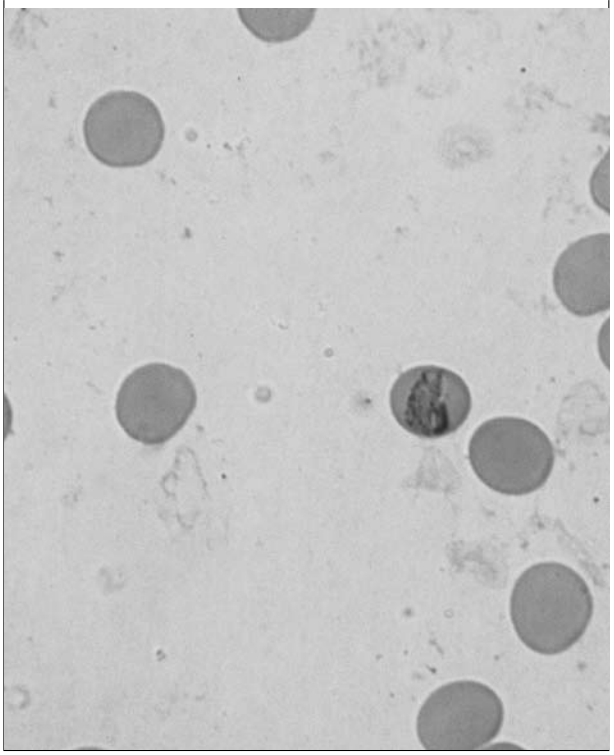
Malaria is one of the world's most important infections and, although it has been eradicated from temperate zones, the growing popularity of travel to the tropics is placing an increasing number of travellers at risk for acquiring the disease.

In this paper we report a case of a woman whose clinical history was unusual in both epidemiological and clinical characteristics.

CASE REPORT

A 35-year-old Italian woman with thalassaemia major, splenectomised and maintained on monthly blood transfusions since she was 10 years old, was admitted to our hospital because of recurrent fever with multiorgan involvement. The patient had been in a stable condition until four months prior to admission, when she become febrile with a 72 to 96 hour cyclical fever reaching 40°C, lasting 12 to 24 hours, and associated with chills and shivering. After unidentified therapies at home were unsuccessful, she was admitted to another hospital in our city. She was discharged with a presumptive diagnosis of polyserositis of unknown origin, and treated with steroids. Nevertheless the patient continued to have recurrent episodes of high fever alternating with apyrexia. On admission to our hospital she was febrile and reported having severe asthenia, mild dyspnoea, arthralgia, myalgia, diarrhoea and oliguria. On examination she appeared ill; her blood pressure was 110/70 mmHg with a heart rate of 105 beats/min. She had marked oedema in the lower extremities, and a haemorrhagic rush extended from her arms to her neck. A chest radiograph disclosed small, bilateral pleural effusions and an enlarged cardiac silhouette. An echocardiogram showed a small pericardial effusion. Blood and urine testing revealed a red blood cell count of 2.7 x 10^{12}/l, haemoglobin 4.6 mmol/l and platelets 56 x 10^{9}/l; mixed bilirubin 62 µmol/l; aspartate aminotransferase 113 U/l; alanine aminotranferase (ALAT) 51 U/l; international normalised ratio (INR) 1.6; creatinine 262 µmol/l, urea 21.5 mmol/l, Na^{+} 130 mmol/l and K^{+} 5.1 mmol/l; serum proteins were 430 mg/l, albumin 240mg/l and urinary protein excretion (24 h) was 0.63 g/d; serological tests for infectious diseases and three haemocultures were negative. On the third hospital day the patient's temperature rose to 38°C and she became anuric, with an increase in creatinine (468.5 µmol/l) and urea (25.3 mmol/l). Extracorporeal dialysis treatment was started, and microscopy of stained thin and thick blood films, at a magnification of 1000 x, was performed. Surprisingly, microscopic examination revealed the presence of erythrocyte inclusions compatible with *Plasmodium malaria* infection (*figure 1*). Our laboratories confirmed the diagnosis of *P. malaria* infection. Therapy with chloroquine (1 g/day) was started and continued for

Figure 1. *Erythrocyte inclusions compatible with Plasmodium malaria infection*



five days. The fever disappeared after three days; hepatic enzyme tests improved and platelets rose to a normal value. The patient was discharged after two weeks and continued ambulatory haemodialysis treatment. Three months later, dialysis was discontinued and, at eight-month follow-up, the creatinine had decreased to 106.08 µmol/l while urinary protein excretion (24 h) was 350 mg/d and blood pressure was normal. A specific investigation performed by the Ministry of Health revealed that the infection was transmitted by an occasional blood donor, a missionary of Philippine origin, who was a chronic and asymptomatic carrier of *P. malaria* infection.

DISCUSSION

Malaria is an acute and sometimes chronic infection caused by protozoan parasites of the genus *Plasmodium*. Malarial parasites undergo a sexual phase in *Anopheles* mosquitoes and an asexual stage in humans. In the vertebrate host, release of merozoites from ruptured hepatic mature schizonts initiates the blood stream infection and eventually the clinical symptoms of malaria. The attack is initiated by the synchronous rupture of erythrocytes with the release of new merozoites; therefore the recurrence of fever at 48-hourly intervals (*P. vivax* and *P. ovale*, sometimes *P. falciparum*) and at 72-hourly intervals (*P. malariae*) depends on the lifecycle of the parasite. Diagnosis is usually established by demonstrating parasites in thick and thin blood films. Species-specific serological tests are useful for detection of infected blood donors, and molecular biology is especially promising. In a prospective study, malaria parasitaemia was present in 38.7% of Nigerian children with nephrotic syndrome.[1] Malaria infections have repeatedly been reported to induce nephritic syndrome and acute renal failure. People who are not immune because they live in a nonendemic area had a higher risk of developing acute renal failure when compared with semi-immune subjects living in endemic areas such as Uganda and Nigeria.[2] It is still not known why the nephritic syndrome seen with *P. malariae* infection is associated with proliferative glomerular lesions in Ugandan patients, whereas Nigerian patients have more membranous lesions. Acute renal failure is a life-threatening complication of malaria infection. In the majority of cases *P. falciparum* is the causative agent of malarial acute renal failure (MARF), although MARF due to *P. vivax* has been occasionally reported.[3] Prevalence of MARF in endemic areas seems to be increasing[4] and the reported mortality of MARF is still very high, ranging from 15 to 45%. The histological picture of MARF consists of a variable mixture of acute tubular necrosis, interstitial nephritis and glomerulonephritis; proteinuria is less than 100 mg/24 h in 60% of cases.[4,5] In *P. falciparum* infection MARF often occurs in association with signs of multiorgan involvement, and jaundice, anaemia and thrombocytopenia are present in more than 70% of cases.[6-8] *P. malariae* is the established cause of chronic malarial nephropathy, although a few cases have been associated with *P. vivax* in children.[5-8] This complication affects children and shows the characteristic histopatological lesion of mesangiocapillary glomerulonephritis with subendotelial immune complex deposits containing IgG, C 3 and malarial antigens.[8] The clinical presentation includes proteinuria and nephritic syndrome. In our report we describe an unusual case of MARF with nephrotic range proteinuria and manifestations of multisystem involvements due to *P. malariae*. The development of MARF as a complication of a *P. malariae* infection is very rare and as far as we know, it has not been previously reported in Western countries. The patient's clinical condition did not allow us to perform a kidney biopsy so that the exact nature of the acute renal failure could not be established. The clinical course of the disease was characterised by a progressive increase in proteinuria which had risen to more than 600 mg/24 h at the time of admission to our hospital. This finding is consistent with the glomerular involvement which is reported in *P. malariae* infection. Both the long duration of the disease before the correct diagnosis, and the unstable haemodynamic conditions of the patient might have significantly worsened the clinical course of the renal disease. In fact, it is noteworthy that in *P. falciparum* infections, MARF is usually associated

with volume depletion, intravascular haemolysis, massive parasitaemia, colestatic jaundice and hypotension. Apart from jaundice, signs of hepatic dysfunction are unusual. In recent years, there have been an increasing number of reports favouring the existence of malarial hepatopathy from Asian countries, especially from India.[9] The liver plays a key role in the lifecycle of the plasmodium and in some cases it is seriously involved; in *Falciparum* malaria, there are reports[10-11] of a spectrum of hepatocellular dysfunction ranging from mild derangement of liver function tests with conjugated hyperbilirubinaemia, elevated ALAT and INR, thrombocytopenia and coagulopathy to liver failure and fulminant hepatic failure; liver damage is said to be related to cyto-adherence of parasitised red blood cells in the portal venous flow with ischaemia, intrahepatic cholestasis, and increased apoptosis and oxidative stress.[12] Most of these features were present in our patient at the onset of MARF. Furthermore, the treatment with steroids before the correct diagnosis was made did not ameliorate the clinical course of the disease, confirming the current concept that there is no definitive evidence for a dominating role of corticosteroids in the treatment of acute malaria complications.[8,13]

The unusual sequence of events which influenced the course of the infection made us consider the many problems associated with managing infective risk:

- the use of occasional blood donors can cause many diagnostic problems in the case of transmitted infectious disease, especially with regard to some nonendemic diseases;
- a single reading of the film by the optic microscope can lead to the correct diagnosis.

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