Annals of Parasitology 2019, 65(4), 427–431
doi: 10.17420/ap6504.231

Case reports

Cerebral malaria and multi-organ dysfunction in an adult woman with *Plasmodium falciparum* infection imported from Cameroon: a case report

Łukasz Pielok[1], Matylda Kłudkowska[2], Stanisław Rzymski[3], Jerzy Stefaniak[1]

[1]Department of Tropical and Parasitic Diseases, Poznan University of Medical Sciences, Poznań, Poland
[2]Central Laboratory of Microbiology, H. Święcicki University Hospital, Poznań, Poland
[3]Intensive Care Unit, J. Struś Multidiscipline City Hospital, Poznań, Poland

Corresponding Author: Łukasz Pielok; e-mail: lpielok@ump.edu.pl

ABSTRACT. Malaria is one of the most life-threatening parasitic diseases caused by the protozoa of the genus *Plasmodium*, occurring in the tropical and subtropical regions. Misdiagnosed infection can progress to a wide range of life-threatening pathologies, including severe anemia and cerebral malaria which can lead to death even few days after first symptoms appearance. Cerebral malaria is rare in adults and most cases are connected to children under 5 years old living in malaria endemic areas. In this article we describe cerebral malaria caused by the *Plasmodium falciparum* in a 45-year-old Polish patient, who traveled to Cameroon without any malaria prophylaxis. The patient had been treated in an intensive care unit because of multi-organ dysfunction as a result of the delayed malaria diagnosis. The presence of thrombocytopenia, anemia, metabolic acidosis, acute respiratory distress syndrome and multi-organ dysfunction involving liver, kidneys, and brain created an image of advanced severe malaria. Loss of consciousness, GCS 6, and the presence of asexual *Plasmodium falciparum* forms in blood films are the evidence of cerebral malaria. To avoid development of cerebral malaria, the illness should be diagnosed immediately. The cerebral malaria can occur also in adult healthy individuals. Appropriate treatment with intravenous artemisine can protect the patient from life-threatening complications. Prolonged anemia after treatment can be a consequence of artemisine usage as well as a severe malaria sequel.

Keywords: cerebral malaria, acute renal insufficiency, *Plasmodium falciparum*, anemia, artemisine

Introduction

Malaria is a mosquito-borne disease caused by the parasites of the genus *Plasmodium (P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, *P. knowlesi*) and acquired through the bites of infected *Anopheles* mosquitos. The disease manifests with fever, chills, headaches, vomiting and tiredness. An infection can progress to a wide range of life-threatening pathologies, including severe anemia and cerebral malaria which can lead to death even several days after first symptoms appearance [1,2]. Cerebral malaria (CM) is one of the most advanced clinical courses of severe cases and it manifests with coma and asexual forms of *Plasmodium falciparum* present in the blood films [3]. It can be diagnosed in patients unable to localize a painful stimulus and no other identifiable causes of encephalopathy [1]. Cerebral malaria is rare in adults and most of cases are connected to children under 5 years old who live in malaria endemic areas [1].

Malaria is also an important cause of anemia in tropical areas which can cause hemolysis of infected and uninfected erythrocytes and bone marrow dyserythropoiesis. Severe malarial anemia requiring blood transfusion is a major cause of hospitalization in endemic countries [4,5].

To avoid severe complications of *Plasmodium* infection immediate diagnosis is necessary. The gold standard in malaria diagnosis are still thin and thick blood films. Malaria should be taken under consideration in every person returning from malaria endemic area, even with non-specific symptoms. Lack of experience in malaria diagnosis

Table 1. The results of laboratory tests in next days of hospitalization and during the follow-up visit

Parameters	09.03	11.03	13.03	15.03	16.03	18.03	21.03	26.04	Reference values
CRP (mg/l)	252.3	275.7	93.6	97.8	76.2	66.6	11.6	0.6	0.5-9.0
PCT (ng/ml)	3.8	66.2	82.9	54.4	13.8	0.9	0.32		<0.1
WBC (G/l)	5.2	15.0	16.4	16.8	13.9	7.3	3.99	4.31	4.0-11.0
PLT (G/l)	20	36	27	68	98	208	391	258	130-440
RBC (T/l)	3.28	3.56	3.37	3.24	3.22	3.53	2.52	3.15	4.0-5.5
Hb (mmol/l)	5.5	6.6	5.9	5.5	5.5	6.0	4.5	6.39	7.4-9.9
Creatinine (µmol/l)	105	139	108	205	263	152	125	49	49-115
Bilirubin (µmol/l)	111.0	158.0	67.0	30.2	24.4	23.3	22.57	8.55	3.0-17.0
Urea (mmol/l)	22.0	29.4	24.2	19.1	22.0	18.7	2.3		1.7-8.0
ALT (U/l)	24	20	26	28	24	26	18	15	14-59
AST (U/l)	46	75	90	59	40	46	36	6	4-35
D-dimer (µg/ml)	1.54	16.06	4.33	5.07	3.86	3.85	2.25		<0.5
pH	7.332	7.005	7.336	7.467	7.473	7.455	7.434		7.350-7.450
BE (mmol/l)	-6.6	-15.1	-4.9	5.1	7.1	-1.5	3.5		-2.5-2.5

in health–care providers, together with misdiagnosis as influenza–like diseases in primary health care, lead to delayed diagnosis, disease exacerbation and ultimately increase mortality risk among patients [6,7]. Currently in malaria treatment artemisinin-based medicaments are drug of choice, what is connected with the presence of chloroquine-resistant *Plasmodium falciparum* strains [8,9].

In this work we present a case of a 45-year-old woman born and living in Poland who traveled to Africa (Cameroon) and was diagnosed with cerebral malaria.

Case presentation

45-year-old woman born and living in Poland, whose father is a Cameroonian, was admitted to the Intensive Care Unit of Multidiscipline City Hospital in Poznań, Poland, because of loss of consciousness, vomiting and subfebrile state. Prior to admission she traveled to Cameroon for 3 weeks to visit her fathers' family, without any malaria chemoprophylaxis. She had traveled to Cameroon previously in 1999, 2000, 2007 also without any malaria prevention.

On admission to the hospital she was unconscious with GCS 6, and tachypnea. CT scan of the brain did not revealed any abnormalities. Laboratory tests, performed in Emergency Department showed increased level of CRP (252.3 mg/l), PCT (3.8 ng/l), bilirubin (111 mmol/l), marked thrombocytopenia (20 G/l), anemia (Hgb 5.8 mmol/l), and metabolic acidosis. The results of laboratory tests in next days of hospitalization are presented in Table 1.

Taking under consideration her epidemiological history and the results of the blood tests, the thick and thin blood films were performed and the *Plasmodium falciparum* infection was detected

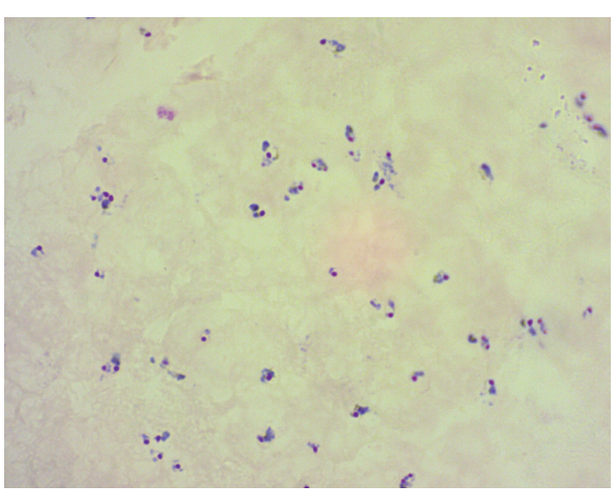

Fig. 1. Numerous *Plasmodium* spp. ring forms (thick blood film, magnification 1000×)

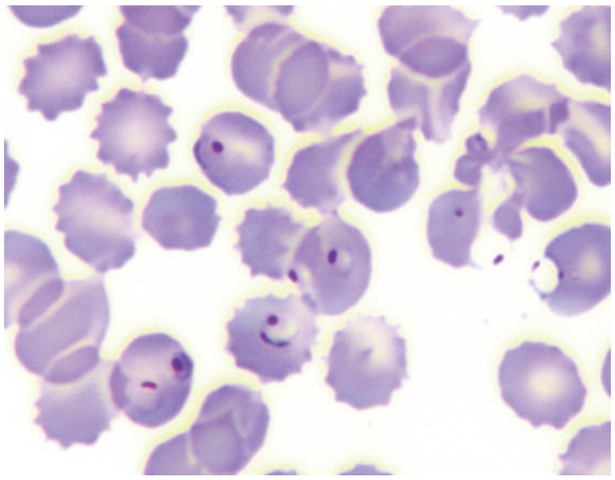

Fig. 2. *Plasmodium falciparum* trophozoits inside RBCs (thin blood film, magnification 1000×)

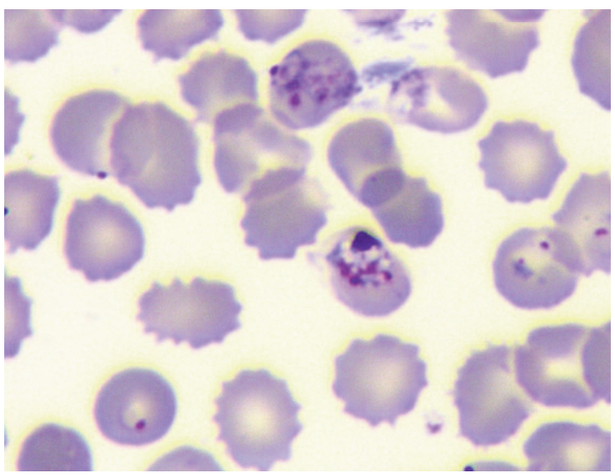

Fig. 3. *Plasmodium falciparum* schizont (thin blood film, magnification 1000×)

(Fig. 1). In the thin blood film the trophozoites (Fig. 2), schizonts (Fig. 3), gametocytes, and hemozoin clumps inside the leukocytes were present (Fig. 4). Parasitemia level was established at 8%. The patient was immediately treated with the first intravenous dose of artemisinin (Falcigo, in a dose 2 mg/kg of body weight) and later 6 times 1 mg/kg of body weight.

The patient's state was worsening, she required continuous catecholamine inflow and finally needed analgosedation with Propofol and Thiopenthal and intubation. She was ventilated with SIMV respiratory mode. The repeated laboratory results showed decreasing erythrocyte and platelets levels

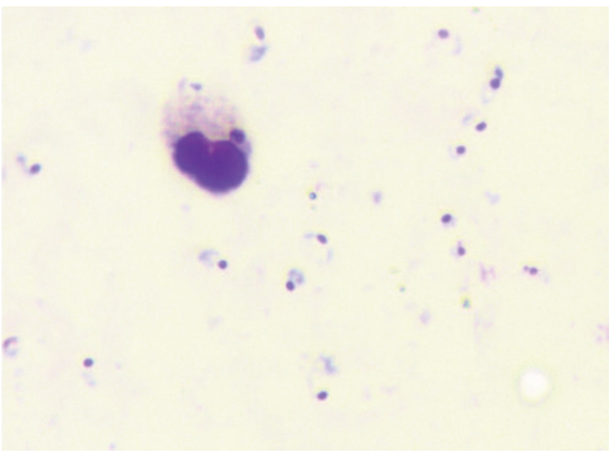

Fig. 4. Hemozoin clump inside the leucocyte and the ring forms (thick blood film, magnification 1000×)

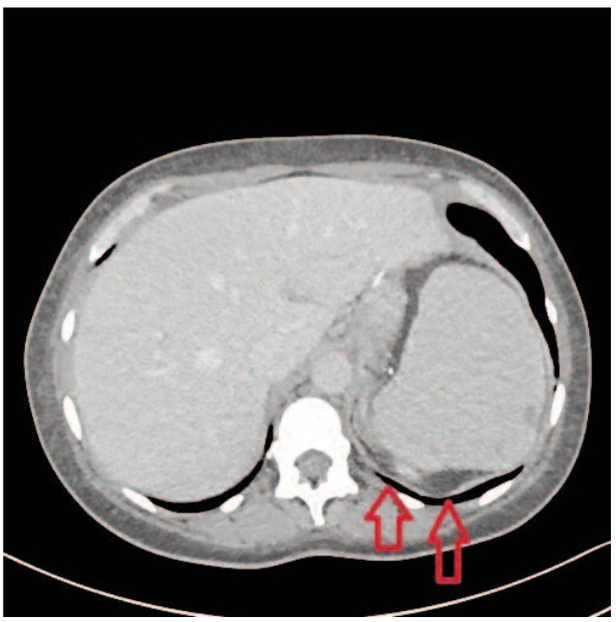

Fig. 5. CT scan of the abdomen cavity: enlarged spleen with disseminated ischemic lesions (red arrows)

so the patient required several red cell concentrates (RCC) and platelet transfusions. PCT level rapidly increased (66–82.9 ng/ml), so empiric antibiotic treatment with levofloxacin was initiated. Because of the acute renal insufficiency continuous hemodialysis was started. Repeated thin and thick blood films showed 25% parasitemia level. Malaria treatment was enhanced with intravenous doxycycline inflow (200 mg/day). Next day parasitemia level decreased to 13%. On the 4th day

Table 2. Parasitemia levels

	09.03	10.03 (06:00)	10.03 (2:00pm)	11.03	12.03	19.03
Parasitemia (%)	8	25	13	2	0	0

of the treatment *Plasmodium* eradication was obtained. The changes in parasitemia level are summarized in Table 2. The renal function gradually improved. The conscious level also improved. Finally the patient was extubated and moved to the Department of Tropical and Parasitic Diseases of Poznań Medical University.

During hospitalization repeated blood tests showed anemia with hemoglobin level 5.2 mmol/l probably as a result of autoimmunological process as well as a side effect of artemisinin treatment. The patient required another RCC transfusion. CT scan of the abdomen cavity performed during hospitalization showed enlarged spleen with disseminated ischemic lesions (Fig. 5). Serological test with *Plasmodium falciparum* antigen was positive (30 NTU).

The patient improved and was discharged home. One month later she was admitted to the Clinic for follow-up. She felt well, and did not complain of any health problems. Laboratory results showed still lower hemoglobin level (6.39 mmol/l) and erythro - penia (3.15 T/l). There were no neurological sequele of cerebral malaria.

Discussion

Malaria belongs to the most dangerous and life-threatening tropical diseases. According to the latest WHO malaria report released in November 2018 the estimated incidence rate in 2017 was 219 mln cases worldwide with the most in the sub-Saharan region (92%). Last year there was an estimated 435.000 malaria deaths worldwide [10]. Travelers from low transmission areas are very susceptible to malaria and its complications especially when they do not take any antimalarial chemoprophylaxis [11,12].

Plasmodium infections result in a spectrum of clinical effects, including asymptomatic parasitemia, uncomplicated malaria, severe malaria and death. Severe and fatal malaria are predominantly caused by *Plasmodium falciparum*, because of sequestration of infected red blood cells in the internal organs blood vessels. This results in microcirculatory obstruction and insufficiency of infected organs [13].

Thrombocytopenia, anemia, metabolic acidosis, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction involving liver, kidneys, lungs and brain create an image of advanced severe malaria [14,15]. Loss of consciousness, GCS 6, and the presence of asexual *Plasmodium falciparum* forms in blood films are the evidence of cerebral malaria, which is a severe form of the disease usually affecting children, pregnant women and individuals with limited immunity. Mortality from CM can reach up to 25%. Severe complications are the result of pathologies in organ microcirculation as well as direct metabolic disturbances caused by the parasites presence, which can cause fatal outcome [12,16]. Disease progression to severe malaria may take days but can also occur within a few hours, thus the diagnosis should be established as soon as possible. If left untreated, severe malaria is fatal in the majority of cases [9]. In treatment of severe malaria either intravenous artemisinin or quinine are used [17–19]. Patients who required mechanical ventilation and vasopressors support have higher mortality rate.

The described case of the Polish traveler, who had spent 3 weeks in Africa (Cameroon) and did not use any malaria chemoprophylaxis complies with all laboratory criteria for severe (parasitemia level, increased levels of CRP, PCT, creatinine, bilirubin, urea), cerebral malaria (loss of consciousness), as well as multi-organ insufficiency (AKI, ARDS, pneumonia, splenomegaly with ischemic changes).

Quick progression to the multi-organ dysfunction was strictly connected to delayed malaria recognition (the patient spent several hours in the Emergency Department). But specific antimalarial treatment with intravenous artemisinin inflow in appropriate dosages together with application of intensive general treatment (catecholamine persistent inflow, RCC transfusions, hemodialysis, respiratory treatment) prevented the patient from fatal complications. However during the infection multiorgan dysfunction was observed (AKI, acute respiratory distress syndrome, ischemic spleen changes, bone marrow insufficiency). The patient's follow–up performed after several weeks showed only long lasting anemia, probably as a result of artemisinin intake [20,21].

In conclusions: 1. To avoid development of cerebral malaria, the illness should be diagnosed immediately; 2.The cerebral malaria can occur also in adult healthy individuals; 3. Appropriate treatment with intravenous artemisinin can protect the patient from life-threatening complications; 4. Prolonged anemia after treatment can be a consequence of artemisinin use as well as severe malaria sequel.

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Received 13 August 2019
Accepted 03 October 2019