

# Exchange Transfusion for Severe Imported Falciparum Malaria with Hyperparasitaemia: Case Report

## Hiperparazitemili Yurt Dışı Kaynaklı Şiddetli Falsiparum Malarya Olgusunda Exchange Transfüzyon

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**ABSTRACT** Severe falciparum malaria is a potentially fatal infection despite optimal antimalarial treatment. Exchange transfusion is successfully used in severe falciparum malaria with hyperparasitaemia. In this paper, we describe a case of severe *Plasmodium falciparum* infection in a 23-year-old man. The patient was referred to our emergency department with high fever after returning from Equatorial Guinea. The thin and thick blood smears revealed the presence of *P. falciparum* ring forms with a parasite density of 30%. *P. falciparum* infection was confirmed by Polymerase Chain Reaction (PCR). The patient was successfully treated by exchange transfusion in addition to anti-malarial chemotherapy. Despite limited evidence of its efficacy in improving survival, exchange transfusion can be used as an-supportive treatment in selected cases where rapid reduction in the parasite load appears necessary.

**Key Words:** Malaria; malaria, falciparum; exchange transfusion, whole blood; parasite load

**ÖZET** Şiddetli falsiparum sıtması uygun antimalaryal tedaviye rağmen potansiyel öldürücü bir enfeksiyondur. Exchange transfüzyon hiperparazitemili şiddetli falsiparum malarya olgularında başarıyla kullanılmaktadır. Bu yazıda şiddetli *Plasmodium falciparum* enfeksiyonu olan 23 yaşında bir erkek olgu tanımladık. Hasta, Ekvator Ginesi'nden döndükten sonra yüksek ateş ile acil servisimize başvurdu. İnce ve kalın yaymalarda %30 parazit yükü ile *P. falciparum* taşlı yüzük formları saptandı. *P. falciparum* enfeksiyonu polimeraz zincir reaksiyonu (PCR) ile doğrulandı. Olgu antimalaryal kemoterapiye ek olarak exchange transfüzyon ile başarılı bir şekilde tedavi edildi. Sağkalımı iyileştirmedeki etkinliği ile ilgili veriler kısıtlı olsa da yüksek parazit yükünün hızla azaltılması gereken seçilmiş olgularda, exchange transfüzyon destek tedavisi olarak uygulanabilir.

**Anahtar Kelimeler:** Sıtma; sıtma, falsiparum; transfüzyon, tam kan; parazit yükü

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**P**lasmodium falciparum malaria is the most dangerous form of malaria. The World Health organization (WHO) defines severe *P. falciparum* malaria as one or more of the following features: cerebral malaria, hyperparasitemia (>5% parasitized erythrocytes or >250.000 parasites/μL), severe anemia (hematocrit <15% or hemoglobin <5 g/dL in the presence of parasitemia >10,000 parasites/μL), renal failure (urine output <400 mL/24 hours in adults, with serum creatinine >3 mg/dL), respiratory distress and pulmonary edema, hypoglycemia (whole blood glucose <2.2 mmol/L or <40

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mg/dL), hypotension/circulatory collapse, abnormal bleeding/clotting, seizures, acidosis (arterial pH <7.25, plasma bicarbonate <15 mmol/L), hemoglobinuria, impaired consciousness, prostration, hyperpyrexia (rectal temperature >40°C) or jaundice (total bilirubin >3 mg/dL).<sup>1</sup> Severe falciparum malaria is reported to have a high mortality rate and prompt treatment is necessary. Exchange transfusion (ET) is often used as an adjunct therapy to reduce the parasite load in hyperparasitemic cases.<sup>2</sup>

In our study, we report a case of severe *Plasmodium falciparum* malaria with hyperparasitemia whose condition improved after ET and antimalarial chemotherapy.

## CASE REPORT

A 23 year old Turkish man was admitted to our hospital with one week history of fever, nausea-vomiting, diarrhea, weakness and anorexia. His complaints had begun three days after returning from Equatorial Guinea where he had been working for 2.5 months. He did not take antimalarial chemoprophylaxis and did not use personal vector avoidance measures during his stay.

On examination, the patient was somnolent. He was febrile (40.1°C) and had a heart rate of 105 beats/min, blood pressure of 83/32 mmHg, respiration rate of 37/min. Abdominal examination revealed common tenderness and no rebound or guarding. There was no evidence of bleeding in the skin and mucous membranes.

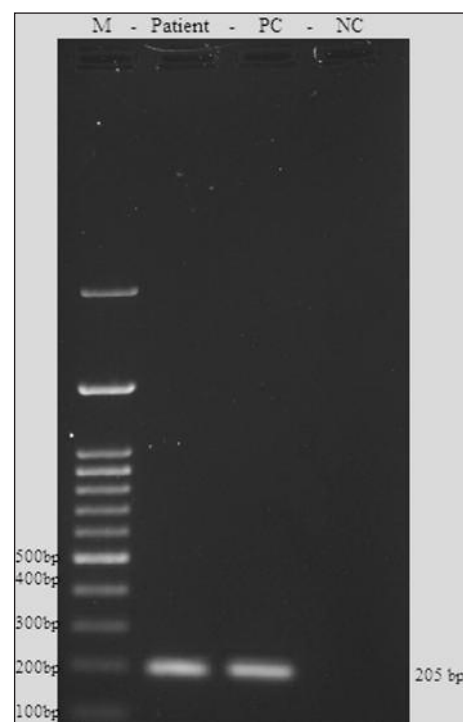
The patient demonstrated some elevated liver function test, anemia, thrombocytopenia and hyponatremia (Table 1). Serology tests for Hepatitis B surface antigen, Anti-HCV and HIV were negative. Blood cultures remained sterile. Abdominal ultrasound demonstrated splenomegaly and no evidence of hepatic pathology. His chest X-ray and brain magnetic resonance studies were negative.

A diagnosis of severe *P. falciparum* malaria was made as determined by the WHO. In the microscopic examination of thin and thick blood

**TABLE 1:** The patient's initial selected laboratory tests and normal ranges are given in Table 1.

Initial selected laboratory tests		Normal range
Hemoglobin	8.9 g/dL	13.6-17.2
Hematocrit	27.4%	40- 53
Platelets	20 x10 <sup>3</sup> /mkrL	150- 350
Total white count	5.80 x10 <sup>3</sup> /mkrL	3.8- 10
Creatinine	1.53 mg/dL	0.7- 1.3
BUN	55.61 mg/dL	6- 20
Sodium	125 mmol/L	136- 145
Albumin	1.5 g/dL	3.5- 5
Total bilirubin	3.2 mg/dL	0.2- 1.2
Conjugated bilirubin	1.62 mg/dL	0- 0.5
AST	137 U/L	5- 34
ALT	17 U/L	0-55
LDH	945 U/L	125- 243
Arterial pH	7.40	7.35- 7.45
Bicarbonate	11.6 mmol/L	22- 26
Procalcitonin	>100 ng/mL	0- 0.5
C-reactive protein	144.24 mg/L	0- 6
D-dimer	> 5000	5-300

BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Laclate dehydrogenase.



**FIGURE 1:** *P. falciparum* species specific PCR with primer rFAL1: TTAACCTGGTTTGGGAAACCAATATATT and rFAL2: ACACAAT-GAATCAATCATGACTACCGTC M: Molecular weight marker (abm 100 bp plus), PC: Positive control; NC: Negative control; bp: Base pair. Expected size: 205 bp.

smears, the presence of *P. falciparum* ring forms with a parasite density of 30% was detected and confirmed by PCR (Figure 1).

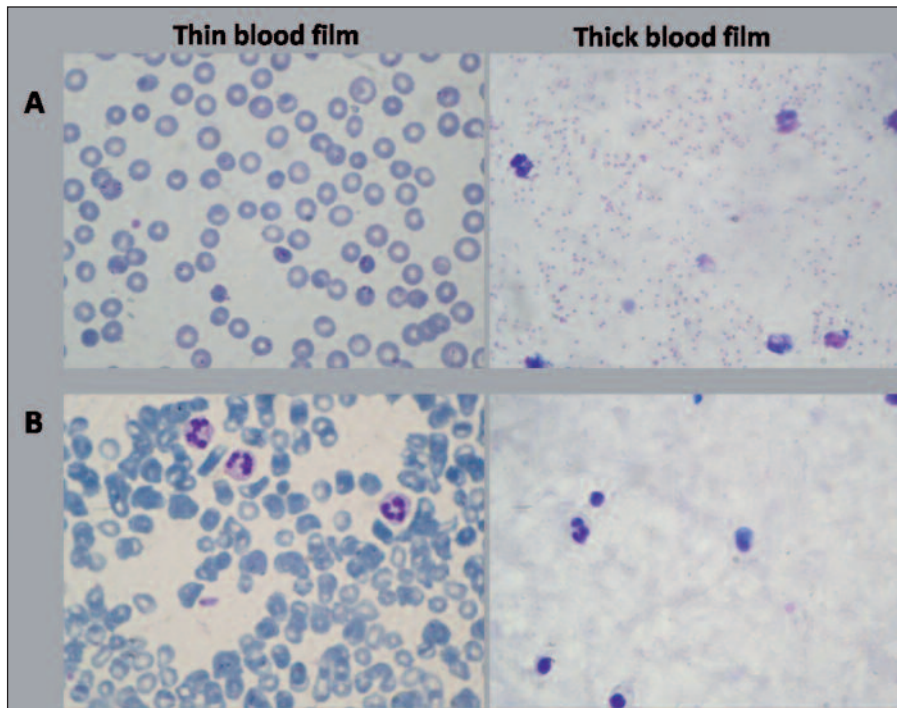
The patient was transferred to the Intensive Care Unit (ICU). He received fluid boluses of isotonic and dopamine infusion. Treatment was started with oral chloroquine and doxycycline. However in consequence of frequent vomiting despite antiemetic medication, he could not tolerate the therapy. It was decided to apply automated erythrocytapheresis. The patient's height was 185 cm, weight was 95 kg. Large-bore peripheral venous catheter was inserted to the right antecubital vein. Automated exchange transfusion (Haemonetics MCS) with 2 units of packed red blood cells was performed without complications. A total of 2535 ml of blood volume processed. The postprocedure parasite burden was approximately 10%. Upon providing artesunate, the treatment was arranged as intravenous artesunate infusion a loading dose of 2.4 mg/kg, followed by 1.2 mg/kg daily in addition to doxycycline 100 mg by mouth twice a day.

The patient's mental status, clinical and laboratory indicators of liver and renal functions were markedly improved, however the anemia persisted. The parasitemia was monitored by daily microscopic examination and on day four no malarial parasites were seen on peripheral smear (Figure 2). The patient defervesced by hospital day 7. Antimalarial therapy discontinued after 7 days. The patient made a full recovery and was discharged from the hospital 12 days after admission.

## DISCUSSION

Imported malaria continues a major threat to travelers, military personnel and immigrants from endemic countries. Mortality rate still reach up to 10% despite improved conditions in ICUs and optimal antimalarial treatment. Older age, neurological impairment, and high parasitemia have been associated with the strongest predictors of death at ICU admission.<sup>3</sup>

Complications of severe malaria include cerebral malaria, acute lung injury and acute respira-



**FIGURE 2:** Thin and thick blood smears.

**A.** Day one (Ring-form trophozoites of *P. falciparum* in thick and thin blood smear) **B.** Day four.

tory distress syndrome, acute renal failure, hypoglycemia, hypotension and shock, hematologic abnormalities.<sup>4</sup> In the patient presented here the findings consistent with severe malaria were hyperparasitemia, impaired consciousness, weakness, hyperpyrexia, acidosis, hemoglobinuria, and jaundice. The patient also demonstrated hypotension, anemia, thrombocytopenia, hyponatremia, impaired renal function and elevated hepatic enzyme levels.

These poor prognostic factors made us to consider adjunctive treatment strategies. In an effort to decrease parasite load and herewith to reduce mortality of severe malaria, erythrocytapheresis is often used as an adjunct therapy.<sup>5</sup> Manual and automated methods are available to perform erythrocyte exchange.<sup>6</sup> In automated systems using an apheresis device erythrocytes are separated from whole blood. In comparison with manual exchange, this technique is better tolerated and have lesser side effects.<sup>2</sup>

Several rational mechanisms of the benefits of ET may be proposed. ET result in a direct removal of circulating parasitized erythrocytes and rapid reduction in the parasite load.<sup>6</sup> Circulating ultralarge von Willebrand factor and factors that reduce ADAMTS 13 activity in plasma have been shown to contribute to the sequestration of infected erythrocytes in the microvasculature of vital organs. ET may also result in the removal of these factors.<sup>7</sup> Both infected as well as uninfected erythrocytes are considerably less deformable in severe malaria. These nondeformable erythrocytes adhere to sequester infected erythrocytes and thereby impair the microvascular blood flow and oxygen delivery. ET with healthy donor erythrocytes may improve microvascular diseases and oxygen-carrying capacity.<sup>8</sup>

Published data about the effectiveness of ET is controversial. Several case reports have described the successful use of ET as an adjunctive therapy for severe malaria.<sup>9-11</sup> However the efficacy of ET has not proven.

A meta analysis of 279 patients from eight studies demonstrated no significant benefit in sur-

vival associated with the use of adjunct ET. However, patients who were treated with ET had higher parasite loads and more-severe malaria.<sup>12</sup>

In another study 101 patients receiving ET were compared to 314 patients not receiving ET. No statistically significant association between ET and survival outcome has been found.<sup>5</sup>

In a retrospective cohort study of 25 patients with severe malaria efficacy and safety of ET as an adjunct therapy evaluated. The parasite clearance times had been found significantly shorter in patients treated with ET, compared with patients treated with quinine only. Case fatalities were not observed in the ET group.<sup>8</sup>

Adverse events of ET were rarely reported, but included fluid overload, transfusion reactions, metabolic disturbances like hypocalcemia, transmissible infection, bleeding, red blood cell alloantibody sensitization, acute respiratory distress syndrome, ventricular fibrillation, and hypotension.<sup>13</sup> Any adverse events did not develop in our patient.

After a single erythrocytapheresis procedure parasitemia was significantly reduced and day 4 there were no parasites on peripheral smear in our patient. It appears that presumably artesunate also have contributed to this decline.

The artemisinin derivatives; artesunate and artemether, kill circulating ring-stage parasites rapidly. So they cannot mature and sequestration of infected erythrocytes in the venules and capillaries of vital organs reduces and thereby consequent microvascular obstruction is prevented.<sup>14</sup> For the treatment of severe *P. falciparum* infections artemisinin derivatives combined with mefloquine, doxycycline or clindamycin are recommended to avoid recrudescence. Artesunate can be given by intravenous or intramuscular injection and well tolerated.<sup>4</sup> However in a study, patients adjunctively received manual ET to parenteral quinine or artesunate were compared with patients not receiving ET. Small beneficial effect of manual ET on parasite clearance determined in quinine group however no benefit found in artesunate group.<sup>15</sup> We could provide artesunate to our patient after ET procedure.

Our patient had severe falciparum malaria complicated with hyperparasitemia. The patient had a rapid and positive symptomatic and laboratory response to red blood cell exchange by automated apheresis. We believe that this case is a contribution to the literature in terms of successful and safe use of ET. In the absence of a randomized controlled trial, it would be more reasonable to evaluate each case indi-

vidually and to compare risk and benefits. In selected cases where rapid reduction in the parasite load appears necessary, erythrocytapheresis can be considered as an adjunct therapy.

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