

# Fatal Postoperative Hemolysis Due to Severe Falciparum Malaria

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## Abstract

A 60-year-old apparently healthy female patient underwent mastectomy for breast cancer. She had sinus tachycardia and no other abnormal finding in the preoperative period. However, the immediate postoperative course was stormy with the development of anemia, thrombocytopenia, hemolysis, and renal failure with severe metabolic acidosis. Peripheral blood smear revealed the presence of ring forms of *Plasmodium falciparum*. Multiorgan failure and death occurred within 36 h of surgery in spite of initiation of antimalarial agents. Diagnosis of malaria should be kept in mind in the event of development of sudden unexplained deterioration or multiorgan dysfunction associated with thrombocytopenia, hemolysis, and severe metabolic acidosis, even in previously asymptomatic patients, especially in residents or recent travelers of the malaria-endemic area.

**Keywords:** Anesthesia, cyclophosphamide, falciparum, general, hemolysis, malaria, thrombocytopenia

## INTRODUCTION

Patients living in endemic areas as well as travelers and migrants from malaria-endemic areas may harbor the malaria parasite without symptoms. Malaria, especially *Plasmodium falciparum*, can be fatal if undiagnosed and untreated or treated late.<sup>[1]</sup> Postoperative relapse of malaria has been documented in patients from malaria-endemic areas.<sup>[2]</sup> We present a case of a previously asymptomatic patient who underwent surgery for breast cancer and then developed severe malaria characterized by parasitemia, hemolysis, and multiorgan failure that lead to death.

## CASE REPORT

A 60-year-old female with history of diabetes and hypertension presented to the hospital with nonmetastatic intraductal breast carcinoma. She was scheduled for elective right modified radical mastectomy 24 days after completing four cycles of cyclophosphamide and doxorubicin based chemotherapy.

On the day of surgery, the patient was afebrile, with heart rate 130/min and blood pressure 110/70 mmHg. Tachycardia was assumed to be due to anxiety, and patient underwent surgery under general anesthesia. Intraoperative course was uneventful except for persistent tachycardia ranging

110–130/min which did not respond to deepening plane of anesthesia, repeated doses of fentanyl for analgesia, and fluid bolus of 500 ml (10 ml/kg). Surgery lasted for two hours, and after extubation, patient was conscious, pain free, and afebrile.

Tachycardia (110–130/min) persisted in the postoperative period. Four hours after extubation, the patient developed significant hypotension with mean arterial pressure (MAP) staying in range of 55–60 mmHg despite fluid boluses. In the next 6 h, the patient received almost 5400 ml (100 ml/kg) of intravenous fluid and required noradrenaline infusion 0.07 µg/kg/min to maintain her MAP of 60–65 mmHg. Invasive hemodynamic monitoring was commenced. Arterial blood gas showed severe metabolic acidosis with high lactates (HCO<sub>3</sub>: 9.4 mmol/l, Base deficit 18.5, lactate: 8.8 mmol/l). Central venous pressure was 20 cm H<sub>2</sub>O. The patient was intubated and ventilated in view of severe hemodynamic instability. The patient remained oligoanuric (60 ml over 8 h)

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with dark-colored urine. Ten hours after surgery, patient was anemic (6 g/dL) and thrombocytopenic ( $26 \times 10^9/L$ ) requiring transfusion of packed red blood cells (PRBC) and platelets.

Electrocardiogram showed sinus tachycardia, and echocardiography revealed global hypokinesia with left ventricular ejection fraction of 35%–40%. Her blood sugar was in the range of 90–140 mg/dl (5–7.78 mmol/l).

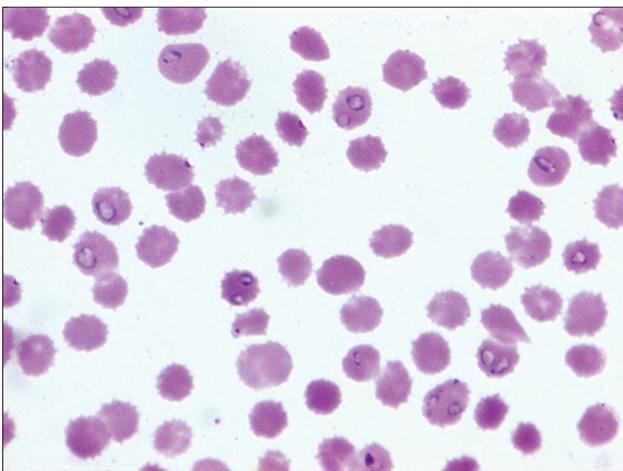
Septic shock with multiorgan dysfunction was strongly suspected due to presence of circulatory shock, severe metabolic acidosis and coagulopathy. Antibiotics were empirically escalated to meropenem.

Over the next 24 h, patient continued to deteriorate requiring incremental doses of vasopressors and developed multiorgan failure. Hemolysis was suspected due to persistently low hemoglobin (<8 g %) in spite of three units of PRBCs transfusions, hemoglobinuria on dipstick, rising serum bilirubin (6.4 g%), high lactate dehydrogenase >1500 IU/L. The peripheral smear [Figure 1] revealed fragmented RBCs and *P. falciparum* with high parasitic index (>10%). Intravenous artesunate was started. However, the patient succumbed within next 12 h. Patient's blood culture which was collected before antibiotic escalation did not grow any organism.

## DISCUSSION

Patient developed severe falciparum malaria in the postoperative period with massive intravascular hemolysis and rapid development of multiorgan failure. The absence of typical clinical features of fever and chills lead to delay in diagnosis and treatment causing a fulminant course and mortality within 36 h of surgery.

The patient did not present with typical symptoms of malaria such as fever and chills. Asymptomatic *P. falciparum* infection has been previously reported in a study of asymptomatic



**Figure 1:** Peripheral smear showing fragmented red blood cells and *Plasmodium falciparum* parasites

refugees originating from malaria-endemic countries in an Italian refugee camp.<sup>[3]</sup> Low asymptomatic parasitemia may persist in migrants from endemic areas long after their arrival in the host country,<sup>[1]</sup> and delayed clinical presentation of *P. falciparum* has been reported up to 8 years,<sup>[3]</sup> after leaving malaria-endemic area.

Surgical stress produces immunosuppression through various neuroendocrine responses leading to increased levels of adrenocorticotrophic hormone, cortisol,<sup>[4]</sup> interleukin 6, and catecholamines.<sup>[5]</sup> Glucocorticoids and catecholamines further suppress cell-mediated immunity by various mechanisms.<sup>[4]</sup> Immunity against malaria reaches nadir at 3 days after surgery.<sup>[6]</sup> Highest level of malaria parasitemia is documented on the 1<sup>st</sup> day of surgical injury in mouse model.<sup>[6]</sup> Postoperative relapse of malaria has been documented in patients from malaria-endemic areas after cardiac surgery.<sup>[2]</sup>

Cyclophosphamide being an alkylating agent is known to suppress both cellular and humoral immunity and to produce quantitative phagocyte defects.<sup>[7]</sup> The patient had received in total 2000 mg/m<sup>2</sup> cumulative dose of cyclophosphamide with last 500 mg/m<sup>2</sup> 24 days before surgery. Plausibly, the patient could have got malaria infection after her last chemotherapy dose and a couple of days before surgery. The combined immunosuppressive effects of surgery and chemotherapy could have led to the fulminant downhill course.

The diagnosis of malaria in the postoperative period can be difficult because of the many competing possibilities. Further, a striking feature in our patient was the fulminant progress of malaria. Transfusion-transmitted malaria also presents with a short incubation period due to the absence of pre-erythrocytic stage. However, it is important to note that the patient had developed shock and multiple organ dysfunction score before transfusion of blood products.

Intravascular hemolysis with rapid development of multiorgan failure can also occur with the hemolytic-uremic syndrome following diarrhea due to *Escherichia coli* (O157:H7), especially in children.<sup>[8]</sup> However, the absence of diarrhea and the presence of ring trophozoites of *P. falciparum* in blood smear favored the diagnosis of malaria.

Malaria is not the problem of developing countries alone. With the revolution in aviation transport, it is also one of the most frequently imported tropical diseases in the developed world.<sup>[9]</sup> Kyriacou *et al.*<sup>[10]</sup> have reported missed diagnosis in 40% and delayed treatment in 80% of falciparum malaria cases presenting to an emergency department in the United States. Eliciting thorough travel history to look for visit to malaria-endemic areas in patients with possible infectious disease might help in early diagnosis and treatment.

History of recent febrile illness should be inquired to residents or frequent travelers to malaria-endemic area. In this group of patients, with the history of recent fever, platelet count should be checked before any stressful intervention like surgery or chemotherapy. The presence of thrombocytopenia

should prompt peripheral smear or malaria rapid diagnostic tests for possible malaria infection. Thrombocytopenia with multiorgan dysfunction in this cohort, should be promptly treated with empirical antimalarial agents pending results of malaria and other tests to avoid delay.

## CONCLUSION

Residents or travelers of a malaria-endemic area can harbor malaria infection without any symptoms. Diagnosis of malaria should be kept in mind in such patients in the event of development of sudden unexplained deterioration or multiorgan dysfunction, especially in the presence of thrombocytopenia, hemolysis, or severe metabolic acidosis. In our opinion, in residents and travelers of malaria-endemic area, one should keep high index of suspicion and low threshold for investigation and should initiate prompt treatment for malaria. Empirical treatment for malaria should be initiated without delay in the presence of both thrombocytopenia and multiorgan dysfunction.

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## Conflicts of interest

There are no conflicts of interest.

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