Anesthetic management of urgent cesarean delivery in a parturient with acute malaria infection
-a case report-

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Malaria is associated with high rates of morbidity and mortality worldwide, particularly in Africa, Southeast Asia and South America. Nonetheless, several cases of malaria have been reported in Western countries involving travelers from endemic areas, though very few involve pregnant women. In this article, we report a case of a young woman born in Sierra Leone who had been living in Italy for two years. She was admitted to our hospital with malaise; worsening of her condition led to *Plasmodium falciparum* infection diagnosis early during her hospital stay, as well as an urgent cesarean delivery. We briefly discuss the features of malaria in pregnancy, the difficulties associated with early diagnosis, and the possible fetal and maternal implications, and also consider how the disease may affect anesthetic management.

Key Words: Cesarean section, Malaria, Premature birth, Spinal anesthesia.

Malaria remains an important cause of morbidity and mortality worldwide. Despite the fact that only three cases of malaria were recorded in 2013 in Western Europe, the global incidence is estimated at 2.36 per 100,000 population per year; in Africa and Southeast Asia, the death rate ranges from 7.5 to > 80 per 100,000 people [1]. Furthermore, pregnancies may also be affected by *Plasmodium* parasites, but studies on the most appropriate anesthetic management during labor and delivery remain scarce [2]. We present herein a case of 28th gestational week (GW) pregnancy with a diagnosis of malaria following an episode of sudden loss of consciousness during a hospital stay; the patient underwent urgent cesarean delivery (CD) under spinal anesthesia.

Case Report

A 27-year-old pregnant G4P2 (28th GW), born in Western Africa but living in Italy since 2012, presented to the emergency department (ED) of our institution with headache, vomiting, diarrhea, and pelvic and low back pain. She contracted malaria in 2007 in Western Africa, but did not mention this on admission. ED laboratory tests were within the normal range, except for a slight increase in lactic dehydrogenase (LDH; 310 mg/dl) and mild anemia (hemoglobin [Hb]; 9.9 g/dl, Table 1). No morphological abnormalities were found on renal echography. Two days after discharge she returned due to persistent symptoms and hy-

Table 1. Laboratory Tests

	ED	After LOC	Before CD	Day after CD
Hemoglobin (g/dl)	9.9	7.8	8.7	8.3
PLT count ($\times 10^9$/L)	229	101	98	121
WBC count ($\times 10^9$/L)	7.08	5.29	7.22	12.02
Parasitemia (%)	N/A	7	8.6	2.5
Bilirubin (mg/dl)	1.15	2.95	2.69	1.64
LDH (UI/L)	310	466	547	505
Glycemia (mg/dl)	84	119	79	95
Lactate (mmol/L)	N/A	N/A	1.4	N/A
CRP (mg/dl)	N/A	219	N/A	N/A

ED: emergency department, LOC: loss of consciousness, CD: cesarean delivery, PLT: platelet, WBC: white blood cell, LDH: lactic dehydrogenase, CRP: C-reactive protein, N/A: not available.

perpyrexia. She was admitted to the obstetric ward and prophylactic ceftriaxone (2 g/day) was administered. Almost 24 h after admission, peak hyperthermia (39.4°C) was reached, with concomitant loss of consciousness. She recovered in approximately 15 min; residual aphasia and evident cognitive impairment improved slowly over a few hours. Neither rigor nucalis nor any signs of focal deficit were present on neurological examination. No pathological abnormalities of the central nervous system were found during an urgent head computed tomography scan. Respiratory and hemodynamic parameters remained stable (SpO$_2$ 99% in room air, blood pressure [BP] = 135/70 mmHg, heart rate [HR] = 95 beats per minute [bpm]). Blood samples were drawn again (Table 1) and exhibited increased C-reactive protein (CRP; 218.68 mg/L), bilirubin (2.95 mg/dl, direct = 1.18 mg/dl) and LDH (466 mg/dl) levels. Notably, Hb decreased to 7.8 g/dl and malaria parasites were found on examination of the peripheral blood smear (blood parasites, 7%). Infectious disease (I.D.) specialist prescribed quinine (600 mg) for 2 h (bolus) followed by 2 g in 24 h, plus clindamycin (600 mg) every 8 h to achieve tight control of glycemia, BP and electrocardiography. Because fetal parasitemia and hemolysis were strongly suspected, a CD was planned. The patient's general condition was stable; no coagulation abnormalities were present and the platelet count was slightly lower than normal (PLT 98.000 /ml). Therefore, 1000 ml of lactated Ringer's solution and ranitidine (100 mg) were administered intravenously. In a sitting position, spinal anesthesia was performed at the L3-L4 interspace. Using a 25-gauge Whitacre needle, hyperbaric bupivacaine 0.5% (10 mg) with sufentanil (5 μg) was injected intrathecally. The patient was left in a supine position with left uterine displacement; the surgery was initiated when the anesthetic block reached the T4 level. BP decreased slightly (from 134/85 mmHg to 120/68 mmHg), then remained stable throughout surgery. At birth, the baby had slight respiratory depression (Apgar score of 8 at 1 and 5 min), and a bloodless umbilical cord on inspection. Her weight was 1.77 kg and she required immediate oxygen support

with a nasal cannula for hypoxemia (SpO$_2$ rapidly decreased to < 80% in room air after aspiration). Oxytocin (20 IU) in 5% dextrose (500 ml at 125 ml/h) was started immediately after birth. Postoperative analgesia was obtained with a patient-controlled analgesia pump that delivered 1 mg/h of morphine for 24 h, with boluses of 2 mg possible on patient request every hour. Additional intravenous acetaminophen (1 g every 6 h) was prescribed. Surgery was uncomplicated and blood loss was estimated to be approximately 500 ml. *Plasmodium falciparum* was identified only 4 days later by real-time polymerase chain reaction. Blood parasites decreased over time (1% in the final blood sample, after 5 days). The patient's antibiotic therapy continued and her symptoms were completely resolved two days after childbirth; 24 h after birth, oxygen therapy for the baby was discontinued. Blood samples drawn from the baby and the umbilical cord revealed no parasites, nor any signs of fetal hemolysis.

Discussion

Among infectious diseases, malaria is most frequently imported into developed countries [3] due to its wide diffusion in Africa, India and Southeast Asia [1]. *Plasmodium falciparum* is the most-common etiologic agent in Africa; *P. vivax, ovale, malariae* and *knowlesi* (recently identified) represent causes of infection in Asia and other endemic regions [4]. Infection is transmitted by the bite of female Anopheline mosquitoes, which inoculates sporozoites that are taken up by hepatocytes; maturation then occurs over 7–10 days to produce schizonts. During the next stage of development, merozoites are released into the blood, which invade red blood cells and mature into gametocytes or schizonts over a period of 24–72 h (depending on the species). Mature schizonts rupture erythrocytes and cause hemolysis and further release of merozoites into the bloodstream. The characteristic clinical manifestations of disease are both caused by hemolysis: hyperpyrexia occurring every 48–72 h and global organ hypoperfusion caused by adhesion of schizonts to

the lining of small blood vessels and resulting occlusion of capillary beds. During their maturation cycle, *P. vivax* and *ovale* also pass through a hypnozoite stage that allows the parasite to hide in hepatocytes for long periods before recrudescence [5]. The clinical manifestations of malaria can vary from no symptoms to mild-to-severe systemic involvement. Manifestations may include hematological compromise with anemia [6], thrombocytopenia, coagulopathy with possible disseminated intravascular coagulation (in the worst cases) [7], shock, respiratory insufficiency [8] that frequently requires supportive therapies in intensive care [9], neurological involvement [10], ranging from mild cognitive impairment to coma; acute kidney injury [11], and hypoglycemic crisis [12].

In Africa, 25% of pregnant women experience malarial infection in regions of stable transmission, compared to 13.7% of pregnancies in areas of low transmission [13]. Pregnancy increases susceptibility to severe infection and complications (such as anemia, hypoglycemia, and pulmonary edema) because of pregnancy-associated alterations in acquired immune responses and the tendency of falciparum species to become sequestered in the placenta [14]. Therefore, death rates from severe malaria in pregnancy are two- to ten-fold higher compared to the non-pregnant population; moreover, malaria doubles the risk of low birth weight and stillbirth. Furthermore, the risk of transplacental transmission of the parasite is not negligible: in one study, more than half (57%) of women with peripheral parasitemia had placental malaria, 3.8% of whom had parasites in their umbilical cord blood [13]. The main risk factor for malaria transmission is the severity of infection at the time of delivery (high-density peripheral and placental parasitemia). If fetal transmission occurs, the baby has a higher risk of anemia with congenital malaria, as seen in 8–33% of births [13]. In our case, I.D. specialist consulted after the patient's hyperpyrexia and loss of consciousness suspected malaria, so peripheral blood film was screened for parasites, even though the patient had not recently traveled to endemic areas. The literature contains no information concerning possible *Plasmodium falciparum* infection relapse in non-endemic areas; therefore, we speculate that increasing estrogen and progesterone concentrations, commensurate with advances in pregnancy, decrease the mother's immunity by reducing natural killer T-cell activity, and possibly also B-cell activity, thus causing a relapse of dormant *Plasmodium* [14]. In our case, although it is unlikely that *Plasmodium falciparum* reactivation occurred more than two years after possible contact with the parasite, a clear diagnosis of malaria was possible because parasites were identified in the peripheral blood smear. A similar event has been described previously [15]. The infection responded to antimalarial therapy; after the first episode of neurologic impairment, our patient showed no signs of cerebral malaria. Her BP and breathing were stable throughout the CD, while the platelet count was slightly lower than normal (PLT 98.000 /ml).

Though few studies have evaluated neuraxial anesthesia in parturients with malaria, we selected spinal anesthesia for the CD due to the absence of significant thrombocytopenia, coagulopathy, secondary bacterial sepsis, or cerebral malaria with raised intracranial pressure (ICP). In two other recent cases, CD was performed under general anesthesia due to severe systemic sepsis, which required a subsequent admission to the intensive care unit for mechanical ventilation due to respiratory failure or multiorgan failure caused by *Leptospira* co-infection [2]. In our case, the mother's parasitemia was severe (7%), but there was no worsening of her general condition after the loss of consciousness episode. Medical therapy was effective for rapid reduction of peripheral parasites. Accordingly, after initial support with an oxygen cannula, the baby was weaned rapidly; her general condition was stable, with no malarial parasites identified in peripheral blood smears. In conclusion, malaria infection is a rare pathology at our latitude, particularly during pregnancy. Fortunately, transplacental transmission is uncommon, but the baby may suffer due to anemia in the mother, with low birth weight or stillbirth occurring in the worst scenarios. It remains unclear whether pregnancy itself can stimulate an infection relapse in people from endemic areas. However, in the absence of signs of sepsis, coagulation abnormalities or raised ICP, spinal anesthesia can be used as an alternative to general anesthesia.

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