Case Report: Delayed Diagnosis of Congenital Malaria by *Plasmodium vivax* in a Newborn of an Eritrean Woman with Varicella Infection

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Abstract. Congenital malaria (CM) is uncommon in both malaria-endemic and non-endemic countries. It may be caused by any *Plasmodium* spp., although *Plasmodium falciparum* and *Plasmodium vivax* are the more frequent etiologic agents. We report a case of delayed diagnosis of CM by *P. vivax* in a newborn of an Eritrean *primigravida*. The mother developed pregnancy-related immunodepression and varicella-zoster viral infection 9 days before natural delivery; therefore, the child was admitted in the neonatal intensive care unit (NICU) to administer specific varicella-zoster immunoglobulin prophylaxis and for clinical monitoring. During the NICU stay, the newborn presented a febrile syndrome with vomiting, anemia, and thrombocytopenia. A *P. vivax* severe malaria diagnosis was made by detecting trophozoites in the thick and thin blood smears. The infant was successfully treated with intravenous artesunate and clindamycin. Our experience suggests that malaria diagnostic tests need to be included in routine blood analyses in newborns with febrile syndrome from mothers with an epidemiologic link to malaria-endemic areas.

INTRODUCTION

Congenital malaria (CM) is a rare manifestation in both malaria-endemic and non-endemic areas. It appears that CM can be caused by placental passage before birth or by direct blood–blood contact during delivery.^{1,2} Congenital malaria can be defined as the presence of malaria parasites in the cord blood entering the fetal blood circulation or as the presence of asexual parasites in the neonate's peripheral blood within the first 7 days of life.^{2–4} The low rate of transmission during pregnancy is due to several factors: first, the effectiveness of the placenta as a barrier to maternal infected red blood cell; second, the passive transfer of maternal antibodies; and third, the protective role of fetal hemoglobin (Hb).^{5,6} *Primigravidae* are more susceptible than *multigravidae* to CM and have a higher incidence of placental malaria. In malaria-endemic areas, pregnant women often present a placenta parasitized by *Plasmodium* spp. without any evidence of infection in the newborns.^{7,8} In Europe, most imported CM cases are caused by *Plasmodium vivax*. This *Plasmodium* is the most frequently found, in these settings, due to the partial loss of protective immunity in migrant women and to the immunosuppression commonly seen in the last pregnancy stages. Even if *P. vivax* does not have the ability to cytoadhere to the placenta (whereas *Plasmodium falciparum* does), it has been associated with maternal anemia, intrauterine growth retardation, premature labor, low birthweight (LBW), and CM.^{9,10} We report a case of delayed diagnosis of severe CM due to *P. vivax*.

CASE PRESENTATION

A preterm (35 weeks and 5 days), LBW (2,500 grams), female neonate born of a mother with varicella-zoster viral infection was admitted in September 2017 to the neonatal intensive care unit (NICU) of the San Camillo-Forlanini Hospital in Rome (Italy) to receive varicella-zoster-specific

immunoglobulin as primary prophylaxis. Despite adequate formula feeding, the preterm infant showed poor physiological growth. On day 13 of the admission, intravenous (iv) ceftriaxone (130 mg daily) was started as empiric therapy for bacteriuria and watery diarrhea episodes. Urine and stool cultures were performed. Urinary tract ultrasound showed no alterations. On day 19, the newborn presented an abrupt onset of fever (peak of 39°C) with normal physical examination. Laboratory evaluation showed anemia (Hb = 9 g/dL), severe thrombocytopenia (platelets 24,000/mm³), and elevated C-reactive protein (14.1 mg/dL). Blood cultures were negative. Chest X-ray did not show alterations. Urine culture was positive for *Enterococcus faecalis* and iv ampicillin at the dosage of 125 mg every 8 hours plus iv gentamycin at the dosage of 11 mg daily were started; 24 hours later, the infant was still febrile. On day 22, the infant was persistently febrile; finally, thick and thin blood smears were performed and *P. vivax* trophozoites with 0.1% parasitemia were detected. The diagnosis was confirmed by polymerase chain reaction (PCR) and by malaria rapid diagnostic test (*CareStart*[™] Malaria HRP2/pLDH [Pf/Pv]; Access Bio, Inc, Somerset, NJ). Intravenous artesunate (2.4 mg/kg given twice daily for the first day and then once daily for 3 days) and iv clindamycin (10 mg/kg as loading dose and then 5 mg/kg every 8 hours for 7 days) were started.

The Hb value reached 5.6 gr/dL (hematocrit: 16%) and the infant received red blood cell transfusion (55 mL). Three days after the beginning of the antimalarial treatment, peripheral parasitemia was cleared, and at day 37, the neonate was discharged from the NICU in good clinical conditions. Clinical characteristics of the newborn are summarized in Table 1. No eradication treatment with primaquine was given considering the absence of the exoerythrocytic cycle. The anamnesis of the mother was then reassessed. She was a *primigravida*, Eritrean immigrant who arrived in Italy in July 2017. She referred one episode of fever with chills in a Libyan refugee camp in December 2016, at the beginning of the pregnancy. We can hypothesize the time of malaria infection for the mother but no microbiological reports or therapeutic info are available. Nine days before delivery, in September 2017, she was admitted to the National Institute of Infectious Diseases “Lazzaro

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TABLE 1
Parameters

	September 13, 2017	September 16, 2017	September 17, 2017	September 19, 2017
Body temperature (°C)	39	38.8	37	36
C-reactive protein (mg/dL)	3.55	14.15	–	4.05
Hemoglobin (gr/dL)	9.20	8.50	5.60	13.20
Platelets count (no./mmc)	37,000	24,000	20,000	92,000
Bilirubin total (mg/dL)	5.10	7.50	5.50	1.9
Thick and thin blood smears	–	Positive	Positive	Negative
Parasitemia (trophozoites/ μ L)	–	3,000	120	Negative

Spallanzani” for varicella-zoster viral infection, confirmed by serological tests and PCR. Thin and thick blood smears and malaria Pf/Pv Ab ELISA rapid diagnostic test were all performed and resulted negative. She was successfully treated with iv acyclovir 10 mg/kg every 8 hours for 7 days and then discharged. At the time of the neonate’s malaria diagnosis, the mother’s thick and thin blood smears were repeated and resulted positive for *P. vivax* malaria. In addition, the mother’s residual whole blood sample, collected at the time of the varicella infection, was obtained from the virology laboratory and the PCR assay for *P. vivax* resulted positive. The Eritrean mother was successfully treated with oral chloroquine (10 mg/kg as the initial dose, followed by 10 mg/kg on the second day, and 5 mg/kg on the third day). Given the normal glucose-6-phosphate dehydrogenase levels, she received oral primaquine (30 mg daily for 14 days) as eradication therapy. The infant and the mother were monitored for a month with weekly thin and thick blood smears, which resulted always negative.

DISCUSSION

This case underlines the relevance of an epidemiologic risk assessment on malaria exposure in pregnant women traveling abroad from a malaria-endemic country. The mother’s first malaria episode probably occurred early in the pregnancy and was not considered both in the first clinical approach and at the time of delivery. This lack of attention delayed the newborn’s CM diagnosis. The onset of severe malaria in newborns is a very rare event. The first report dates back to 1876 and showed a CM incidence of 0.18–0.3%. More recent studies suggest a wider range of incidence (from 0.3% to 33%).^{11–14} In the literature, there are no consistent data on CM in non-endemic countries. In our case, the fact that the pregnant woman had developed varicella-zoster viral infection derailed the medical staff attention, becoming the main focus of diagnostic examinations and therapeutic efforts. Only the diagnosis of CM in the newborn made the medical personnel think about the possibility of a mother-to-child transmission, and this was confirmed by the positive PCR for *P. vivax* in the mother’s residual blood from the first sample collected. The mechanisms of malaria transmission during birth or pregnancy are reported as direct penetration via chorionic villi or penetration through premature rupture of membrane. Parasites may interfere with the placental circulation, thickening the trophoblastic basement and increasing fibrinoid necrosis, thus reducing the blood flow resulting in LBW and prematurity.¹⁵

The newborn was not treated with primaquine like her mother; in fact, *P. vivax* CM is transmitted by trophozoites and not by sporozoites and the absence of an exoerythrocytic phase precludes the need to eradicate latent hepatic forms.^{16,17} Although oral chloroquine is the standard of care for *P. vivax* CM, iv quinine (or quinidine gluconate) may be an alternative option.¹⁸ Conversely, in *P. falciparum* CM, high dosage of artesunate (3 mg/kg/day) should be considered. In our case, the newborn was treated with iv artesunate because of the severity of her clinical condition according to the 2015 World Health Organization guidelines on malaria treatment.¹⁹ In conclusion, we suggest that CM should be included in the differential diagnosis of infants displaying signs and symptoms of a febrile syndrome with hemolytic anemia, thrombocytopenia, or any other septic-like manifestation if they are born from women who may have recently traveled from malaria-endemic countries. Early diagnosis is essential for prompt treatment and may prevent an unfavorable outcome.

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