It is All in the Smear

An Unusual Cause of Puerperal Sepsis

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Abstract: Puerperal sepsis is the leading cause of direct maternal mortality in the United Kingdom. In recent years, efforts have been made to increase awareness and reduce the burden of sepsis in pregnancy. We report the case of a 29-year-old Pakistani lady admitted to a London hospital at 37 + 3 weeks' gestation with signs of infection and fetal distress. She had an emergency cesarean delivery and was treated for presumed chorioamnionitis. In the early postpartum period, she had a rapid deterioration exhibiting signs of septic shock. As part of her investigations, a blood smear demonstrated *Plasmodium vivax* parasitemia. *Plasmodium falciparum* is well documented as causing severe illness in pregnancy, whereas *P vivax* is often considered a benign form of malaria. The complex manifestation seen in this case reinforces the changing opinion of *P vivax* and its implications in pregnancy. It is prudent for physicians outside of endemic areas to remain vigilant of imported malaria.

Key Words: Pregnancy, puerperal sepsis, *Plasmodium vivax*, algid malaria, chorioamnionitis

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A 29-year-old Pakistani primigravida presented to an east London hospital at 37 + 3 weeks' gestation with a 4-day history of fever, abdominal pain, and reduced fetal movements. Antenatally, she was at low risk at booking, and the pregnancy had been unremarkable thus far. There was no significant medical or surgical history. Her initial observations were the following: pulse, 130 beats per minute; blood pressure, 117/77 mm Hg; and temperature, 37°C. Result of general examination was normal, and the cervix was found to be long and closed. Cardiotocography was commenced, which immediately demonstrated a pathological trace: a complex fetal tachycardia with late decelerations.

An emergency cesarean section for fetal distress and suspected chorioamnionitis was undertaken within an hour of assessment. The initial blood test results demonstrated a normal hemoglobin (12.1 g/dL), leukocytosis (14.2×10^9), normal eosinophils (0.1×10^9), and thrombocytopenia (82×10^9). Renal function and coagulation were normal.

A small-for-gestational-age male infant, weighing 2.35 kg, was delivered with Apgars of 2 at 1 minute and 9 at 5 minutes. Umbilical cord blood was analyzed, with an arterial pH of 7.241 and a base excess of −6.9.

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Intraoperatively, the placenta and amniotic fluid were noted to be foul smelling. Placental swabs were taken for culture, and the placenta was sent for histopathological analysis. Surgical blood loss was 600 mL; the cesarean delivery was otherwise uncomplicated. In view of suspected chorioamnionitis, intravenous cefuroxime and metronidazole were commenced. The neonate was transferred to the special care baby unit for management of hypoglycemia and presumed infection.

Postoperatively, the patient was initially monitored in the maternity high-dependency area; her vital signs normalized and she appeared to be making a good recovery. After 24 hours, she was transferred to the postnatal ward for continuation of treatment and routine postcesarean care.

Mother and baby continued to make good progress; the mother's blood results began to normalize, and the baby was feeding well. Late on her second postoperative day, the patient had a rapid deterioration. She became pale and clammy and complained of a headache. Her vital signs were consistent with shock: pulse, 115 beats per minute; blood pressure, 70/30 mm Hg; temperature, 37.3°C; and respiratory rate, 22/min. The blood pressure was initially resistant to colloid and crystalloid fluid replacement. Brief history and examination revealed no obvious source for the infection. Once new cultures were taken, the patient was given intravenous gentamicin; and a plan was made to transfer her back to maternity high dependency. Venous blood gas was normal, with pH of 7.407; however, the lactate was raised at 6.33 mmol/L. New blood test results showed a dramatic drop in hemoglobin (7.8 g/dL), platelets (46×10^9/L), and white blood cell count (1.7×10^9/L). Senior obstetric, anesthetic, and microbiological advice was sought and a plan made for the patient to be transferred to the intensive care unit if not responding to treatment.

The patient began to stabilize with continued supportive treatment. The following day, a blood smear was prepared for investigation of thrombocytopenia. This resulted in an incidental finding of *Plasmodium vivax* malaria.

Further history taking revealed that the patient had been in Pakistan for a duration of 2 months and had returned 4 months ago. She had not taken any malaria prophylaxis.

The patient was treated according to local protocol and with guidance from infectious disease specialists. Oral chloroquine was given for 3 days, followed by primaquine for 2 weeks, once glucose-6-phosphate dehydrogenase levels had been confirmed as normal.

The neonatal team was informed at the time of diagnosis, and consecutive blood smears were performed. All neonatal blood smears were negative for malarial parasites.

Results of maternal blood cultures; urine cultures; and vaginal, placental, and uterine swabs were negative. Placental histology was unremarkable, with no evidence of chorioamnionitis or malarial sequestration.

At follow-up 6 weeks later, both mother and infant were well. Maternal blood test results had all returned to normal, and a new blood smear was clear of malarial parasitemia.

DISCUSSION

This case alerts the physician to 2 important points regarding the management of pregnant women with malaria.

First, there must be a suspicion of the diagnosis when evaluating women with an infective picture, either during pregnancy or in the puerperium, especially if having previously visited an endemic area.[1]

Second, whereas *Plasmodium vivax* is considered a "benign tertian malaria," it has the potential for severe and overwhelming infection, notably in the presence of comorbidities.[2] This case is a timely reminder as the Malaria Policy Advisory Committee (MPAC) to the World Health Organization (WHO) showed concern that the disease had been overlooked in previous malaria protocols. The MPAC recommended in September 2012 that "a global strategy for *P vivax* malaria was urgently needed[3]" and for a steering committee to develop a plan for its control and eradication.

A PubMed search of recently published case studies demonstrates that this is not an isolated case of incidental finding of maternal *P vivax* in the UK. Milne et al[4] describe a similar case at 29 weeks' gestation in Aberdeen, also not clinically suspected but diagnosed on a blood smear taken to investigate hematological abnormalities. It is well documented that malaria can present in atypical ways, particularly during pregnancy, which further hinders the physician from considering it as a primary diagnosis. Furthermore, during pregnancy, blood smears may be negative for parasitemia in an infected adult, although this is generally associated with *Plasmodium falciparum* and placental sequestration.[1,5] The risks of malaria in pregnancy are well documented; however, the puerperium has not enjoyed the same scrutiny.[6]

The case presented is unusual, as the patient developed profound hypotension and significantly deranged hematological markers, signifying complicated malaria.[7] There is an increasing awareness that *P vivax* can cause severe illness[8,9] and that if untreated can have dire consequences, particularly during pregnancy.[10,11] This case demonstrates a woman treated appropriately for suspected chorioamnionitis, with latter events possibly representing a symbiosis between the chorioamniotic pathogens and *P vivax* resulting in "algid malaria". It is recognized that negative blood cultures do not rule out such a diagnosis,[1] and the patient's positive response to gram-negative cover would support this hypothesis. Algid malaria is reported to be more common and more severe in the pregnant patient[7] although usually associated with *P falciparum* rather than *P vivax*.[12]

The current interest in *P vivax*'s nature has demonstrated that not only is "benign" a misnomer, but that neglect has led the species to become dominant in areas of *P falciparum* coexistence.[13,14] There is also mounting evidence that *P vivax* too has significant maternal and fetal consequences including anemia and low birth weight.[15] This has led to an impetus for further research and *P vivax*–specific protocols for its management in pregnancy. "Pregvax" is a multinational collaborative project geared toward addressing this dearth in knowledge and formulating a clinical response.[16] This is encouraging when considered in combination with the aforementioned MPAC to the WHO commitments, and the ongoing research being produced by other institutions, such as the Shoklo Malaria Research Unit on the Thai-Burmese Border.[17]

The last triannual report of UK maternal deaths,[18] reported that the leading cause of direct maternal death is infection, with mortality reported to be as high as 60% in the event of septic shock.[19,20] This is an alarming change from previous reports, and has resulted in renewed attention on hygiene around delivery and awareness of the signs of infection during and after childbirth. The Royal College of Obstetricians and Gynaecologists (RCOG) have produced a series of guidelines for the diagnosis and management of maternal collapse and sepsis.[19–21] The initial resuscitation and treatment in this case of puerperal sepsis broadly followed these guidelines. In none of these RCOG guidelines is malaria mentioned as a consideration for differential diagnosis or investigation. Given the itinerant nature of some of the UK population, and as the above case illustrates, this would be a worthy amendment to future editions. The RCOG has however recognised the need for UK clinicians to be aware of malaria presenting in pregnancy through the publication of two separate guidelines.[7,22] These offer a comprehensive review of both prevention and management of malaria during pregnancy.

In ethnically diverse areas with highly mobile populations, such as east London, it is imperative that malaria remains a differential in any infective presentation. Even where a potential source of infection is identified, as in the above case, malaria may prevail. More specifically, in non-falciparum strains the clinician would be wise to consider the diagnosis even when travel has not been recent as *P. vivax* is known to present more than a year after exposure.[1,13] Imported cases of *P. vivax* to the UK have been rising in recent years,[23] it can therefore be inferred that clinicians should keep suspicions of the disease high alongside other differential diagnoses.

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