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CASE REPORT

Maternal Sepsis in the Third Trimester Due to Plasmodium falciparum: A Case Report

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ABSTRACT

Sepsis is a leading cause of maternal mortality internationally. Early detection and intervention improve both maternal and fetal outcomes. We describe a case of sepsis in a pregnant patient who had recently immigrated to the United States from Tanzania. She was transferred to our quaternary maternal facility at 31 weeks gestation for fever and sepsis of unknown origin. She required critical care management with broad testing to determine the etiology of her presentation. The source of her sepsis was ultimately attributed to a maternal malarial infection following two positive blood smears and PCR assays for Plasmodium falciparum with low parasitemia. She was appropriately treated leading to the patient's eventual term delivery without complication. This case report will detail the above patient's clinical course in addition to a discussion regarding severe malaria and severe sepsis.

Introduction

Globally, sepsis is the third leading cause of maternal mortality, accounting for about 11% of pregnancy-related deaths. [1,2] Low and middle-income countries have historically experienced higher rates of mortality attributed to infections in pregnancy (10.3 to 13.7% versus 4.7% in high-income countries), but recent reports estimate that infection or sepsis now accounts for 13.9 to 48.8% of all pregnancy-related deaths in the United States[2-4]. These estimates place infection or sepsis as a leading cause of maternal mortality in the United States. [5,6]

During pregnancy, septic etiology is most often linked to genitourinary, intrauterine, or fascial sources; septic pelvic thrombophlebitis, pneumonia, and appendicitis are other commonly recognized inciting factors. [3,7] In the United Kingdom, only 64% of causative organisms were detected through laboratory testing, and 74% of cases had an identified infectious source. [3] Given the improved outcomes associated with early detection of sepsis, several scoring systems have been proposed to help diagnose sepsis and provide prognostic information for these patients. [3,7-9] The Third International Consensus Definitions for Sepsis and Septic Shock Task Force in 2016 define sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection." [9] Organ dysfunction can be defined as a score of 2 or greater on the Sequential Organ Failure Assessment (SOFA) score, which takes into account respiratory status, platelet count, bilirubin levels, mean arterial pressure, Glasgow Coma Score, creatinine level, and urine output.[8] Of note, these early detection tools are imperfect when accounting for the physiologic changes of pregnancy. For this reason, the Society for Maternal Fetal Medicine concluded that institutions should develop their own protocol for identifying sepsis in pregnant patients, incorporating principles from more than one available screening tool.[3]

Once sepsis is identified, optimal management involves early administration of broad-spectrum intravenous antibiotics, plasma volume expansion using crystalloid or blood products, maintaining proper ventilatory status, monitoring maternal and fetal hemodynamics, and initiation of vasopressor therapy as indicated.[7]

Malaria is a febrile disease caused by a protozoa in the genus Plasmodium.[10-12] Malarial infections are classified as either uncomplicated or severe.[10] Malarial infection is considered "severe" when there is clinical or laboratory evidence of vital organ dysfunction.[13, 14] Table 1 Severe malarial infection and sepsis can have significant overlap including findings such as acidosis, kidney injury, and pulmonary edema.[14] Of note, shock is less common in severe malaria as compared to severe sepsis.[15]

Case Presentation

The patient is a 22-year-old G3P2001 who was transferred to our facility at 31 weeks of gestation in the setting of fever and sepsis of unknown origin. She had presented to an outside hospital with a severe headache, subjective fevers, and chills that had persisted for 1 week. She was taking antipyretics at home without relief of her symptoms. She reported no nasal congestion, shortness of breath, chest pain, palpitations, urinary symptoms, or obstetric complaints.

She immigrated from Tanzania to the United States 4 months prior to presentation. The patient and her family members spoke Swahili only. She received prenatal care through a community center and described pregnancy dating based on her last menstrual period. Her obstetric history was notable for a term cesarean delivery due to fetal malpresentation when the patient was 16 years old; at age 21, the patient then had a successful vaginal delivery of a female neonate. Unfortunately, her daughter passed away 1-2 days after delivery. The patient thought that her neonate was healthy throughout pregnancy and at birth – thus, the cause of death remains unknown. Both of the patient's previous deliveries occurred at a refugee camp where she resided in Tanzania. She was asked about a history of malaria and initially answered yes to this. On clarification, the certified medical interpreter stated that in East Africa, the term "malaria" is colloquially used for any febrile illness. The patient recalled negative blood testing for malaria prior to immigration and denied previous treatment for a Plasmodium infection.

At the outside hospital, the patient was febrile to 39.4 degrees Celsius, tachycardic with a heart rate up to 152 beats per minute, and tachypneic with a respiratory rate between 33 and 38 breaths per minute. Blood pressure range was 88 to 110/50 to 71 mmHg with mean arterial pressures between 64 and 82 mmHg. She was saturating between 99 and 100% on room air. Fetal tachycardia was noted with a persistent heart rate between 170 and 180 beats per minute, but monitoring was reactive with moderate variability and no decelerations. Her cervix was closed on examination and tocometry exhibited irregular contractions. She was resuscitated with intravenous (IV) fluids and started on piperacillin-tazobactam 3.375 grams every 6 hours.

The patient's white blood cell (WBC) count was 4K/uL, hemoglobin (Hgb) was 9.4g/dL, and platelets were 101K/uL. Creatinine, liver function tests, and bilirubin were within normal limits. Lactic acid was 0.9mmol/L. An extended respiratory virus panel was collected and negative for adenovirus, five strains of coronavirus including SARS-CoVID, human metapneumovirus, rhinovirus, influenza A and B, parainfluenza virus 1, 2, 3, and 4, respiratory syncytial virus, Bordetella pertussis, chlamydia pneumoniae, and mycoplasma pneumoniae. Urinalysis revealed yellow urine with a normal specific gravity and no nitrites or hemoglobin but 100 mg/dL of protein, 12 mg/dL of urobilinogen, 25 U/L of leukocyte esterase, 4 WBC per high-powered field (HPF), and 4 squamous epithelial cells per HPF. Subsequent urine protein creatinine ratio was 0.6. A chest X-ray revealed hypoinflated lungs with no effusions or consolidations. Blood and urine cultures were collected and pending. When the patient had minimal improvement with resuscitation, she received a dose of betamethasone and was transferred to a higher level of care.

On admission at our institutions surgical intensive care unit (SICU) (unit where obstetrical monitoring capabilities are additionally available), the patient was noted to have continued pancytopenia with a WBC count of 2.85K/uL,

Hgb of 8.2g/dL, and platelet count of 76K/uL. Absolute neutrophil count was 2.4K/uL and haptoglobin was low at 23mg/dL. PT was 14.9 seconds, INR was 1.2, and fibrinogen was 280mg/dL. Her signs of systemic infection (reflective by her vital signs) in the setting of laboratory derangements ruled her in for sepsis by our institutional as well as Society of Maternal Fetal Medine guidelines. Standard prenatal infectious labs for HIV, hepatitis B and C, gonorrhea, chlamydia, syphilis, and rubella were obtained and within normal limits. Parvovirus B19 titers were obtained and indicated no acute infection or previous immunity. Blood parasite screen returned negative. Physical examination revealed a nontoxic-appearing patient with pale, non-jaundiced sclera, nontender sinuses, lungs clear to auscultation, no hepatosplenomegaly, and improved tachycardia and tachypnea. She reported resolution of her headache with Tylenol.

The infectious disease service was consulted, and a blood smear was recommended to evaluate for malaria. Cyclic shedding of parasites can lead to missed laboratory capture, so a repeat blood parasite screen was collected with the peripheral blood smear. The blood parasite screen was again negative, and the peripheral smear noted no intracellular or extracellular organisms, including plasmodium, Babesia, anaplasma, and Ehrlichia.

On hospital day 4, the patient remained afebrile with normal vital signs for more than 2 days. She was both hemodynamically and obstetrically stable with no further need for IV fluid support. Outside records were obtained and indicated growth restriction, with an estimated fetal weight (EFW) at the 8th percentile a few weeks prior to presentation. A comprehensive anatomic and growth survey was completed at our institution, and EFW was at the 12th percentile. The patient was continued on empiric IV antibiotics while hospitalized, but given her improved clinical picture and negative blood, urine, and fungal cultures at the time of discharge, the infectious disease team recommended against continued antimicrobial therapy. She was only deemed stable for outpatient management following 48 hours in the SICU and additional two days on the antepartum high-risk obstetrical service. At the request of the infectious disease team, an additional blood smear, blood parasite screen, and serum plasmodium polymerase chain reaction (PCR) assay were collected before the patient was sent home.

Shortly after the patient was discharged, the pathology lab called the obstetrics team with a positive blood parasite screen, positive Plasmodium falciparum PCR assay, and peripheral blood smear results that demonstrated rare intra-erythrocytic ring forms of malaria, representative of a parasite load of <1%. One of the two blood cultures collected at the outside hospital eventually grew diphtheroids and gram-positive rods that were resistant to penicillin, susceptible to vancomycin, and ultimately thought to be a contaminant. The patient was called with an interpreter and informed of her malaria diagnosis. She declined reevaluation and readmission for IV antimalarial treatment andrequested an oral regimen instead. She was prescribed a combination antimalarial, Coartem (artemether and lumefantrine) for her acute malaria.

The patient elected to continue receiving care with her outside obstetrics provider. She completed her antimalarial treatment but did not follow up with the infectious disease team at our institution. She had an uncomplicated term delivery of a male neonate 8 weeks after discharge.

Discussion

Malaria is a protozoan disease endemic to regions inhabited by more than 3 billion people worldwide.[11] Five species of the Plasmodium genus affect humans via transmission from the female Anopheles mosquito, including Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and Plasmodium knowlesi.[11] In 2023, approximately 597,000 global deaths were attributed to malaria, with the majority affecting children in sub-Saharan Africa.[16] This is in stark contrast to malaria related deaths in the United States, where in recent years, approximately 2,000 annual cases of malaria have been reported to the United States Centers for Disease Control and Prevention (CDC), with over 50% of these cases were due to P. falciparum.[10,11] Cases in non-endemic areas are generally associated with immigrants or travelers from endemic areas and only rarely occur due to vertical transmission or blood product exposure.[10,11]

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

Presentation and prognosis of malaria varies based on the species of Plasmodium, but often include nonspecific symptoms like fever, chills, headaches, myalgias, and gastrointestinal distress, like those experienced by our patient.[10] Patients affected by malaria due to Plasmodium falciparum species generally experience symptoms within 1 month of returning from an endemic area; the incubation period ranges from 9 to 60 days after exposure, but in an immunosuppressed state such as pregnancy, reactivation may occur at a later interval.[10] P. falciparum's virulence is attributed to peripheral sequestration in microvasculature and vital organs, as well as its ability to affect erythrocytes of any age.[10,11] Those who have lived in endemic areas may experience milder forms of infection due to acquired immunity, whereas travelers without previous exposure are more likely to experience severe or fatal malaria.[10,11] The patient described in our case reported immigration 4 months prior to presentation but was born and raised in a sub-Saharan African country where she is likely to have developed some immunity before relocation. She did not meet World Health Organization (WHO) criteria for severe malaria, but qualified for a diagnosis of sepsis using more than one diagnostic schema.[1,3,7,12]

While pregnancy leads to immunosuppression and an overall heightened susceptibility to bacterial, viral, and parasitic infections, certain physiologic changes of pregnancy and characteristics of the plasmodium species contribute to specific malaria-associated morbidities and mortality.[3,17] Even potentially immune patients residing in malaria-endemic regions are at risk for severe anemia and fetal growth restriction, especially during their first two pregnancies.[17] This is because the placenta acts as a unique site for parasite sequestration, causing congestion in the intervillous space when P. falciparum infected erythrocytes and microvascular chondroitin sulfate A

adhere to one another.[17] This immunogenic process creates an inflammatory state and alters angiogenesis, explaining the increased risk of fetal growth restriction, intrauterine fetal demise, and preterm delivery.[17] Placental immunity develops throughout each pregnancy, and the antibodies formed will subsequently inhibit this sequestration process in later pregnancies, reducing the chances of abnormal placentation and its sequelae.[17] By similar mechanisms, the abnormal coagulation studies seen in this patient can be explained in part by parasitic erythrocyte sequestration but were likely additionally exacerbated by the thrombotic state associated with a septic inflammatory response.[7]

DIAGNOSIS

In the case of this patient, the overall clinical picture was largely driven by the underlying pathophysiology of an acute plasmodium infection, and our high clinical suspicion for malaria was the reason for repeat diagnostic testing despite initially negative blood parasite screening. Additional etiologies for systemic disease consistent with sepsis had been excluded. The gold standard for diagnosis of malaria involves microscopic examination of a peripheral blood smear, with preparation of thick and thin blood smears, application of appropriate stain, and observation via 100x oil immersion objective lens.[18] Generally, microscopy will detect the presence of parasites in the thick smear, and further examination of the thin smear affords species identification and quantification of the degree of parasitemia.[18] Our patient had two blood smears completed at our institution, the first of which was negative but remarked on the unlikely microscopic detection of malaria in the setting of low-level parasitemia, and the second of which identified an extremely low level of parasitemia. At the time of the second peripheral smear report, the pathologist's note suggested that in the absence of symptoms, such low levels of parasitemia would likely not correlate with an acute malarial infection as >5% parasite load typically corresponds to severe P. falciparum.[10] If appropriate risk factors and symptoms were present, our pathology department recommended PCR testing for plasmodium speciation. The PCR testing and third blood parasite screen obtained on the same day eventually returned positive for P. falciparum.

Due to plasmodium's cyclic shedding and peripheral sequestration, several diagnostic and treatment guidelines typically recommend obtaining serial blood smears in cases where clinical suspicion for malarial infection is high; three sets of negative blood smears obtained every 12 to 24 hours is generally considered sufficient data to rule out plasmodium infection.[10,12,17,18] There are several rapid diagnostic tests (RDTs) approved for international use, but the federally approved BinaxNow RDT was not available at our institution. While RDTs allow for a result within 15 minutes of testing, they must be confirmed with microscopy. Finally, as seen in our case, while molecular testing with PCR assays is more sensitive than microscopy, this technique may delay diagnosis in critically ill patients.[18] In the future, if treatment resources are available and clinical suspicion for malaria remains high, patients like ours should be empirically treated with antimalarials while diagnostic testing is completed and other etiologies are ruled out.[10, 17]

TREATMENT AND PREVENTION

Definitive treatment of malarial infections is based on plasmodium species and illness severity. When diagnosis eventually confirmed acute uncomplicated malaria, our patient was hemodynamically stable and clinically improved at her home. Standard treatment for uncomplicated malaria is artemisinin-based combination therapy (ACT), with the caveat that artesunate + sulfadoxine-pyrimethamine and artesunate-pyronaridine are not recommended for treatment in the first trimester of pregnancy.[12] Some alternative antimalarial regimens are contraindicated in pregnancy or breastfeeding due to fetal and neonatal pharmacologic effects.[10]

The World Health Organization focuses on effective treatment, eradication, and the prevention of long-term maternal and fetal sequelae from plasmodium infections. Thirty-four percent (12.4 million) of pregnant patients living in the WHO African region were infected with malaria in 2023.[19] Over the same year, an immunization method known as intermittent preventative treatment of malaria in pregnancy (IPTp) used sulfadoxine-pyrimethamine and is estimated to have prevented low birth weight in over half a million neonates.[19] Globally, malaria is the most frequently identified infectious etiology of fetal growth restriction and low levels of parasitemia could have contributed to the early onset fetal growth restriction identified on our patient's outside growth scan.[20, 21] Repeat biometry performed during this patient's antepartum admission determined that her fetus was no longer growth restricted and outpatient antepartum testing was not indicated at discharge. Retrospective studies have demonstrated an increased risk of preterm birth and placental dysfunction in patients with antepartum sepsis who did not deliver during their sepsis hospitalization, and repeat biometry may be considered in patients like the one described here.[3]

CONTRIBUTING SOCIAL DETERMINANTS

Our institution is relatively well equipped to care for a diverse patient population. While we do not have in-person Swahili interpreters available, we have access to remote translation services, a resident physician workforce interested in providing equitable patient care, and a team of social workers eager to assist with transportation, nutrition, and healthcare needs. Despite these resources, our patient opted to follow up with her community health care center and delivered at a hospital closer to where she lived. In the weeks shortly after her hospitalization, we were able to speak with her via telephone with assistance from Swahili translators, but ultimately were unable to obtain more information about the remainder of the patient's antepartum course or additional delivery details aside from confirmation of a healthy term birth. Language and educational barriers prevented this patient from understanding written communication, so obtaining permission for health information sharing between healthcare entities was impossible. The follow-up recommended by both the infectious disease and obstetrics teams was only verifiable via telephone, and as time passed, the patient stopped answering all phone calls from our healthcare system. As of February 2025, the new United States presidential administration has enacted executive orders that have thus far resulted in the removal of several previously available CDC guidelines that enumerate

diagnosis and treatment plans for infrequently seen infectious diseases like malaria. Additionally, administrative threats of immigrant deportation have prevented patients from engaging with a healthcare system where they may be identified and reported to governing agencies. While we are unaware of all the specific circumstances of the patient described in this case, this report highlights some of the institutional

challenges associated with caring for an immigrant population that is already vulnerable to healthcare inequities and systemic racism.

Conclusion

While primarily a disease affecting low-income countries, malaria during pregnancy carries a high risk of sepsis and its obstetric sequelae. Internationally, providers should maintain appropriate clinical suspicion for febrile patients at risk of plasmodium infection in order to prevent maternal and fetal morbidity and mortality.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

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WHO criteria for severe malaria
• Impaired consciousness • Pulmonary edema • Recurrent or prolonged bleeding • Shock • Acidosis • Hypoglycemia • Several malarial anemia • Acute kidney injury • Jaundice of hyperbilirubinemia • Hyperparasitemia • Prostration • Multiple convulsions

Table 1

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