

Cerebral and *Plasmodium ovale* Malaria in Rhode Island

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ABSTRACT

We report two cases of malaria diagnosed in Rhode Island. First, a 21-year-old female who presented with 5 days of fevers, chills, headache, and myalgias after returning from a trip to Liberia, found to have uncomplicated malaria due to *P. ovale* which was treated successfully with atovaquone/proguanil and primaquine. Second, a chronically ill 55-year-old male presented with 3 days of headache followed by altered mental status, fever, and new-onset seizures after a recent visit to Sierra Leone, found to have *P. falciparum* malaria requiring ICU admission and IV artesunate treatment. The diagnosis and management of malaria in the United States (US), as well as its rare association with subdural hemorrhage are subsequently reviewed.

KEYWORDS: malaria, cerebral malaria, artesunate, plasmodium

INTRODUCTION

Malaria remains a significant international health concern with over 200 million cases and 400,000 deaths annually.¹ Malaria is the result of infection by intracellular parasites of the *Plasmodium* genus transmitted by the female *Anopheles* mosquitos during blood meals. Due to the life cycle of the *Anopheles* mosquito, the disease is endemic in many tropical and subtropical climates. Over half the world's population is at risk of transmission, particularly those in sub-Saharan Africa (>90%) and Southeast Asia (~5%), where the majority of cases originate.² Despite its prevalence abroad, malaria has become a relatively uncommon diagnosis in the United States, with around 1,700 cases reported annually.² Malaria was once endemic in the Tennessee River valley and southeastern states, with 200–350 cases per 100,000 between 1920–1935. The disease was successfully addressed by the efforts of the National Malaria Eradication Program and by 1949 malaria was no longer considered a significant public health concern in the US.² Consequently, modern US clinicians may have less experience diagnosing and treating malaria, potentially resulting in a missed or delayed diagnosis with significant associated morbidity and

mortality. While the CDC currently reports a stable incidence of malaria in the US, climate change is predicted to affect disease dynamics, and it remains unclear how the US incidence will be affected by climate change in the future.^{2,3}

Given the potentially fatal consequences of a missed diagnosis of malaria and the relative inexperience of US clinicians with the disease, we review two cases of malaria recently diagnosed in Rhode Island that are representative of the spectrum of the disease one could expect to encounter in the US. The first is a classic, uncomplicated presentation of malaria in a 21-year-old female and the second is an example of severe malaria in a chronically ill 55-year-old male.

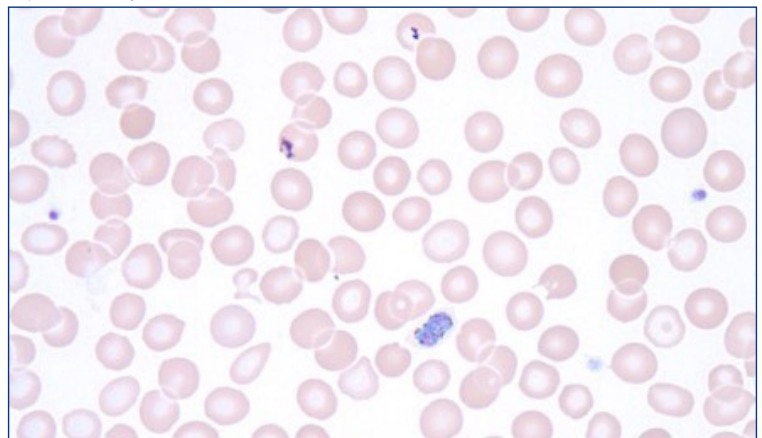
CASE 1

A 21-year-old female with a history of iron-deficiency anemia presented with 5 days of daily fevers, chills, headache, and myalgias after returning from a trip to Liberia during which she took no medications for malaria prophylaxis. She denied any other associated symptoms, sick contacts, or known exposures.

The patient's vital signs were notable for temperature 105°F, pulse 99 beats per minute, blood pressure 95/66 mmHg, respirations 18 breaths per min, SpO₂ 98% on room air. The physical exam was notable for an ill appearance but was otherwise normal.

Initial work-up was pertinent for hemoglobin of 8.7 g/dL, white blood cell count of 3.4 x 10⁹/L, platelets 77 x 10⁹/L,

Figure 1. Peripheral blood smear from case 1 demonstrating *P. Ovale*.



sodium 132 mEq/L, potassium 3.4 mEq/L, and normal urine studies. Blood parasite smear was notable for *Plasmodium* species, non-falciparum and a parasite burden of 0.07% infected erythrocytes. On further review, the hematopathologist suspected *P. ovale* due to the presence of enlarged, elongated red blood cells with polar fimbria. Molecular testing by the CDC later confirmed *P. ovale* as the culprit species (Figure 1).

Empiric treatment of non-falciparum *Plasmodium* infection was initiated in the emergency department with atovaquone/proguanil. After three days of inpatient therapy with atovaquone/proguanil, the patient was discharged and successfully completed a 14-day outpatient course of primaquine to cover any potential *P. ovale* hypnozoites.

CASE 2

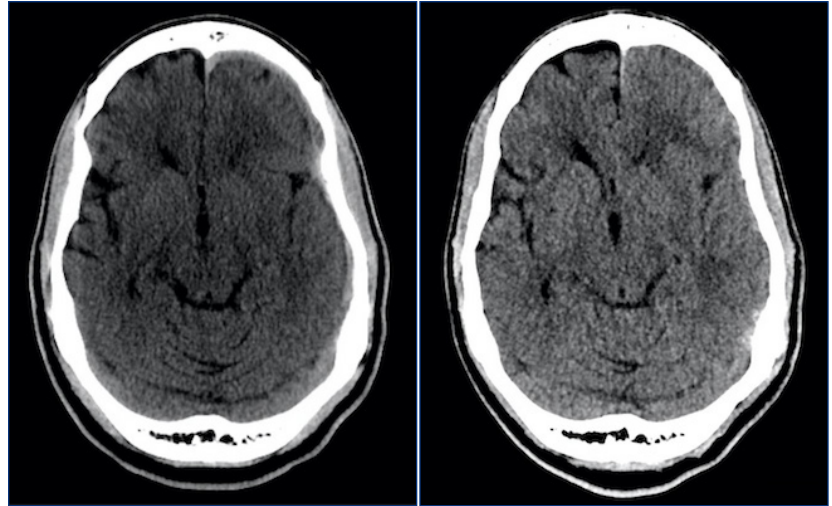
A 55-year-old male with an extensive past medical history (Hodgkin lymphoma status post remote treatment; coronary artery disease status post bypass; heart failure with reduced ejection fraction and biventricular ICD placement; mechanical aortic valve replacement on warfarin; hypertension; hyperlipidemia; and diabetes mellitus) presented to the emergency department with 3 days of severe headache followed by altered mental status and fever. Nine days prior to this presentation, he had been hospitalized for an atraumatic subdural hemorrhage.

During his initial hospitalization, the patient reported 5 days of intermittent headache with photophobia as well as a transient episode of right-sided extremity weakness and heaviness. There were no infectious symptoms at that time, nor any history of trauma. However, he did endorse a recent trip to Sierra Leone (2 weeks prior) at which time he may have inadvertently taken an excess of enoxaparin (was bridging from warfarin) and was not on any form of malaria chemoprophylaxis. His workup revealed a new thrombocytopenia and an acute left-sided subdural hemorrhage. During the hospitalization, his neurologic exam remained stable, and he underwent cerebral angiography which revealed no evidence of causative vascular malformation. His coagulation status was optimized, and he was discharged home on warfarin.

The patient initially did well after discharge, but then developed three days of a severe headache with nausea and vomiting. His wife noted progressive somnolence and confusion, which prompted the return visit to the emergency department. There was no new travel, trauma, or exposures in the interim.

His vital signs were notable for a fever of 101.3 °F, pulse 107/min, blood pressure 158/83 mmHg, respirations 16 breaths

Figure 2. Non-contrast head CT of patient in case 2 during initial hospitalization (left) and re-presentation with altered mental status (right).



per minute, and SpO₂ 95% on room air. He was ill appearing, spoke nonsensical words, and was unable to follow simple commands. There was no nuchal rigidity. He could spontaneously move all extremities, albeit with constant agitation, while tossing and turning in the stretcher.

Further evaluation revealed platelets 108 x 10⁹/L, INR 4.0, sodium 124 mEq/L, glucose 321 mg/dL, and a stable subdural hematoma on repeat CT (Figure 2). Peripheral blood smear demonstrated *P. falciparum* with a parasite burden of 2.48% infected erythrocytes. Parasites were not detected during his initial hospitalization. Due to recent subdural hematoma and elevated INR, lumbar puncture was deferred.

The patient was empirically treated with vancomycin, cefepime, and ampicillin for suspected meningitis. Atovaquone/proguanil was added following identification of *P. falciparum* on blood smear. Given the severity of his presentation and associated comorbidities, the patient was admitted to the ICU where, in conjunction with the CDC, his antimalarial therapy was escalated to IV artesunate for presumed cerebral malaria. Empiric treatment for meningitis was discontinued due to low clinical suspicion and an alternate etiology.

Although the patient demonstrated clinical improvement and resolution of parasitemia after completion of artesunate and atovaquone/proguanil therapy, he had a protracted hospital course complicated by seizures. After an extensive evaluation, the seizures were attributed to both the subdural hematoma and the cerebral malaria infection. Ultimately, the patient was discharged home on multiple antiepileptic medications. On outpatient follow-up he was doing well without further seizure activity and a return to his normal mental status.

DISCUSSION

While uncommon, malaria remains a diagnosis that should remain within the minds of US clinicians. The above cases illustrate the spectrum of disease in malaria: from classic, uncomplicated disease to a more severe presentation with cerebral involvement. Moreover, the latter case may represent a rare case of malaria presenting with subdural hematoma. Given its nonspecific and sometimes subtle presentation, malaria should be considered in any patient presenting with otherwise-unexplained infectious or flu-like symptoms and a history of recent travel to an endemic region.

If there is clinical concern for malaria, work-up should include a thorough travel history (destination, duration of stay, type of travel, activities performed, and prophylactics used), complete blood count, a comprehensive metabolic panel, and a broad infectious work-up as clinically indicated. Most importantly, a peripheral blood smear for parasites should be performed, as this remains the gold standard for diagnosis of malaria.^{2,4}

Treatment and disposition are dependent upon the clinical status of the patient, the infecting *Plasmodium* species, the region of infection acquisition, and any previous antimalarial use. Due to evolving resistance patterns, it is appropriate to reference the most recent CDC guidelines or consult with local infectious disease experts prior to treatment. In all cases, admission should be considered to monitor for response to therapy and potential decompensation.^{2,4,5}

Severe disease is most commonly caused by *P. falciparum* and is broadly characterized by evidence of organ dysfunction, high degree of parasitemia (greater than 5%), and inability to tolerate enteral therapy. Specific complications include severe anemia, hemolysis, hypotension, renal failure, and, in the case of cerebral malaria, alterations in mental status, seizure, and coma.^{5,6} The treatment of choice for severe disease, regardless of pathogen, is intravenous artesunate. In the US, this medication can only be obtained through the CDC. As the disease can rapidly progress, interim therapy with artemether/lumefantrine or atovaquone/proguanil should be started while awaiting the arrival of artesunate.^{2,5}

Special consideration should be given to cases of uncomplicated malaria caused by *P. falciparum*. Patients who are non-immune (i.e. do not live in endemic regions) are at very high risk of rapid progression to severe disease and should always be admitted to the hospital for monitoring. Patients with *P. knowlesi* infection should also be admitted as co-infection with *P. falciparum* is highly possible.⁴ In both cases, repeat blood smears for parasite burden should be performed every 12-24 hours until clinical improvement is seen.^{2,4} Lastly, patients diagnosed with *P. vivax* and *P. ovale* malaria will require treatment with either primaquine or tafenoquine to eradicate hypnozoites and prevent relapse once the acute phase of infection has been managed.²

The latter case is of particular interest due to the subdural hemorrhage which may represent a rare complication

of malaria. Although this patient had increased risk of subdural hemorrhage due to his coagulation status, he denied a history of trauma and had normal cerebral angiography. While the association between malaria and subdural hemorrhage is poorly understood, multiple cases have been reported in patients without any other clear cause for hemorrhage.⁷⁻¹² Past cases have been documented in association with *P. falciparum* and more rarely *P. vivax*.¹² It is hypothesized that infected, misshapen erythrocytes cause microvascular injury in small cerebral vessels which subsequently leads to hemorrhage that is further perpetuated by thrombocytopenia and coagulopathy.⁹⁻¹¹ Tumor necrosis factor- α (TNF- α) may also play a role in compromising endothelial integrity.¹³ While, there is no way to confirm that this was the cause for the patient presented above, it is plausible given his risk factors and otherwise normal cerebral imaging.

CONCLUSION

Although malaria remains endemic in many equatorial countries, it has become an uncommon diagnosis in the US. With its sometimes-nonspecific presenting signs/symptoms and its potential morbidity, malaria requires US clinicians to maintain a high index of suspicion in patients who present with infectious symptoms after recent travel to endemic areas. Peripheral blood smear followed by molecular studies can confirm the diagnosis. In severe cases, intravenous artesunate is treatment of choice.

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