Exotic infection presentation of *Plasmodium ovale* malaria in Morgan County, Alabama

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**ABSTRACT**

Malaria is commonly associated with the virulent form of parasite species known as *P. falciparum*. Another species that has the capability of causing severe disease is *Plasmodium vivax*; however, in contrast to these two species, *Plasmodium ovale*, discovered in 1922, is much rarer and have been known to cause a benign version of malaria. The case of an exotic infection was presented in the non-malaria-endemic North Alabama area imported from Sub-Saharan Africa. *P. ovale* was discovered in a 41-year-old woman complaining of fever and myalgia. First peripheral blood smear microscopic analysis was negative for malaria parasites. However, second blood smear confirmed the presence of *P. ovale* with a 1% parasitemia. Challenges in diagnosing this strain stem from the fact that *P. ovale* is not endemic to the United States and that the relapse phenomenon has not been adequately researched. It remains for a large part unexplained and warrant further investigation.

Keywords: Infectious disease, Malaria, Non-endemic malaria, Plasmodium, *P. ovale*
reproduce [9]. Once the infected mosquito bites, mainly at dusk and dawn, it will transmit the parasite haploid form, known as sporozoites, from its saliva into the human blood stream [10–12]. These organisms then travel to the liver to complete the hepatocellular phase. Inside the liver, the parasites multiply and mature until they are released back into the bloodstream as merozoites. [1, 8, 13]. Merozoites invade red blood cells where they further divide and grow with schizonts. Two to three days later, the merozoite cells burst, infecting unparasitized red blood cells which ultimately become trophozoites [9]. Merozoites can also asexually reproduce in the erythrocytic cycle to form male/female gametocytes to be taken up by healthy mosquitoes [9, 14]. If hypnozoites remain dormant in the liver, unique to P. ovale and P. vivax, then a recrudescence or relapse can occur weeks to months after initial transmission [15].

The diagnosis of malaria is fairly complex and challenging due to the broad nature and delayed manifestation of the symptoms. Gathering a detailed patient history, including travel to foreign countries, performing a thorough physical examination, and conducting a blood analysis are critical factors in properly diagnosing malaria. The standard diagnostic tool for detection is blood smear microscopy analysis, Giemsa Stain, which detects the presence of parasites in the blood within a few hours [16–17]. If available, diagnosis can be made by Rapid Detection Test, RDT. This immunochromogenic test can be conducted with a dipstick or cassette format, and results are available 2-15 minutes later [10]. A positive detection to plasmodium can be followed up with a PCR to confirm the species prior to treatment [18]. PCR analysis is often not used due to time constraints and patient sensitivity.

Although there are prevention efforts for malaria treatment and control, no vaccine exists. Consequences of not providing prompt treatment include hemolysis, capillary clogging, vital organ function loss, and even death. Antimalarial medications are specific to the type of plasmodium transmitted, the severity of the disease, and the region where the infection was acquired [9]. According to the Center for Disease Control, strict guidelines for treating P. vivax and P. ovale include a combination therapy of primaquine phosphate with either chloroquine phosphate or hydroxychloroquine. Primaquine is essential because it is anti-hypnozoitocidal treatment and prevents relapse [19] The combination primaquine with either chloroquine phosphate or hydroxychloroquine allows for the treatment of the liver hypnozoites and the blood parasites [20].

CASE REPORT

A 41-year-old female was seen in Morgan County, Alabama due to a constant, alternating fever of 40°C (104°F). She had no medical history, but a travel history indicated an occupation to a malaria-endemic country, South Africa. The patient reported that her previous residence in South Africa had many insects such as mosquitoes. No intravenous drug use, surgical intervention, blood transfusion, or other risk factors for transmission of malaria were reported.

Upon physical examination, the patient did not appear to be chronically ill and no hepatosplenomegaly was noted. Hematology lab results indicated a low hemoglobin level of 8.2 g/dL, low hematocrit of 26.1%, low MCV or mean corpuscular volume of 80.6 FL, low MCH or mean corpuscular hemoglobin of 25.3 PG, low MCHC or mean corpuscular hemoglobin concentration of 31.4 g/dL, low lymphocyte number of 1.09 x10⁹ per liter, high level of monocytes of 0.67 x10⁹ per liter, high basophils of 1%, normal WBC 5.76x10⁹ per liter, and normal platelet level of 164x10⁹ per liter. Pathology review was requested, and a Wright-Giemsa stained peripheral blood film was examined. First thick and thin blood smear noted no detection of parasites. Second sampling and examination of blood smears showed 1% parasitemia (Figure 1).

Upon examination of the peripheral blood smear, red blood cells appeared normocytic and normochromic with mild anisocytosis. Total leukocyte count was elevated with neutrophils while no basophils and myeloblasts were seen. Leucocytes and monocytes were seen with minimal reactivity. Platelets appeared normal in number, distribution, and morphology. Surprisingly, a non-falciparum type malaria, Plasmodium ovale, was noted.
on the infected erythrocytes with a parasitemia index of 1%. Patient was treated with chloroquine phosphate 1000mg immediately followed by 500mg every 6, 24, and 48 hours. In addition, 30 mg of primaquine phosphate for 14 days was given.

DISCUSSION

Malaria is a commonly contracted disease from the bite of a mosquito infected with *P. falciparum*. While the disease has been most commonly associated with Africa, cases have been reported worldwide for over a century. *P. ovale* is a more difficult strain of malaria to diagnose because of its rarity, the broad nature of its symptoms, and the difficulty in microscopically diagnosing due to low parasite density and the parasitic morphology resembling that of *P. vivax* [21]. *P. ovale* was initially discovered in a patient from East Africa by Stephens in 1922. While malaria has been a commonly diagnosed disease for well over a century, with over 700,000 deaths in 2016 alone, observations of the relapse of symptoms deriving from *P. ovale* have only been cited in less than 20 cases since 1922 [14].

Though mortality and morbidity are not typically associated with *P. ovale*, this disease can be fatal as evidenced by a few cases [7, 10, 22]. The recurrence of parasites dormant in the liver further complicates the difficulty of diagnosing this disease [19, 20]. In 2010, two sub-species of *P. ovale*, *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri*, were discovered, and discrepancies between the two are still being researched [17]. These factors validate the need for further research into this parasite strain. From 2007 to 2012, the number of *P. ovale* cases has increased by 80% in travelers [18]. This correlates with this case report of an individual traveling from a malaria endemic country to the USA. Despite this increase, the rarity and complicated nature of diagnosing this strain presented significant challenges.

While malaria was never endemic to America, it did experience a spike in reported cases following World War II, around 1947-1950 [10, 16]. Swift government action in the 1950s significantly reduced transmission, and small outbreaks that continued were controlled. In fact, according to the CDC, there have been only 63 cases of malaria being transmitted in the U.S. from 1957-2015 [17, 23]. In particular, the Tennessee Valley Authority (TVA) implemented measures to confront the malaria issue by building reservoirs on the Tennessee River and addressing the issue of stagnant water. Government records indicate these efforts successfully suppressed this disease. This case illustrates the rarity of this disease being diagnosed in Alabama: according to the CDC’s 2013 records 0.34% of reported cases came from Alabama [23].

Over the last century, primary research has focused on *P. falciparum* with *P. ovale* largely being neglected and underdiagnosed. Risk factors and the pathophysiology for *P. ovale* remain undetermined. This uncertainty can be attributed to diagnostic difficulties related to the low parasitemia levels and drawbacks to the use of thick as well as thin blood films [3, 5, 24]. These challenges are particularly alarming because *P. ovale* often gets diagnosed as *P. vivax*, also a much milder form of malaria. Severe cases of *P. ovale* are often missed by not identifying the correct plasmodium species. These misdiagnoses contribute to the ongoing public perception that malaria is not a debilitating disease needing immediate attention. Over 10 published cases, however, have shown *P. ovale* exhibiting severe symptoms including acute respiratory distress syndrome, metabolic acidosis, acute renal failure, hypertension, and splenic rupture [10, 12, 14]. With the number of *P. ovale* cases being underreported, these symptoms represent only a known summary of the possible symptoms related to *P. ovale*.

One of the major factors contributing to the misdiagnosis of *P. ovale* relates to the acquisition of a thorough patient history, a proper initial assessment, and physical examination. A patient’s travel history, timeline of symptoms, and previous medical history are essential in properly diagnosing malaria. The rarity of this disease along with the vagueness of the symptoms contribute to this difficulty. Better diagnostic measures need to be implemented to more accurately identify the plasmodium infecting the individual. Traditionally, thick and thin blood smears are utilized for determining if malaria is present and parasitemia levels, respectively. This includes performing a repeat blood smear, which helped in our case, based on the fluid life cycle of the parasites. Other tests that could aid in the proper diagnosis include PCR or rapid antigen testing. Therefore, performing thick and thin blood smear is preferable in order to ensure correct diagnosis. Treatment options for malaria are vast and specific to the type of infected plasmodium. Early treatment allows for a better long-term prognosis. The gold standard for *P. ovale* includes a combination therapy, chloroquine and primaquine, that targets the different blood-stages [25]. However, it has been noted by other studies that anti-hypnozoite treatment is not 100% effective in preventing release. Recrudescence in the liver cells has been researched on and shown to only be dormant for a limited time. Furthermore, non-human studies have shown that dormancies can also occur in the epidermis, brain, kidneys, and lungs [26]. These discoveries warrant the need for further research into targeting the hypnozoites in an accurate mechanism of action. In conclusion, this case presents a number of challenges to the proper diagnosis and treatment of *P. ovale* and exhibits the need for further research into this strain of malaria.

CONCLUSION

Unique to *P. ovale* and *P. vivax*, hypnozoites remain dormant in the liver which can cause relapse occurring...
weeks to months after initial transmission. Thick and thin blood smears are utilized to detect malaria presence and parasitemia levels, respectively. People at risk for malaria include travelers to areas that are malaria-endemic, pregnant women, children, and immunocompromised individuals. Symptoms of malaria appear 10–15 days after transmission are alternating high fever, chills, anemia, jaundice, and flu-like symptoms.

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