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Case Report: The Sleeping Parasite.

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ABSTRACT

Malaria has been a highly prevalent disease in the U.S. service members since World War II. According to the WHO 2022 World Malaria Report, a total of 247 million cases of malaria were reported worldwide resulting in roughly 619,000-with the majority of those occurring in Sub-Saharan Africa. The diagnosis and management of malaria can be difficult given its relapsing and remitting nature. There are not many reported cases of malaria diagnosis and treatment months after initial infection. This case report presents an unusual presentation of *Plasmodium vivax* in a U.S. service member who was deployed to Afghanistan and presented twelve months after initial deployment with new symptoms and diagnosis of malaria.

Keywords: Malaria; Plasmodium falciparum; Plasmodium vivax; Aenopheles mosquito

INTRODUCTION

The WHO describes malaria as a life-threatening disease caused by one of five species of the parasite family *Plasmodium*– which are transmitted through the mosquito bite of an infected *Aenopheles* mosquito[1-3].

The five major species that are known to infect humans are *Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, and Plasmodium knowlesi.* Sporozoites are inoculated into the skin when mosquitoes feed on blood. After skin inoculation, the sporozoites are transited through the dermis, enter the bloodstream, and are eventually carried to the liver. After invading hepatocytes, the sporozoites begin schizogony during which they grow and divide exoerythrocytic merozoites. *Plasmodium. vivax and Plasmodium. ovale* can uniquely form hypnozoites which are a form of the parasites that can lay dormant for several months to years. After completing schizogony, merozoites are released from hepatocytes into the bloodstream and invade erythrocytes to begin a new cycle of schizogony. This new cycle leads to the progression from the classically known ring-stage forms to trophozoites and schizont stages. Mature schizonts produce many daughter merozoites which then subsequently invade new erythrocytes and destroy the host cells[4].

The dormant hypnozoites can stay inactive in the liver for long periods of time (how long give estimate?) after initial infection and can lead to issues with relapsing blood-stage infections. *Plasmodium. vivax* is most prevalent in Asia, Africa, and Central and South America, but mainly concentrated in India, Afghanistan, and Pakistan in Asia. Due to hypnozoites' ability to cause relapsing infections, *Plasmodium. vivax* has a large global burden and has is difficult to control. Exact reasons for hypnozoite reactivation are unknown but postulated to be due to "a systemic febrile illness and parasite-induced hemolysis." This species preferentially invades reticulocytes, which leads to predominance of the parasites tin the bone marrow and subsequent extravascular hemolysis. This then lowers hemoglobin levels circulating in the blood and can lead to delays in diagnosis. One can see labs consistent with a non-immune hemolytic anemia with elevated LDH, low haptoglobin, negative DAT[5,6].

Malaria can present in many ways. Most individuals afflicted with malaria will present with nonspecific signs and symptoms resembling a "flu-like illness," which can include fever, headaches, rigors, arthralgias, myalgias, fatigue, loss of appetite, diarrhea nausea, and vomiting. Patients can present suddenly as early as seven days after exposure with the usual range of symptom onset being between 10-21 days. Severe malaria can present with the inability to drink, shortness of breath, impaired consciousness, convulsions, and jaundiced eyes. High risk groups for severe malaria include: pregnant/postpartum women, infants/young children, elderly patients (>65 years old), splenectomy patients, immune compromised patients (HIV/AIDs, etc), and patients non-immune to malaria. The symptoms of malaria can mimic many other diseases such as viral hepatitis, meningitis, pneumonia, dengue fever, and trypanosomacruzi infections making the diagnosis very tricky at times.

Physical exam findings can include cyclical fevers, pallor, petechiae, jaundice and a palpable spleen in otherwise healthy individuals exposed to endemic area. Fevers occur every 48 hours for those with plasmodium vivax, ovale, and falciparum. Labs can reveal parasitemia, anemia (hemolytic in some cases), thrombocytopenia, elevated aminotransferases, mild coagulopathy, elevated BUN and Cr. Diagnosis can be made with rapid diagnostic tests (detects malaria parasite antigens) and peripheral blood smear.

Treatment depends on the type of plasmodium species. In the case of *Plasmodium. vivax*, anti-malarial selection is based on chloroquine resistance of the area of exposure. In those areas with high or unknown chloroquine resistance, one could administer artemisinin combination or drugs such as atorvaquine-proguanil, doxycycline, tetracycline, and mefloquine. In cases of recurrence, one may need to add primaquine for prevention of relapse. In those with exposure to a chloroquine sensitive region, treatment with artemisinin combination or chloroquine is acceptable. This case report focuses on an unusual presentation of *Plasmodium vivax* in a member of the U.S. service member deployed to Afghanistan and presented for the first time with splenomegaly and cyclical fevers twelve months after exposure.

CASE DESCRIPTION

A 24 year old male with no significant past medical history presented to the hospital with hypotension, fevers, and a concern for sepsis. Patient had reported one week of fevers, headaches, nausea, vomiting, cramping epigastric abdominal pain, and diarrhea. Patient could not tolerate much by mouth and had been using tylenol

and motrin to help control the abdominal pain. The patient reported a history of travel to Texas and was deployed to Kabul, Afghanistan from 1/2017 to 9/2017 and was on doxycycline daily while deployed. Other travel history included Texas, California, and Florida in the last five years. Initial vitals showing T-max of 104.2 F, HR 114, BP 80/50s. Physical exam remarkable for marked tachycardia, hypoactive bowel sounds, epigastric tenderness, and hepatosplenomegaly. Initial labs significant for WBC of 3.5, platelet count of 79, AST 100, ALT 179, ALP 62, T-bilirubin of 1.9, direct bilirubin of 0.5, lactic acid 1.9. CXR without any abnormalities. CT of abdomen and pelvis revealed massive splenomegaly and small amount of nonspecific free fluid within the pelvis. Patient was initially treated as sepsis and given aggressive IV fluid resuscitation and broad spectrum antibiotics with vancomycin, cefepime, and flagyl[7,8]. Initial differential thought to be related to sepsis: peritonitis, splenic vein thrombosis, CMV, EBV, acute HIV, hepatitis, lymphoma, DIC, TTP, or ITP. Patient did not improve and was febrile every 48 hours. Peripheral blood smear was obtained, which revealed 1-2 trophozoites on each 5 high power field. Patient was then treated with atovaquone-proguanil and completed 14 days of primaquine (Figure 1).

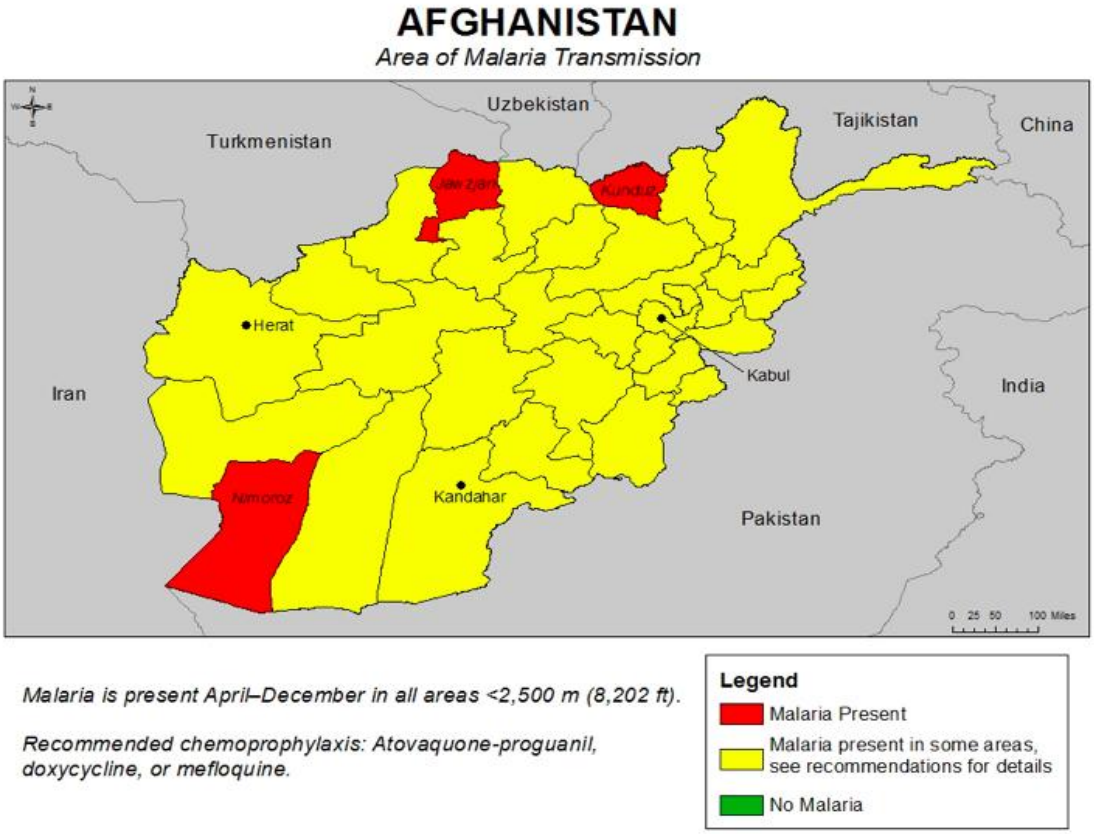


Figure 1: Areas of Malaria Transmission

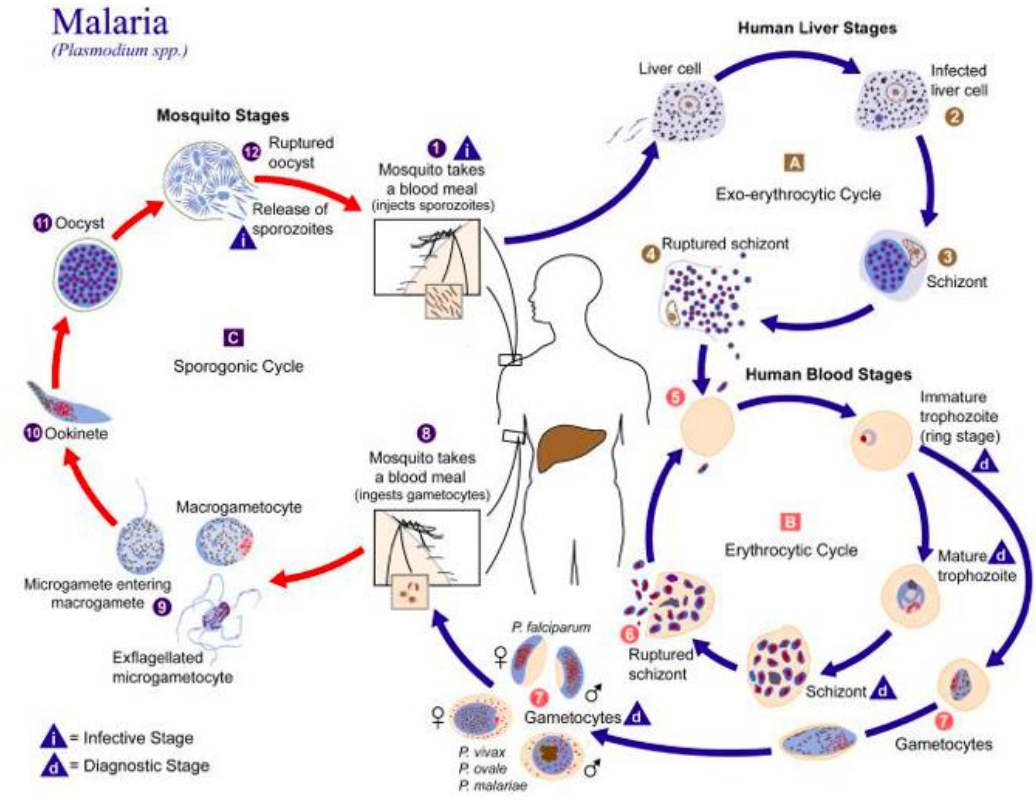
DISCUSSION

Malaria has been observed among members of our military since World War II, where thousands of troops suffered from the disease while being stationed in the South Pacific extending all the way to Sicily, Italy. In

general, military personnel are at increased risk for contracting malaria (in addition to other vector-borne illnesses) because of the length and intensity of environmental exposure of their various deployments across the world. At the time, there was little research done on preventive measures against malaria and as a result there were an estimated 572,000 casualties between 1943-1945. Following World War II, treatment improved with the emergence of chloroquine and other similar drugs. The Korean War saw a large incidence of malaria cases treated with chloroquine, but many service members were returning to the U.S and presenting with symptoms weeks after returning home. At the time, chloroquine was used for treatment, but was not effective against P vivax[9]. In response to the Korean Conflict and the large number of veterans presenting with malaria during and post Korean War, the U.S. government came to recruit inmates from a penitentiary in Illinois and to study and test the drug we know now as primaquine which was immediately adopted by the U.S. government for treatment of malaria in its troops[9].

A 2005 JAMA article described an outbreak of malaria in troops in eastern Afghanistan, where a total of 38 soldiers where all were found to be infected with plasmodium vivax. The majority of soldiers presented with fevers along with chills, headache, nausea. Laboratory findings were significant for anemia and thrombocytopenia similar to our patient in this case. The median time of diagnosis was 233 days. Individuals had received weekly 250 mg mefloquine two weeks pre-deployment to four weeks post-deployment. Of those deployed, 521 of the 725 filled out a questionnaire regarding their experience with malaria. Only 52% were fully compliant with their regimen of medicine and additional precautionary measures (ex- netting, spray, etc). In a 2003 NEJM article, 300 cases of malaria were identified in travelers returning from Israel between 1994 to 1999. Of those 300 cases, 134 (44.7%) of individuals developed symptoms more than two months after returning to the U.S with the majority of those cases caused by plasmodium vivax. One case report in the Journal of Travel Medicine comments on two separate cases of plasmodium ovale that presented for the first time five to six years after initial exposure in the Ivory Coast. The literature does cite that plasmodium vivax and ovale have been known to be dormant at times and recur, but there have been very few case reports or literature citing specific cases of malaria presenting for the first time six months after exposure.

Malaria in humans can be caused by five major species of Plasmodium (falciparum, vivax, ovale, knowlesi, and malariae); the former two represent the majority of infections. Its lifestyle consists of the exoerythrocytic stage (outside the red blood cell or in the liver) and the erythrocytic (inside the red blood cell) stage. The exoerythrocytic stage occurs when the parasites move into the hepatocytes of the liver and multiply (known as schizonts). Unlike the more well known and serious plasmodium falciparum, vivax can populate into the bloodstream with sexual stage parasites which can lead to persistence of symptoms or lack thereof despite immediate treatment[5]. Some P. vivax and P. ovale sporozoites do not immediately develop into exoerythrocytic-phase merozoites but produce a dormant form of the parasite[4].” This dormant form called the hypnozoite has the ability to become dormant in the liver for days to years causing no symptoms and remaining undetectable in the blood[6]. The erythrocytic stage occurs (Figure 2) when parasites invade the erythrocytes, can multiply further, and burst causing clinical illnesses with cyclical fevers (time frame depends on type of plasmodium)[12].



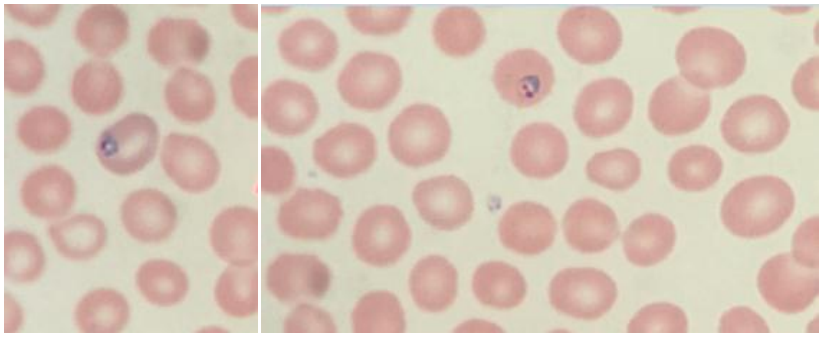


Figure 2: Species of Plasmodium

In 2011, 124 service members were diagnosed with malaria from 25 different medical facilities across the world. In 2016, this number was nearly reduced by 50% to a total of 57 cases. This decrease in the incidence of malaria is largely due to the withdrawal of troops in Afghanistan in the last few years, reflecting the problem of malaria in Afghanistan with our servicemen [2]. Afghanistan has the fourth highest malaria burden and accounts for 11% of cases in the WHO Eastern Mediterranean Region. 95% of cases can be attributed to p falciparum versus 5% caused by p vivax, making this case of vivax extremely rare given our patient's deployment history. Over 76% of Afghans are at risk of malaria with those in the eastern side of the country with the highest prevalence. The majority of malaria cases in Afghanistan and Iraq are due to P. vivax[10]. The U.S. army instructs its members of the proper wear of uniform along with bed nets embedded with permethrin and DEET to exposed skin in

addition to drug prophylaxis[11]. But as referenced above, only roughly 50% of troops are compliant with all precautionary measures and pre and post drug prophylaxis.

Prior use of chloroquine medications that targeted blood schizonts has increased its resistance among Plasmodium species; therefore its use is limited to areas with chloroquine sensitive P. falciparum[13]. The drug of choice for malaria in U.S. service members in Afghanistan in the recent past was weekly mefloquine as mentioned above. Around 2009, the U.S. quickly prohibited the use of mefloquine in its service members after realizing its detrimental effects on mental health disorders, TBI, and PTSD. The U.S. then adopted daily doxycycline as the drug of choice in its service members and atorvaquone-proguanil in those with contraindications to doxycycline. While doxycycline is 92-98% effective as chemoprophylaxis, malaria has emerged resistance to the drug and treatment failures have been attributed to its short half life, which requires strict compliance and adequate dosing[13,15].

An additional medication, primaquine, is the only known drug that can attack parasites in its liver form. When atorvaquone-proguanil was used for primary prevention, primaquine was co-administered for the last seven days and an additional seven days[13]. Primaquine should be used with an antimalarial drug that kills blood schizonts to prevent relapses[17]; however due to risk of intravascular hemolytic anemia in G6PD patients its use has been limited. The question to answer now is whether we should provide primaquine to all individuals prophylactically in addition to daily doxycycline? Studies from deployed personnel in Indonesia and Papua New Guinea demonstrated that concomitant use of doxycycline and low dose primaquine did not offer full protection against malaria upon the soldiers' return to their homeland[16]; higher doses of primaquine would be effective in combination with doxycycline. Administration of this regimen would require careful scrutiny of risks versus benefits and strict medical surveillance[17].

Primaquine would allow individuals traveling to endemic regions to stop their prophylaxis seven days after leaving the endemic area as opposed to other regimens where you would continue prophylaxis for 4 weeks post-exposure, thus increasing compliance as well compared to those individuals that may need post-exposure prophylaxis as well[12]. Due to the extended duration of prophylactic therapy following discontinuation of primary therapy such as doxycycline or atovaquone-proguanil, only 41% of soldiers deployed to Afghanistan completed primaquine therapy[18]. According to the CDC, primaquine has been the most effective medication for preventing plasmodium vivax; however it is not used as much due to the cost of obtaining the expensive G6PD assay prior to starting the treatment. However, in patients who test negative for G6PD, use of primaquine alone as primary prophylaxis, which is currently off-label use, should be addressed and encouraged because it would increase compliance given shorter duration of treatment[18].

In a recent article that analyzed randomized-controlled trials in four countries (Afghanistan included) with over 2000 patients, the evidence suggested that 14-day course with primaquine was not superior to 7-day course in preventing relapse in 12 months. This shorter duration of therapy would significantly impact compliance. However, all patients studied had normal G6PD levels, which limits the study's generalizability. It was noted in this study that while primaquine's efficacy was dependent on total dose over seven or fourteen days, its

hemolytic toxicity was dependent on daily dose, specifically at the beginning of treatment[14]. And in areas where G6PD is prevalent, primaquine is not widely used due to concern for side effects over efficacy. While it is difficult to obtain G6PD testing in malaria-endemic countries, approximately 30% can still be performed via point-of-care rapid diagnostic tests[14]. This would revolutionize short-term primaquine use in a population very similar to where our patient had served.

CONCLUSION

The hypnozoite form of *Plasmodium vivax* and relapsing nature of this species, leads to delays in clinical diagnosis and difficulty in eradication in infected patients. Even more, the presentation of *Plasmodium vivax* a year after exposure is unusual. Our case highlights that while malaria is not common in the U.S., army members stationed abroad are at increased risk of contracting malaria despite preventative and prophylactic measures. Our patient was effectively treated with atorvaquone-proguanil and primaquine 12 months after exposure. While doxycycline and atorvaquone-proguanil are the most common forms of pre- and post-exposure chemoprophylaxis, strict compliance is a common obstacle of effectiveness due to their long treatment course. Recent research suggests a much shorter course of pre- and post-exposure chemoprophylaxis with the use of primaquine which could increase compliance among at-risk patients. However, costly G6PD screening tests prior to primaquine prescription hinders clinicians from choosing it. Our case aids clinicians in being more aware of the high prevalence of dormant *P. vivax*. In summary, the importance of malaria chemoprophylaxis should be emphasized to military members who are at risk of contracting malaria. Clinicians should be made more aware of *Plasmodium vivax* predominance in U.S. military members. Short-term use of chemoprophylaxis therapies, such as primaquine, should be explored to improve outcomes.

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