OCCULT *PLASMODIUM VIVAX* INFECTION DIAGNOSED BY A POLYMERASE CHAIN REACTION–BASED DETECTION SYSTEM: A CASE REPORT

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Abstract. After a trip to Zambia, a previously healthy adult traveler presented with a prolonged illness characterized by low-grade fevers and fatigue. Although malaria smears and antibody test results for *Plasmodium* species were negative, a diagnosis of malaria was ultimately determined by polymerase chain reaction (PCR) amplification and species-specific nucleic acid hybridization techniques. The patient was successfully treated and cured. Clinical use of PCR technology may facilitate the identification of cases of smear-negative malaria, which up to the present time, have been difficult to diagnose.

INTRODUCTION

We report the case of a previously healthy returning adult traveler who presented with a prolonged illness characterized by low-grade fevers and fatigue. Malaria smears and antibody test results for *Plasmodium* species were negative. A diagnosis of malaria was made by polymerase chain reaction (PCR) amplification and species-specific nucleic acid hybridization techniques.

CASE REPORT

The patient was a 23-year-old woman with no significant prior medical history. She presented with daily low-grade fevers, malaise, and fatigue for three weeks after returning from Zambia. She had spent the month of March 2002 in Zambia volunteering at an acquired immunodeficiency syndrome (AIDS) orphanage. Prior to travel to Zambia, she had been seen in the Travel Clinic at University Hospitals of Cleveland. She had received appropriate vaccinations. She used malaria prophylaxis that she had acquired locally in Zambia but was not able to recall its name. She reported no illnesses in Zambia. One year previously she had spent a month in Mozambique where she also volunteered at an AIDS orphanage. She reported having no illnesses from that trip. Her current symptoms were assessed at this initial visit with a thick and thin malaria smear, which showed no organisms. Results of all other tests including a complete blood count (CBC), chemistry panel, and liver function tests were unremarkable.

Two weeks later, she returned to Travel Clinic with persistent fatigue, low-grade fevers to 38.1°C, and occasional nausea that did not significantly limit her food and liquid intake. She had a repeat malaria smear that was unremarkable. Her thyroid stimulating hormone level was normal.

She was followed up one month later at which time the daily fevers, nausea, and fatigue were still present. She was able to continue working and denied other symptoms of headache, cough, shortness of breath, joint pain, joint swelling, rash, and diarrhea. On her examination at that visit, she was a slightly obese woman with no acute distress. She had a temperature of 38.0°C, a pulse rate of 74, a respiratory rate of 18, and a blood pressure of 117/80 mm of Hg. There was mild epigastric tenderness but no hepatosplenomegaly. The remainder of her examination results was benign. She had a repeat CBC that was normal. Her erythrocyte sedimentation rate and C-reactive protein level were normal. A test result for human immunodeficiency virus was negative. A repeat malaria smear was also unremarkable. The result of a right upper quadrant ultrasound examination was normal. A stool examination for ova and parasites was negative, as was that for *Giardia* antigen. Serology for *Brucella* was negative and blood cultures at that visit and a previous visit showed no growth.

By the time of her next appointment at Travel Clinic the symptoms had been present for more than two months. It was then decided to give her a trial of anti-malarial therapy. She received atovaquone (250 mg/tablet)/proguanil (100 mg/tablet), four tablets per day for three days. She suffered nausea with the medications but took them as prescribed. When she was followed up two weeks later, the patient reported complete resolution of her fevers and marked improvement in her fatigue and malaise.

She then called back one week later stating that her symptoms had returned. She was seen again in the clinic, where test results for antibody levels to all four human *Plasmodium* species were negative. Her blood was then sent in EDTA-coated Vacutainer® (Becton Dickinson, Franklin Lakes, NJ) tubes to a research laboratory for PCR amplification of malarial parasites and species-specific nucleic acid hybridization analysis as previously described.1 The results of these studies were positive for *Plasmodium vivax* (Figures 1 and 2). She was retreated for malaria with chloroquine (a loading dose of 600 mg base orally, followed by 300 mg base given six hours after the first dose and again on days 2 and 3) and given a course of primaquine (15 mg base per day orally for 14 days) after the results of a test for glucose-6-phosphate dehydrogenase were normal.

After receiving definitive treatment for *P. vivax* infection, she has remained afebrile and her energy level has returned to baseline. The PCR testing was repeated on three blood samples collected in EDTA-coated tubes at follow-up and the results were negative for *Plasmodium* species.

DISCUSSION

Malaria is always a primary consideration when travelers complain of fevers after returning home from abroad. The disease has been eradicated from most temperate zone countries, but there are still > 100 million cases of malaria worldwide per year. Although most of these cases occur in the disease-endemic regions of the tropics, there are still a small number that are recognized in returning travelers from areas...
As PCR technology improves, it may allow malaria in patients who do not have a parasitemia diagnosis was made by a small subset of ribosomal DNA-based nested PCR. At this time, efforts are being made to address these limitations and develop a reliable PCR method with a fast turnaround. As PCR technology improves, it may allow increased recognition of the syndrome of smear-negative malaria that up to this time has been difficult to diagnose. Currently, 30,000 travelers from industrialized countries are found to have malaria each year. Other returning travelers with persistent fevers and undiagnosed Plasmodium infections may benefit from this technology.

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REFERENCES


