A 38-year-old man with fever and a history of malaria

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A 38-year-old man presents to his family physician with a three-day history of fever and chills. He has no localizing symptoms and is worried that he has malaria, because he has had several previous infections with the parasite and now has similar symptoms. He has not been in an area endemic for malaria since arriving in Canada from Pakistan 14 months ago.

What sources of infection should be considered?

This patient could have a delayed presentation of malaria. Given that he has been in Canada for 14 months, the differential diagnosis of fever related to infections acquired in Pakistan is narrowed to those that can reactivate months to years later, such as malaria, tuberculosis, strongyloidiasis and histoplasmosis, among others. Other potential causes of this patient's symptoms are influenza and other common viral infections acquired in Canada, including upper respiratory tract infections, Epstein–Barr virus or cytomegalovirus. Infections with compatible localizing signs, symptoms or specific risk factors should also be considered (e.g., pneumonia, sexually transmitted diseases or urinary tract infections).

Could this patient have malaria so long after exposure?

Plasmodium species that cause malaria in humans can present long after the patient leaves an endemic area. Infection with *Plasmodium falciparum* is associated with the highest mortality. More than 90% of cases involving *P. falciparum* tend to present within two months of leaving an endemic area.[1,2] However, a milder clinical presentation of *P. falciparum* or *Plasmodium malariae* infection can occur in those who are semi-immune after having lived in an endemic area and have chronic asymptomatic parasitemia from untreated or partially treated infections. This process, known as recrudescence, may occur months or years after leaving an endemic area (up to 15 years in an individual chronically infected with *P. falciparum*).[3]

Both *Plasmodium vivax* and *Plasmodium ovale* have life cycles that include a dormant hepatic stage called hypnozoites. These hypnozoites can be released from the liver, resulting in parasitemia and clinical symptoms months to years after the initial infection (a condition known as relapse).[4] Relapses occur most frequently when only the initial blood stage of the infection was effectively treated, but treatment of the liver stage was omitted.[2,5]

The clinical presentation in this patient raises concern for infection with *P. vivax,* which is the most common species causing symptomatic malaria that presents six months or more after a patient leaves an endemic area.[1,2] *Plasmodium vivax* caused nearly 20% of all cases of malaria in patients presenting to travel clinics in Canada[6] and 24% of all cases of malaria among travellers in the GeoSentinal Network, a global surveillance network for travel-related illness, with variation depending on region of travel.[1] In the GeoSentinal study, most cases of late-onset infection caused by *P. vivax* presented within 12 months of the patient leaving an endemic area; only 1% of cases presented more than 12 months after travel.[1] However, there are case reports of patients presenting with malaria caused by *P. vivax* more than one year after exposure,[5] with one case presenting four years after the patient had left an endemic area.[7]

What tests should be ordered?

The clinical signs and symptoms associated with infection caused by *P. vivax* are not sufficiently sensitive or specific to distinguish it from other species of malaria or other febrile illnesses. Given the patient's absence of localizing symptoms, initial investigations could include complete blood cell count, creatinine, electrolytes, glucose, liver function tests, lactate, blood cultures, along with Giemsa staining of thick and thin films of blood.[8] A nasopharyngeal swab for influenza (if seasonally appropriate), urinalysis, urine culture, radiograph of the chest and specific investigations for sexually transmitted infections may also be considered depending on risk factors and presentation.

Where available, urgent rapid diagnostic tests should be ordered to assess for falciparum malaria; many of these tests can also detect and distinguish between falciparum and non-falciparum malaria to help guide immediate treatment. Laboratory protocols ensure rapid evaluation and reporting of these results. The sensitivity of these tests is thought to be much higher for *P. falciparum* than for *P. vivax*, although this may not be the case at higher densities of parasites.[9] Furthermore, results from blood films are also important to determine the level of parasitemia and type of species.

If testing shows that the patient is infected with *Plasmodium vivax*, what treatment should he receive?

The patient should be treated with chloroquine, followed by a course of primaquine to eradicate hypnozoites (Box 1), as recommended by the Canadian Committee to Advise on Tropical Medicine and Travel, World Health Organization and Centers for Disease Control and Prevention; this regimen is backed by strong evidence of treatment efficacy.[8,10,11]

Typically, patients with infection caused by *P. vivax*, clinical stability and normal results for laboratory tests can be treated for uncomplicated non-falciparum malaria with therapy administered orally as an outpatient. Eight hours of observation is recommended to ensure the patient tolerates the treatment and that parasitemia is decreasing;[8] however, practices may vary among institutions. Conversely, patients with infection caused by *P. falciparum* or features of severe malaria from any species should be referred to the hospital for further management.[8]

Deficiency in glucose-6-phosphate dehydrogenase must be ruled out before starting primaquine to prevent hemolytic anemia.[8] Chloroquine resistance should be considered in those who have travelled through Papua New Guinea and Indonesia, and alternative treatment regimens should be used.[10–12] Chloroquine resistance has also been documented but is less common in parts of India, Southeast Asia, and South and Central America.[11,12]

Box 1: Recommended treatment of uncomplicated malaria caused by *Plasmodium vivax* in adults*[8]

Initial treatment

- Chloroquine phosphate: 620 mg of base (equivalent to 1000 mg of the salt) initially administered orally, followed by 310 mg of base (equivalent to 500 mg of the salt) administered orally at 6, 24 and 48 hours
- Total dose: 1550 mg of base (equivalent to 2500 mg of the salt)

Hypnozoite eradication (following initiation of chloroquine treatment and after ruling out deficiency in glucose-6-phosphate dehydrogenase)†

- Primaquine phosphate: 30 mg of base per day administered orally for 14 days

*Excludes treatment of suspected malaria caused by chloroquine-resistant *Plasmodium vivax* from Papua New Guinea, Indonesia and other regions. Alternative non-chloroquine regimens are available; expert medical advice should be sought in this situation.
†Alternative regimens are available for those with deficiency in glucose-6-phosphate dehydrogenase. Primaquine should not be given to women who are pregnant or lactating; in these situations (or for other concerns), expert medical advice should be sought.

Although infections caused by *P. vivax* are generally milder than those caused by *P. falciparum*, if left untreated severe malaria may develop, which can include renal failure, anemia, hepatic dysfunction, pulmonary edema, acute respiratory distress syndrome, and multisystem organ failure and death.[13]

Patients should be followed with repeat blood films at 28 days and six months to ensure clearance of the parasite.[8]

Case revisited

A rapid antigen test for malaria showed a positive result for non-falciparum malaria in this patient. Blood films confirmed that he was infected with *P. vivax,* with a parasitemia of 1%. Other blood tests were normal. The patient was treated as an outpatient with chloroquine and, after excluding deficiency in glucose-6-phosphate dehydrogenase on laboratory testing, he completed a two-week course of primaquine. He recovered quickly without complications. Repeat blood films at 28 days and six months confirmed parasite clearance.

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The clinical scenario is fictional.

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