CASE REPORT

Fever in the returning traveller: the importance of sensitivity

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Accepted 28 September 2015

SUMMARY

We report the case of a 28-year-old man, presenting with episodes of fever and rigours, having recently returned from Cameroon and Uganda. Initial investigations for malaria were negative, and the patient was sent home without a clear diagnosis. Subsequent review of the blood film revealed the presence of *Plasmodium ovale*. This case highlights the importance of repeated and careful inspection of blood films, given the relatively low sensitivity of rapid diagnostic tests in *P. ovale* infection. It also illustrates the importance of the travel history in the diagnosis of malaria.

BACKGROUND

Fever in the returning traveller is a common presentation to primary care and A&E departments. Although many of the potential causes are self-limiting, and not likely to result in significant morbidity or mortality, the differential diagnosis also includes a number of serious illnesses, which must be confidently ruled out. Owing to the relatively low sensitivity of malarial diagnostics for non-falciparum *Plasmodium* spp, multiple tests on different samples are required if clinical suspicion of malaria is high, and an emphasis on clinical history, rather than simply on laboratory diagnostics, is required.

CASE PRESENTATION

A 28-year-old British doctor presented with a history of one episode of shivers, followed by a high fever and rigours lasting 2 h, and a further 10 h of diaphoresis. Associated symptoms included general malaise and headache. No previous episodes had been noted, and no rash was visible at this point. The patient reported no photophobia, neck stiffness or confusion; no urinary symptoms, abdominal pain or change in bowel habit; and no cough, dyspnoea or chest pain.

The patient had no significant medical history and was on no regular medications. Recent travel history included 2 months in rural Cameroon working on general medical wards, followed by 6 weeks in Uganda performing laboratory research. He had returned to the UK 35 days prior to presentation. Within the past 5 years, he had also spent extended periods in Latin America, Ethiopia and East Africa. While abroad, there had been no needle stick or splash injuries, and appropriate personal protective equipment (PPE) was worn during all clinical procedures. Significant environmental exposure included swimming in the river Nile 8 months previously, going on safari and significant time spent in malarious areas.

While in malarious areas, insect repellent was used and the patient slept under treated bed nets. Doxycycline (100 mg once daily) was used for malaria prophylaxis while in Africa, with good adherence for this period and for the initial 2 weeks on returning to the UK. However, compliance was poor for the past 2 weeks, of the recommended 4 weeks, for which doxycyline should be continued after leaving malarious areas. Although insect bite avoidance measures had been taken while in Africa, the patient had sustained mosquito bites, but was not aware of any other arthropod or animal bites. There was no sexual contact during this period. Full pre-travel vaccinations had been received as directed by the travel clinic.

On initial presentation to the emergency department, the patient was afebrile and bedside observations were within normal range. Physical examination found a clear chest, no rashes, and a soft, non-tender abdomen with no masses palpated. Initial investigations showed mild lymphopaenia of 0.84×10^9/L (normal range 1–4), thrombocytopaenia of 69×10^9/L (normal range 140–450), raised C reactive protein of 120 mg/L (<6), a negative malaria rapid diagnostic test (RDT), and negative thick and thin blood film for malaria. The patient was discharged from the A&E department with a provisional diagnosis of a non-specific viral illness, and advised to return to the A&E department should he develop any further symptoms.

The blood film was reviewed the following day and found to be positive for *Plasmodium ovale* malaria (figure 1). The patient was telephoned and advised to attend his general practitioner immediately for initiation of specific treatment. An appointment was arranged with the Infectious Diseases consultant the next day, who conducted further investigations as discussed below. Forty-eight hours following initial presentation, and 4 h after starting therapy, the patient experienced another 12 h episode of shivering, fever and diaphoresis, similar to the initial episode.

INVESTIGATIONS

The malaria RDT was negative, as was the initial interpretation of the thick and thin blood films, though review of this film was positive for *P. ovale*. Two further blood films were negative for malaria (though the third sample was taken 30 h after initiation of treatment). Full blood count showed mild lymphopaenia and thrombocytopaenia. Stool was negative for pathogenic ova, cysts and parasites in three samples, and terminal urine samples were negative for ova. HIV and viral hepatitis screens were negative.

To cite: Philip KEJ, Baddeley R, Jenkins M, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2014-209140

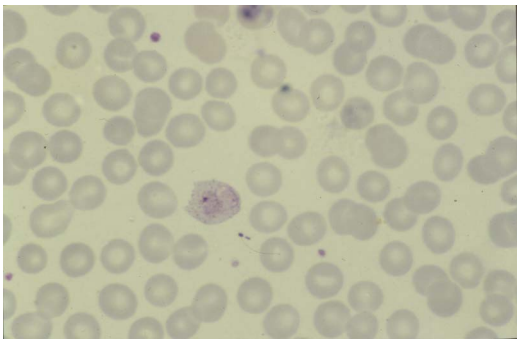

Figure 1 A *Plasmodium ovale* trophozoite within a red blood cell.

DIFFERENTIAL DIAGNOSIS

The primary differential diagnoses include both imported infections such as malaria (*P. ovale*, *P. falciparum*, *P. vivax*, *P. malariae*), acute schistosomiasis, foodborne and waterborne diseases such as typhoid or hepatitis A and E, and native infections such as viral influenza, HIV seroconversion, Gram-negative sepsis and meningococcal infection.

TREATMENT

In light of identification of a *P. ovale* infection by an experienced laboratory, the patient was treated with 3 days of oral chloroquine (600 mg base, followed by 300 mg 6 h after, then 300 mg once daily for 2 days), followed by 2 weeks of oral primaquine (15 mg once daily) to eliminate hypnozoites. G6PD enzyme levels were normal. Of note, atovaquone/proguanil can also be considered for treatment of *P. ovale* in patients unable to take the first-line treatment.

OUTCOME AND FOLLOW-UP

No further malarial paroxysms occurred after completion of the chloroquine treatment. The patient experienced ongoing headaches, anorexia and general malaise for another week, before complete resolution of symptoms. Repeat bloods at 2 weeks showed normalisation of parameters. To date, no recurrence of symptoms has occurred.

DISCUSSION

Malaria is the most common imported tropical infection seen in the UK, with a reported 1500–2000 cases each year, and 10–20 deaths due to *P. falciparum*.[1] Malaria is therefore an important differential diagnosis when assessing fever in the returning traveller. *P. ovale* is less common than other *Plasmodium* spp, with recent global estimates suggesting that *P. ovale* causes 0.5–10.5% of all malarial disease, with the majority of cases being found in sub-Saharan Africa, though *P. ovale*-related malaria is also found in multiple islands in the western Pacific, and also in mainland Asia.[2]

While malarial data from Uganda are relatively scarce, a landmark study by Onori,[3] which assessed the distribution of malaria species in Uganda, found the prevalence rate of *P. ovale*, in relation to malaria infection from all species combined, ranged from 0.0% to 3.4%. This was dwarfed by the prevalence of *P. falciparum*, which was found in 82.5–97.5% of infections. However, it should be noted that these data are old, and the degree to which they represent the current situation is unclear.

The pre-patent period (interval between inoculation with sporozoites and initial detection of peripheral blood parasites) for *P. ovale* in humans is 12–20 days.[2] In the present case, the patient had returned to the UK 35 days prior to the onset of symptomatology, suggesting that this presentation likely represented a relapse due to reactivation of hepatic hypnozoites rather than a primary infection, and that the initial inoculation may have taken place months or even years before.[2] However, another explanation could be that the use of doxycycline delayed the onset of clinical symptoms from a recent primary infection. This highlights the importance of an extensive travel history.

Thick films remain the gold standard for malarial diagnosis. RDTs are a useful adjunct, but do not currently achieve a diagnostic accuracy to safely replace direct microscopy.[4] The sensitivity of RDTs depends on a number of factors including the RDT used, the species being looked for and the specific antigen being detected. Regarding *P. falciparum* malaria, the main antigens targeted by RDTs are Histidine Rich Protein 2 (HRP-2) and *P. falciparum* lactate dehydrogenase (pLDH). A Cochrane review[5] found the sensitivity of HRP-2-based RDTs to be 95%, and pLDH to be 93.2%. Regarding RDTs testing for non-falciparum malaria, a recent Cochrane review[6] found that they have good specificity (range 98–100%), however, they are not very sensitive (range 78–89%). This suggests false-negative results for non-falciparum malaria may occur in from 11% to 22% of cases. The diagnostic sensitivity of blood films is also impaired in the context of a low parasitaemia. In the present case, though the exact parasitaemia level was not calculated, the report stated that it was 'low', which would have therefore made the initial interpretation more prone to error.

The deleterious role of a low parasitaemia on the accuracy of malarial diagnostics is one of the reasons that clinical guidelines emphasise the importance of repeat blood films taken at 12 and 24 h after patient assessment, to increase the detection of malaria in febrile travellers returning from endemic areas.[4] A persistent fever, despite three negative malaria films, should prompt further clinical and laboratory investigation.

Cases of *P. ovale* malaria in returning travellers to the UK are not frequently reported in the literature, perhaps because they are not particularly rare. The Health Protection Agency Malaria Reference Laboratory (HPA MRL) is the UK body to which cases of malaria are reported. They recorded 757 cases of malaria resulting from *P. ovale* spp between November 2003 and August 2011, including people returning from both Cameroon and Uganda, as well as at least 15 other African countries.[7] The importance of this case lies not in its clinical rarity, but in the learning points that it raises for clinicians assessing these patients.

A final consideration should look to the future. While the rapid diagnosis and treatment of malaria has for many years been vital for reducing morbidity and mortality in those patients returning to our shores from overseas, it may yet become an important consideration for UK public health bodies. A recent UK study found a relative abundance of mosquitoes capable of acting as vectors for human disease, including *Anopheles plumbeu*—a potential vector for malaria.[8] Historical evidence suggests that malaria has, until relatively recently, been endemic in the UK, and that with the correct mix of variables, could become so again, or at least be subject to outbreaks.[9] It is therefore in our interest to equip our clinicians with the skills and knowledge, to effectively and safely treat this growing patient group.

Learning points

- Malaria is a common and potentially serious cause of fever in a returning traveller.
- Blood films and rapid diagnostic tests (RDTs) can have a low sensitivity for diagnosis of malaria, especially non-falciparum *Plasmodium* spp, though this can be improved through taking multiple samples, and by the addition of molecular diagnostics.
- Malaria needs at least three negative films on three consecutive days, before it can be ruled out.
- Accurate history-taking, including any history of travel and environmental exposures, is key to establishing potential differential diagnoses.
- *P. ovale* and *P. vivax* have hypnozoite stages capable of staying dormant for months or even years before symptomatic presentation.

Contributors BB, MJ and RB made significant contributions to the patient's management. KEJP, BB, MJ and RB contributed to the concept, information gathering, drafting and revising the case report, and approval of the final draft.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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