

A case of severe *Plasmodium vivax* malaria

A Case Report and Clinical Pearls

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Jill Westlund BScPhm¹, M. Elizabeth Wilcox MD MPH¹, Kevin Duplisea PharmD¹, Abdu Sharkawy MD¹, Jay Keystone MD MSc¹, Linda Dresser PharmD¹

¹ University Health Network

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Abstract

In North America, imported malaria is the principal cause of febrile illness and life threatening infection in travelers and immigrants arriving from endemic areas. Severe malaria due to *Plasmodium vivax* is an emerging infectious disease that requires prompt identification and appropriate management. Malaria symptoms may present in a gradual or fulminant fashion. With treatment, severe malaria has a case fatality of 10 to 20%; if left untreated or with a significant treatment delay, severe malaria is usually fatal with death due to multiorgan dysfunction including adult respiratory distress syndrome. Consultation with an infectious diseases or tropical medicine specialist is strongly recommended in the management of malaria, as timely diagnosis and treatment are essential. Parenteral artesunate or quinine is recommended for treatment of severe malaria. Speciation of plasmodium is required, as *P. vivax* and *P. ovale* require additional treatment to eliminate dormant parasites (radical cure).

Introduction

Imported malaria is the principal cause of febrile illness and life threatening infection in North America among travelers and immigrants arriving from endemic areas. Most severe malaria is caused by *Plasmodium falciparum*; we present a case of severe malaria due to *Plasmodium vivax*, a species historically associated with benign disease.

Case Presentation

A 30-year-old Canadian citizen who emigrated from India in 2007 returned from a five-week trip to New Delhi and Mumbai. As on previous visits to the same region, he did not take antimalarial chemoprophylaxis. Twelve days after returning to Canada, he presented to his general practitioner with fever and chills. After taking clarithromycin 500 mg orally twice daily for five days, he presented to the emergency department with complaints of ongoing fever, increasing weakness, dizziness, nausea and diarrhea. His blood pressure was 77/46 mm Hg, heart rate 140 beats/min, and respiratory rate 40 breaths/min. Laboratory tests revealed platelets 15,000/?L, creatinine 321 µmol/L (3.6 mg/dL), bilirubin 91 µmol/L (5.3 mg/dL), and lactate 5.6 mmol/L (50 mg/dL). After 2 liters of intravenous saline and 2 units of adult pooled platelets were infused, he remained hypotensive and norepinephrine was initiated. The patient was prescribed ceftriaxone (1 gram intravenous [IV] every 24 hours) as empiric coverage of enteric fever (e.g. *Salmonella typhi*).

Thick and thin blood films showed malaria parasites, and the infectious diseases service was consulted. Parasitemia was quantified at 1.3%. The rapid diagnostic *P. falciparum* assay was negative, but positive for non-*P. falciparum* malaria. Artesunate (2.4 mg/kg IV at 0, 12, 24 and 48 hours) and Malarone® (atovaquone 250 mg/proguanil 100 mg 4 tablets p.o. daily) were prescribed.

The following day, molecular testing confirmed *Plasmodium vivax* and atovaquone/proguanil was changed to chloroquine. Parasitemia was 0.0% on hospital day 3. After completion of initial therapy, the patient was definitively managed with primaquine 30 mg p.o./day, for 14 days for radical cure of *P. vivax*.

Discussion

Until recently, *Plasmodium vivax* malaria has been considered a relatively benign infection unassociated with severe complications or death. However, recent cohort studies in Papua New Guinea¹ and elsewhere have confirmed an increase of severe *P. vivax* malaria that may have a mortality approximating that of *P. falciparum*. Presenting symptoms usually include fever or a recent history of fever. Other clinical features of severe malaria, as per the World Health Organization (WHO) definition for *P. falciparum*, can exist together or evolve in rapid succession (See Table 1)^{2,3} Even if treated, severe malaria has a case fatality of 10 to 20%; if left untreated, it is fatal in the majority of cases² In one case series, death from *P. vivax* infection was most often due to multiorgan dysfunction, acute respiratory distress syndrome (ARDS), or splenic rupture³

Diagnosis of malaria

Timely diagnosis (within hours of presentation) is essential in cases of severe malaria; thick and thin blood films should be promptly examined for the presence of parasites.⁴ Alternatively, where available, a rapid diagnostic test for malaria antigen may be performed.⁴ If a returned traveller remains symptomatic despite an initial negative blood film, films should be repeated at 12-hour intervals for at least 24 to 48 hours, as the exclusion of malaria requires three separate negative blood film results⁵ Once a diagnosis of malaria is made, an examination of the thin film should be performed to quantify parasite density.⁴ WHO guidelines define severe *P. falciparum* malaria as greater than 2% infected erythrocytes in areas of low malaria transmission (reflecting a non-immune population), and greater than 5% infected erythrocytes in areas of high and stable transmission (reflecting a semi-immune population).² Parasitemia counts in severe *P. vivax* malaria are generally lower than in severe *P. falciparum* malaria, but are too variable to be diagnostic (personal communication: Dr. Jay Keystone). In *P. falciparum* malaria, parasites may be sequestered in the microcirculation, and the total parasite load thus may not be reflected in a peripheral blood analysis, especially in non-immune people. In such cases, severe malaria may be fatal despite a low parasite count in peripheral blood.⁶ Repeated evaluations of parasite density during treatment are necessary to ensure an appropriate response to antimalarial therapy.⁴

Initial treatment of malaria

Where possible, treatment of severe malaria should be provided in an intensive care setting. Supportive care including measures to treat respiratory, circulatory and renal complications should be provided. Once malaria infection is confirmed, full doses of parenteral antimalarial medication should be administered without delay.⁷ Intravenous artesunate is the preferred agent over quinine for the initial treatment of severe malaria in adults. To avoid the potential risk of antimalarial drug resistance, initial drug therapy should be combined with, or followed by, administration of another antimalarial with a different mechanism of action.²

Radical cure of *P. vivax* malaria

Plasmodium vivax species produce hypnozoites, a persistent liver stage. Elimination of these dormant-stage parasites (so-called radical cure) is necessary to prevent relapse that may otherwise occur weeks to months after the original infection.² Primaquine (0.5 mg [base form]/kg/day, up to 30 mg/day, for 14 days) is recommended by the U.S. Centers for Disease Control and Prevention.⁸ G6PD deficiency should be ruled out prior to treatment with primaquine to avoid drug-induced hemolysis.² The WHO guidelines for radical cure differ from CDC's, recommending a lower dosage of primaquine: 0.25 mg[base form]/kg/d (up to 15 mg/day) for 14 days, perhaps out of concern for G6PD deficiency.²

Reporting malaria cases

Although malaria is a reportable disease in North America, the surveillance system is passive and therefore subject to incomplete reporting. In the United States, all laboratory-confirmed cases of malaria should be reported to a local or state health department. The National Malaria Surveillance System (NMSS) collects data to inform the Centers for Disease Control and Prevention (CDC). Although the total number of cases of malaria in Canada is unknown, the Canadian Malaria Network (CMN) requires that the use of parenteral medication for severe malaria be formally documented and reported. As of 2013, 7 cases of severe *P. vivax* malaria have been reported to the network (personal communication: Dr. Anne McCarthy, National Program Director, CMN).

Prevention of malaria

Infection with malaria is preventable provided recommended precautions are implemented. Pre-travel risk assessment should include assessment of baseline risk, destination, setting (urban versus rural), season, planned duration of travel, and baseline immunity.⁹ Importantly, travellers returning to their country of origin should be made aware that they may be only partially or non-immune to malaria due to lack of continuous exposure.²

Conclusion

Severe malaria due to *Plasmodium vivax* is an under-recognized emerging infectious disease in North America that requires prompt identification and appropriate management.

Criteria for Severe Malaria

Compatible history (recent possible exposure with no other identifiable pathology)

Or

Malaria parasites seen on blood smear

And

Any one or more of the following features:

- Prostration with extreme weakness
- Impaired consciousness or coma
- Repeated generalized convulsions
- Severe normocytic anemia
- Acute renal failure
- Clinical jaundice with evidence of other organ dysfunction
- Pulmonary edema or acute respiratory distress syndrome
- Circulatory collapse/shock
- Hypoglycemia
- Spontaneous bleeding / disseminated intravascular coagulation
- Acidemia/acidosis
- Hemoglobinuria not associated with oxidant drugs or red blood cell enzyme defects
- Hyperparasitemia
 - o *P. falciparum*
 - > 2% in non-immune individuals
 - > 5% in semi-immune individuals
 - o *P. vivax*
 - Not formally defined
 - Less than for severe *P. falciparum*

Table 1. Criteria for severe malaria.

References

1. Rogerson SJ, Carter R. Severe vivax malaria: newly recognised or rediscovered. PLoS Med. 2008 Jun 17;5(6):e136. PubMed PMID:18563965. [REFERENCE LINK](#)
2. World Health Organization Guidelines for Treatment of Malaria. 2nd ed. Geneva: World Health Organization; 2010. [REFERENCE LINK](#)
3. Lacerda MV, Fragoso SC, Alecrim MG, Alexandre MA, Magalhães BM, Siqueira AM, Ferreira LC, Araújo JR, Mourão MP, Ferrer M, Castillo P, Martin-Jaular L, Fernandez-Becerra C, del Portillo H, Ordi J, Alonso PL, Bassat Q. Postmortem

characterization of patients with clinical diagnosis of Plasmodium vivax malaria: to what extent does this parasite kill? Clin Infect Dis. 2012 Oct;55(8):e67-74. PubMed PMID:22772803.

REFERENCE LINK

4. Canadian Recommendations for the Prevention and Treatment of Malaria Among International Travellers. June 2009, Volume 35S1.

REFERENCE LINK

5. Suh KN, Kain KC, Keystone JS. Malaria. CMAJ. 2004 May 25;170(11):1693-702. PubMed PMID:15159369.

REFERENCE LINK

6. Wilairatana P, Tangpukdee N, Krudsood S. Definition of hyperparasitemia in severe falciparum malaria should be updated. Asian Pac J Trop Biomed. 2013 Jul;3(7):586. PubMed PMID:23835631.

REFERENCE LINK

7. Medical Access to Artesunate or Quinine for Malaria Treatment Streamlined in Canada through the Canadian Malaria Network, Public Health Agency of Canada website.

REFERENCE LINK

8. Centers for Disease Control and Prevention, "Guidelines for Treatment of Malaria in the United States," updated July 2013.

REFERENCE LINK

9. World Health Organization, World Malaria Report 2014, 9 December 2014.

REFERENCE LINK