Case report

Successful Treatment of Severe Falciparum Malaria With Adjunctive Use of Exchange Transfusion

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Abstract

Although malaria is no longer endemic in Canada, it remains an important imported disease, principally among immigrants and travellers. The role of exchange transfusion in malaria treatment, in addition to standard anti-malarial treatment, remains controversial and is not well established. We report a case of severe malaria in a male traveller, complicated by multiorgan failure, septic shock, myositis, and unusual *Streptococcus pneumoniae* bacteremia. Manual exchange transfusion was used, in addition to artesunate-based therapy, and the patient responded well. This report shows that malaria remains an important differential diagnosis for travellers returning with fever and emphasizes the importance of prompt diagnosis and appropriate treatment.

Case Presentation

A frequent traveller to malaria-endemic areas, a 50-year-old Canadian, without a significant medical history, returned from a 4-week trip to Nigeria. His malaria chemoprophylaxis was stopped prematurely due to side effects. During the trip, he adopted appropriate measures to prevent mosquito bites and was up-to-date on his vaccinations. Four days after returning to Canada, he became ill; his symptoms included fever, chills, sweating, headache, and joint pains, followed by diarrhea, jaundice, shortness of breath, and a noticeable darkening of urine.

He presented to a local hospital's emergency department where malaria was suspected; thin/thick blood smears confirmed an infection by *Plasmodium falciparum*. The parasitemia level was markedly high at 26%. Upon admission, he was in respiratory distress; his temperature was 38 °C, heart rate 118 beats/minute, blood pressure 110/70 mm Hg, respiratory rate 28/minute, and oxygen saturation level 94%, using a 40% FIO2 face mask. The patient's physical examination revealed icterus, fine bilateral inspiratory crackles, tachycardia, and mild tender hepatomegaly. Figure 1 shows two peripheral blood smears taken from the patient which demonstrate red blood cells heavily infected with malaria parasites.

The time between confirmation of his malaria diagnosis and the start of malaria treatment was approximately 1 hour. The patient's complete blood count showed a leukocyte count of 7.4×10^9/L (4.5-11.0), a hemoglobin level of 154 g/L (120-160) and a platelet count of 12×10^9/L (150-350). His urea was 10 mmol/L (2.9-9.3) and creatinine 186 μmol/L (37-96). A liver test revealed the following: alanine aminotransferase 131 U/L (14-54), aspartate aminotransferase 165 U/L (15-41), lactate dehydrogenase 548 U/L (98-193), total bilirubin 130 μmol/L (0-16), and alkaline phosphatase 105 U/L (32-92), his creatine kinase peaked at 2103 U/L (10-35U/L). The findings of an initial chest x-ray were normal.

The patient's condition deteriorated rapidly in the emergency department, prior to admission to the critical care unit, where he was intubated, sedated, mechanically ventilated, and started on intravenous artesunate (2.4 mg/kg). A repeat chest x-ray revealed signs of acute respiratory distress syndrome (ARDS). Artesunate was re-administered at 12, 24, and 48 hours after the first dose.

His hemoglobin levels dropped to 60 g/L, and his platelet count remained very low (12×10^3/μL), necessitating multiple blood and platelet transfusions. A manual exchange transfusion (ET) was done within the first 24 hours, replacing 3000 mL of blood with 3517 mL; the duration of the ET was 8 hours.

His renal function worsened, resulting in acute kidney failure, which required urgent hemodialysis. The patient's blood cultures were positive for *Streptococcus pneumoniae* and methicillin-sensitive *Staphylococcus aureus*. He was started on ceftriaxone (1 g intravenously daily), which was stepped down to amoxicillin/clavulanic acid, based on culture sensitivities.

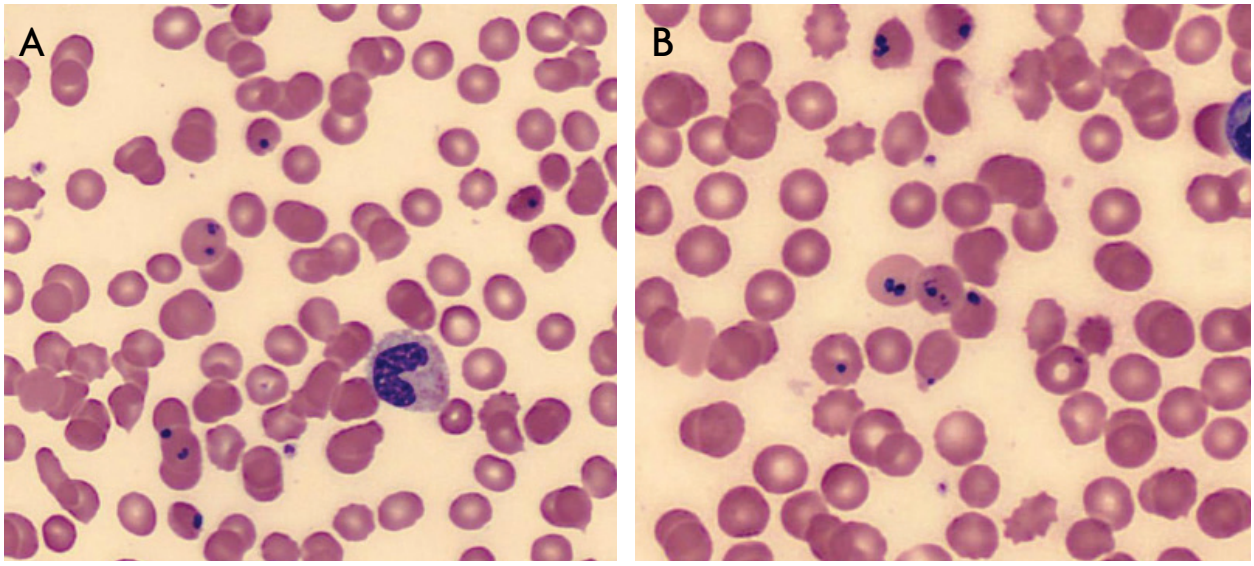

Figure 1. Malaria peripheral blood smears.

Repeated blood smears showed a dramatic decrease (to 5%) in his parasitemia level after 36 hours and to 1% after 72 hours of treatment. After artesunate therapy was completed, oral atovaquone and proguanil (Malarone) was administered (4 tablets/day) for an additional 4 days. The patient was sent home in stable condition after 2 weeks of hospitalization. However, he required intermittent dialysis over the following 6 weeks until his renal function recovered.

Discussion

Malaria is endemic in most tropical countries.[1,2] The World Health Organization (WHO) estimated that the number of cases of malaria increased from 233 million in 2000 to 244 million in 2005, but decreased to 225 million in 2009.[3] Concurrently, the number of deaths due to malaria is estimated to have decreased from 985,000 in 2001 to 781,000 in 2009,[3] with most deaths being caused by P. falciparum infection. It is estimated that each year 1 million Canadians travel to areas where they may be at risk of contracting malaria, resulting in 350 to 1000 cases.[4] In 2004, MacLean et al. published a detailed survey about the incidence of this disease in Canada.[5] They reported that the majority of *P. falciparum* cases imported into Canada were acquired in sub-Saharan Africa, whereas the majority of *P. vivax* cases were acquired on the Indian subcontinent.[4] In 1997, 2 cases of fatal falciparum malaria were reported in Canadians.[6] An additional 7 falciparum malaria deaths were reported to have occurred between 1997 and 1999 in Canada or in Canadian travellers.[7] From June 2001 to March 2007, there were 88 cases (33% were children) of severe or complicated malaria reported in Canada, a mean of 14 cases per year.[4] The incidence of malaria and its related deaths in Canada are shown in Table 1.[8]

Severe malaria is an acute disease, caused almost exclusively by *P. falciparum*, with major signs of organ dysfunction and/or high levels of parasitemia (>10%) in blood smear, as described by WHO.[3,9,10]

The symptoms of malaria may develop as early as 7 to 8 days after initial exposure, or may be delayed for months to years. The *P. falciparum* infection can rapidly become lethal, with multiple organ failure and can lead to death. In children, hypoglycemia, convulsions, and severe anemia are fairly common; acute renal failure and pulmonary edema are more common among adults, whereas, cerebral malaria with coma, shock, and acidosis can occur in both age groups, with increased morbidity and mortality rates.[11] Progression of malaria from no symptoms to severe and complicated malaria can be extremely rapid, with death occurring within 36 to 48 hours. The diagnosis of malaria is often difficult in absence of specific symptoms of malaria, but an accurate diagnosis can be confirmed by demonstration of malaria parasite in the blood smear.

The malaria infection presents with a broad array of clinical presentations, such as; fever, chills, rigor, sweat, headache, nausea, vomiting, diarrhea, abdominal pain, malaise, muscle ache, joint pain, tiredness, and may be associated with severe breathing difficulties, low blood sugar, severe anaemia and jaundice. In more severe cases it may include seizures, coma, kidney and respiratory failure, and shock which may lead to death.

Malaria in Canada is the most common specific diagnosis for a fever in a returned traveller.[35] Other common infections include acute travellers' diarrhea, respiratory tract infection, Dengue Fever and enteric fever. All other possible diagnoses need to be excluded when fever begins within few days (7-8 days) after return from malaria endemic area, but can be reliably excluded if symptoms do not appear until >2 weeks.[35]

Management of patients with severe malaria presents a broad array of clinical challenges, given the complex pathophysiology of the infection and the involvement of multiple organ systems.[1,12,13] These challenges are magnified by the emerging resistance of malaria to available treatment options.[14] Artemisinin-based therapy is now the recommended first line of therapy for treatment of adults with severe falciparum malaria, in areas where intravenous artesunate is available.[15-17] This recommendation is based on multiple, well-designed, randomized clinical trials that were conducted globally and on a recent Cochrane meta-analysis.[17-19]

ET has been proposed as an adjunctive anti-malarial treatment to remove infected red blood cells from circulation, thereby lowering the parasite burden.[20,21] Other mechanisms may involve the removal of toxic substances, reducing microcirculatory sludging, and increasing the oxygen-carrying capacity of the blood.[22] WHO, however, suggested that the lack of consensus on the indications, benefits, dangers, and practical details of the procedure make it impossible to reach any conclusions regarding the use of this procedure.[3]

Table 1. Incidence of malaria and death due to malaria in Canada

Year	Recorded Cases	Deaths Due to Malaria
1989	284	-
1990	417	-
1991	674	-
1992	422	-
1993	504	-
1994	446	-
1995	665	-
1996	1018	-
1997	1058	-
1998	387	-
1999	390	-
2000	462	1
2001	445	2
2002	366	0
2003	370	0
2004	-	0
2005	-	3
2006	-	0
2007	-	2
2008	-	2

An English language literature review, conducted using the PubMed and Embase databases, from their inception through 2012, identified that use of ET was first reported in 1974 as a therapeutic adjunct for severe malaria. Although the efficacy of this procedure has not been established by randomized controlled trials, its benefits have allowed the rationale of use of ET in severe and complicated malaria.[23] Many case reports, case series, and retrospective studies have reported about the successful use of ET in severe malaria. The meta-analysis concluded that "exchange transfusion does not appear to increase the survival rate"; however, authors concluded that the reviewed articles had significant problems with their comparability of the treatment groups, including the lack of a standardized assessments system.[24] While there are numerous publications on the matter, they are all of small sample size and of lower overall quality. Moreover, there are no evidence-based guidelines on the use of ET in patients with severe malaria.[21,24-32]

There are some questions regarding how to perform ET appropriately.[3] The two methods used are the traditional manual ET approach and automated erythrocytapheresis. Manual ET was primarily used before 2000; the procedure is relatively time-consuming and may be associated with hemodynamic disturbances, which limit its use and may be a principal cause of the disagreements regarding the benefits and risks of the technique. Automated erythrocytapheresis has significant advantages over manual ET in terms of speed, efficiency, hemodynamic stability, and retention of plasma components, and may represent an improvement in adjunctive therapy for severe malaria.[33] The other technical issue is the amount of blood that should be removed or exchanged. One author concluded that the volume of a patient's blood involved in ET should be 2,000 mL for an average parasitemia of 10%, 4,000 mL for parasitemia of >20%, and 2,000–4,000 mL for parasitemia of 10–20%.[34] Those results were confirmed and detailed in other studies.[31,32]

In summary, Canadian physicians need to remain alert to the possible diagnosis of malaria in patients who may have recently travelled to areas where malaria is endemic. In cases of severe malaria, ET, especially if automated, may be considered as an adjunctive treatment to standard anti-malarial treatment. If automated erythrocytapheresis is not available, manual ET maybe performed, but only in an intensive care unit setting with close monitoring of patient hemodynamics.

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