

Transfusion-transmitted malaria in Canada

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Abstract

THREE CASES OF TRANSFUSION-TRANSMITTED MALARIA in Canada are described. Although very rare, this diagnosis should be considered in transfusion recipients who have undiagnosed symptoms consistent with malaria. Thick and thin blood smears should be urgently examined to exclude this possibility.

Transfusion-transmitted malaria was first reported in 1911, and a review of cases worldwide from that year until 1979 showed an increase from about 6 cases to 145 per year.¹ The risk of acquiring malaria via the transfusion of blood components is extremely low in countries where malaria is not endemic, such as Canada and the United States. It has been estimated that there may be 1 case of malaria contracted through blood transfusion in the United States per 4 million donor units,¹ with a fairly steady incidence of 1–3 cases per year reported by the US Centers for Disease Control and Prevention.^{2–5} In countries where the disease is endemic, there may be more than 50 cases per million donor units.¹ From 1994 to 1999, the Bureau of Biologics and Radiopharmaceuticals, Health Canada, received reports from the Canadian Red Cross of 3 cases of malaria associated with the transfusion of blood components. These cases are briefly reported here (one of these cases has been previously reported⁶), and current blood donor safety measures that are intended to decrease the risk of malaria transmission are summarized.

Case histories

Case 1

In 1997, a 62-year-old woman in Ontario received 2 units of red blood cells and 1 unit of fresh frozen plasma. Three weeks later, she began to experience recurrent fevers. Approximately 5 weeks after the onset of symptoms, *Plasmodium falciparum* malaria was diagnosed by blood smear, and the patient was successfully treated. Malaria species diagnosis was subsequently confirmed by methods based on the polymerase chain reaction (PCR).^{7,8} The patient had no history of residence or travel outside the country. Two donors of red blood cells were investigated. One had no history of malaria infection or exposure and had repeatedly negative blood smears. Blood from this donor was also negative for *P. falciparum* malaria by PCR and by histidine-rich protein 2 antigen detection.^{7,8} The other donor was a 19-year-old woman from Ghana, who came to Canada in 1993 and was a first-time donor. This donor had answered negatively to all questions related to malaria on the donor questionnaire at the time of donation. According to the donor's father, she had not been ill with malaria since her arrival in Canada. However, she was not available for follow-up, and it was not possible to obtain further information or blood samples from this donor for malaria testing.

Case 2

In 1995, a 24-year-old woman in Ontario received 4 units of red blood cells. She became febrile 15 days after transfusion, and 3 days after the onset of fever *P. falciparum* malaria was diagnosed by blood smear. The malaria species identification was confirmed by PCR-based methods. This patient responded to antimalarial therapy.

Review

Synthèse

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One of the 4 investigated donors was a man originally from Mali, Africa, who had been treated for malaria in 1991 with chloroquine. He had been in Canada for 4 years prior to blood donation and was free of malaria symptoms during this period. However, PCR testing confirmed the presence of *P. falciparum* malaria in his blood. DNA was extracted from both donor and recipient blood samples, and the parasite isolates were subjected to DNA fingerprinting analysis.^{9,10} The analysis revealed a match between the isolates, confirming the donor as the source of the infection.

Case 3

As previously reported by Long and colleagues,⁶ a 63-year-old man was admitted to hospital with fever and convulsions in Quebec in 1994. He was diagnosed with *P. falciparum* malaria 3 weeks later by blood smear and was treated successfully. During 1 month in 1994, he had received 25 units of blood components (red cells, platelets and plasma), and an investigation of multiple donors was required. A donor from Cameroon with a history of malaria there 13 years earlier was discovered. As with the case 2 donor, this donor had been symptom free for more than 3 years. After an intensive search, a *P. falciparum* gametocyte and rare trophozoites were found in this donor's blood smears. The patient had received a platelet donation from this donor 16 days prior to his admission for fever.

Lookback investigations were carried out after the identification of the 2 donors with malaria in cases 2 and 3 and the donor implicated in case 1; no other malaria infections in recipients were discovered. According to the terminology of the World Health Organization,¹¹ cases 2 and 3 can clearly be classified as "induced malaria due to transfusion." The term "induced" refers to malaria transmitted by mechanical means such as transfusion of blood or blood products, organ transplantation, deliberate infection for malaria therapy, or contaminated needles or injection equipment. These routes should be considered in patients with malaria with no exposure to areas where the disease is endemic, as should the possibility of transmission by infective local or imported anopheline mosquitoes. Strictly speaking, case 1 would be classified as a "cryptic case" because confirmation of infection in the suspect donor was not possible and, thus, the source of transmission was not conclusively identified. All 3 of these donors' files have been coded to prevent further donations of components for transfusion. Plasma donations for further manufacturing can still be accepted from donors with a past history of malaria, because plasma is acellular. Any red cells infected with a parasite would be excluded during cryoprecipitation and fractionation, and merozoites would not survive in the absence of red cells and would probably be killed or eliminated by the manufacturing process (Hing Chong, Bureau of Biologics and Radiopharmaceuticals, Health Canada, Ottawa, Ont.: personal communication, 1998). No cases of malaria attributable to fractionated products have been reported.

Discussion

The 3 cases of transfusion-transmitted malaria described here are of public health importance for several reasons. First, all 3 were caused by *P. falciparum*, which may be associated with a potentially fatal outcome, particularly if there are delays in recognition and treatment.^{5,12,13} Cases 1 and 3 were diagnosed after approximately 6 and 3 weeks of symptoms respectively, whereas case 2 was diagnosed a few days after the onset of symptoms. In all cases, astute laboratory personnel made the diagnosis while examining blood smears ordered for reasons other than malaria. Fortunately, there were no fatalities among these cases. In the United States, transfusion-transmitted *P. falciparum* malaria has resulted in 2 recent fatalities and has also been the most common cause of transfusion-transmitted malaria, responsible for 37% of 91 cases reviewed.⁵ Cases of imported *P. falciparum* malaria are increasing in Canada as more Canadians travel to areas where malaria is endemic, and as drug-resistant *P. falciparum* malaria continues to evolve and spread.^{14,15}

Second, confirmed or suspected source donors met donor-screening criteria designed to prevent transfusion-transmitted malaria. The donors implicated in cases 2 and 3 were asymptomatic carriers of *P. falciparum* malaria. At the time of their donation, individuals with a history of malaria who had been symptom free for 3 years were allowed to donate blood. As a result of these 2 cases, the Bureau of Biologics and Radiopharmaceuticals, Health Canada, and the Canadian Red Cross changed the deferral criterion for past history of malaria. Beginning in July 1995, donors reporting a history of diagnosis or treatment of malaria at any time in the past were permanently deferred from donating components for direct transfusion. However, as illustrated by case 1, even with this added precautionary measure, complete prevention of transfusion-transmitted malaria may not be possible. In the absence of any practical donor-screening program for malaria, the management of the risk of malaria from blood transfusion is entirely based on the donor's answers to specific screening questions. Donors may give inaccurate information intentionally or unintentionally, or because they misunderstand the question posed, or because they are unaware or have forgotten that they previously have had malaria.

Third, it is unusual that *P. falciparum* persisted in the donors involved in these cases for over 3 years after they had left areas where malaria was endemic. In case 2, and probably in the other cases, there is a history of preceding inadequate therapy for malaria with chloroquine. Such noncurative therapy *potentially* may facilitate persistent infection, which increases the risk of transfusion-transmitted malaria in the population, particularly if infected individuals develop a semi-immune state (minimal symptoms but persistent parasitemia).

Finally, it is notable that transmission to the case 3 patient occurred through the transfusion of a platelet rather than a red-cell unit, and despite the apparently low level of parasitemia in the donor. This observation suggests that

even a small number of infected red cells are sufficient to transmit malaria.

We are aware of one previous report of possible transfusion-transmitted malaria in a Canadian.^{16,17} Although this patient had been transfused an extremely long time (12 years) prior to the onset of *P. falciparum* infection, making transfusion a very unlikely source, no other exposure could be identified. An alternative diagnosis of babesiosis could not be excluded.

Conclusion

The 1995 decision to defer blood donors with a past history of malaria has resulted in Canadian criteria that are more stringent than those in the United States, where the Food and Drug Administration and the American Association of Blood Banks do not require permanent deferral due to a history of malaria.¹⁸ The 1995 decision was made to reduce the risk of transfusion-transmitted malaria in Canada to an absolute minimum, recognizing that many new Canadians will be prevented from donating blood; a "history" of malaria is common in individuals from countries where malaria is endemic, because fevers are often labelled as malaria without appropriate laboratory confirmation by blood smear.

It is also worth noting that Canada routinely reports a per capita rate of imported malaria that is 5–10 times greater than that reported in the United States.¹⁴ If this higher rate is accurate, and not an artifact of better diagnosis and reporting in Canada, there may be a greater risk of malaria transmission through transfusion in Canada, which supports the more stringent Canadian donation criteria. In countries where a past history of malaria or exposure to areas where the disease is endemic is relatively common in donors, screening donations for malaria antibodies has been suggested as a way to reduce unnecessary deferrals.^{19,20} However, such tests currently suffer from a lack of both sensitivity and specificity, and none are currently licensed for use in Canada or the United States. Although potentially useful where the prevalence of malaria in donors is high, these tests would probably have a very poor positive predictive value in the Canadian setting and would lead to unnecessary rejection of donors with false-positive test results.

The present donor deferral system seems optimal at present, although a small risk of transfusion-transmitted malaria remains, as illustrated by case 1. Safety strategies should, therefore, be periodically re-examined in the light of large-scale population movements globally and the continued increase in travel by all Canadians. Transfusion-transmitted malaria should be considered in transfusion recipients who have undiagnosed symptoms consistent with malaria, such as fever or chills, and thick and thin blood smears should be urgently examined to exclude this possibility.

Competing interests: None declared.

Contributors: Dr. Slinger took part in the design, analysis and interpretation phases of the research and prepared and revised the manuscript. Dr. Giulivi investigated the first 2 cases and supervised manuscript preparation. Ms. Bodie-Collins investigated the most

recent case, summarized earlier cases and reviewed the manuscript. Dr. Hindieh investigated the cases and summarized the findings reported by blood services to the Bureau of Biologics and Radiopharmaceuticals, Health Canada. Dr. St. John wrote the initial Health Canada analysis of the 3 cases as a briefing note and helped revise the manuscript. Dr. Sher investigated the most recent case and helped revise the manuscript. Dr. Goldman investigated and prepared the report concerning the earliest case and helped revise the manuscript. Dr. Ricketts helped coordinate the initial Health Canada analysis and revised the manuscript. Dr. Kain performed specialized laboratory investigations for cases 2 and 3, provided expert guidance regarding malaria and made a substantial contribution to the writing of the manuscript.

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