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Transfusion-Transmitted Malaria — Missouri and Pennsylvania, 1996–1998

Malaria is a rare but potentially serious complication of blood transfusion. During 1958–1998, 103 cases of transfusion-transmitted malaria in the United States were reported to CDC. This report summarizes the investigation of three cases that occurred during 1996–1998 in Missouri and Pennsylvania and illustrates the key features of transfusion-transmitted malaria and the importance of donor screening.

Case 1, Missouri

A 70-year-old man with Waldenström's macroglobulinemia received 3 units of packed red blood cells (RBCs) on November 12, 1996. On November 27, he was hospitalized with fever; peripheral blood smears showed intraerythrocytic parasites suspected to be either *Plasmodia* or *Babesia*. Despite treatment with oral quinine and clindamycin, the patient developed respiratory and renal failure and died on November 30. He had not traveled outside the United States since the 1940s but had received 7 units of packed RBCs during 1996 (two in May, two in June, and the three received in November).

CDC confirmed *Plasmodium falciparum* parasites in the patient's blood smears (6% parasitemia). Stored serum samples from all donors were tested for antimalarial antibodies at CDC by the indirect fluorescent antibody (IFA) test. One of the donors, a U.S. Army reservist whose blood was collected by a civilian blood center, had elevated titers (1:16,384 to *P. falciparum*, 1:256 to both *P. malariae* and *P. ovale*, and 1:64 to *P. vivax*). Blood smears obtained from this donor in March 1997 demonstrated rare *P. falciparum* rings, and DNA of the same species was detected by polymerase chain reaction (PCR) of whole blood. The donor reported no fever at the time of blood donation. He had immigrated to the United States from west Africa in April 1996 (*1*). He was treated with quinine and doxycycline.

Transfusion-Transmitted Malaria — Continued

Case 2, Missouri

An 85-year-old man was hospitalized October 9–11, 1997, for gastrointestinal bleeding and received 5 units of packed RBCs. He was again hospitalized on November 1 with recurrent gastrointestinal bleeding and fever, and peripheral blood smears showed *P. falciparum* infection. Treatment was initiated with oral quinine and doxycycline but changed to intravenous quinidine and doxycycline when his mental status deteriorated the following day. A computerized tomography scan showed a cerebral vascular accident; the patient died on November 18. He had not traveled outside the United States since the 1940s.

Stored serum samples from all donors were tested. One donor, a recruit at a military training base whose blood was collected by a civilian blood center and who had immigrated to the United States from west Africa in 1995 (*1*), had positive malaria serology (titers were 1:16,384 to *P. falciparum*, 1:4096 to *P. malariae*, 1:1024 to *P. ovale*, and 1:64 to *P. vivax*). Blood smears obtained from this donor in November 1997 did not show malaria parasites, but *P. falciparum* DNA was detected by PCR of whole blood. He was treated with quinine and doxycycline.

Case 3, Pennsylvania

A 49-year-old man received 4 units of packed RBCs during surgery for hip replacement on January 15, 1998. He was again hospitalized on February 19 with fever, hypotension, and renal failure. Blood smears showed *P. falciparum* (12% parasitemia). He was treated successfully with intravenous quinidine and doxycycline and exchange blood transfusion. He had never traveled outside the United States.

Stored serum samples from all donors were tested, and one donor had elevated IFA titers (1:16,384 to *P. falciparum*, 1:16,384 to *P. malariae*, 1:1024 to *P. ovale*, and 1:256 to *P. vivax*). This donor was born in west Africa, had lived in Europe, then had returned to west Africa where he had lived for approximately 20 years before immigrating to the United States in 1996. PCR performed on a stored sample from the time of donation detected *P. falciparum* DNA.

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Editorial Note: Transfusion-transmitted malaria is rare in the United States, occurring at an estimated rate of 0.25 cases per million blood units collected (*2*). Because no approved tests are available in the United States to screen donated blood for malaria, prevention of transfusion-transmitted malaria requires careful questioning of prospective donors (*3*). Recommendations for deferral of such donors have been published by the Food and Drug Administration (FDA) (*3*); the American Association of Blood Banks (AABB) has published standards consistent with FDA recommendations (*4*). Correct application of these standards should have prevented these three cases.

Transfusion-Transmitted Malaria — Continued

Donors who are residents of nonmalarious countries are deferred for 1 year after return from travel to a malarious area. Donors who have had malaria are deferred for 3 years; immigrants, refugees, citizens, or residents of malarious areas are deferred for 3 years after leaving such areas. These criteria are supported by observations that 97% and 99% of reported malaria cases in U.S. and foreign civilians occur within 1 and 3 years, respectively, of having been in a malarious area (CDC, unpublished data, 1995).

Persons who emigrate from highly malarious areas and have acquired malarial immunity may have asymptomatic parasitemia that can persist for varying periods, depending on the species. *P. falciparum* rarely persists longer than 2 years, although it has persisted for up to 13 years (*5,6*). *P. malariae* can persist asymptomatically in the blood at low levels for up to 40 years. Therefore, rare cases of transfusion-transmitted malaria will continue to occur despite correct application of donor exclusion criteria. FDA, in consultation with CDC, is developing a new guidance document for blood collection centers, with revised recommendations for donor questioning about exposure to malaria and exclusion criteria for donor deferral.

In the three cases described in this report, the screening process at the time of donation, which is critical to reducing the risk for transfusion-transmitted malaria (particularly infections caused by species other than *P. malariae*), did not yield accurate information. A history of having been in a malarious area within the previous 3 years was elicited only during subsequent questioning. In cases 1 and 2, the screening questions about travel to malarious areas, previous malaria infection, or antimalarial drug use within the previous 3 years were not successful in preventing donation. The AABB has recommended uniform donor-history questions that, instead of relying on donors to determine whether they have been in a malarious area, inquire generally about travel outside the United States or Canada within the previous 3 years. Blood bank staff then determine whether travel was to a malarious area. In case 3, these questions were asked but failed to elicit accurate information, presumably because the donor misunderstood the travel-related questions.

Donors who have been implicated as the infection source in transfusion-transmitted malaria cases typically have very low levels of parasitemia that may be undetectable, even with microscopic examination of several thick blood films. Of 60 cases reported in the United States during 1963–1998 where a blood smear was obtained, only 18 (30%) of implicated donors had *Plasmodium* parasites detected on the blood smear. Detection of malaria antibodies provides evidence of an immune response to current or past infection, but these tests may remain positive for more than 10 years after parasitemia has resolved; therefore, malaria antibody detection to screen blood donations would result in the exclusion of otherwise healthy persons. PCR has increased sensitivity over blood film examination, positivity indicating current malaria infection (*7*), and species differentiation when microscopic examination may be inconclusive (*8*). The availability of testing for malaria by antibody detection or PCR is limited by lack of commercial reagents. In previous investigations of transfusion-transmitted malaria cases, antibody detection has been the method of choice to identify infected donors (*9*). However, since detection of antibodies does not necessarily indicate parasitemia, the use of PCR is a helpful tool for investigations.

These cases illustrate the importance of considering malaria in diagnosing a febrile illness following blood transfusion in any patient. Transfusion-transmitted malaria

Transfusion-Transmitted Malaria — Continued

usually occurs in patients with underlying diseases or who have undergone surgery (*10*) and can be life-threatening. Diagnosis may be delayed because fever may be attributed to the underlying illness, postoperative infection, or tissue reaction to surgical trauma (*10*).

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