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Transfusion-transmitted malaria

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Sir: An 81-year-old man with type 2 diabetes and coronary heart disease was admitted in August, 2002, for bleeding from a duodenal ulcer, which was successfully treated by sclerosis and a transfusion of four units of packed red cells from four different donors. Thirteen days later he was readmitted for acute fever of unknown origin, for which he received ceftriaxone. On the fourth treatment day, coma, anemia and thrombocytopenia developed and he was transferred to the ICU of another hospital. He had a coma without focal signs or neck stiffness and a fever of 38.5°C. Invasive mechanical ventilation was started and amoxicillin and acyclovir were given intravenously. A slight increase in protein (1.3 g/l) was noted in the cerebrospinal fluid. Cerebral computed tomography was normal. Blood tests showed normocytic anemia of 86 g/l without schistocytes, 16×10^9/l platelets, 168 µmol/l creatinine, 60 µmol/l unconjugated bilirubin, 0.01 g/l haptoglobin, 880 U/l lactate dehydrogenase and 5.7 mmol/l lactic acid. Blood and urine cultures were negative. A thin blood smear was strongly positive for *Plasmodium falciparum*, with 15% of parasitized erythrocytes. Quinine was given intravenously starting with a loading dose, but multi-organ failure developed with brain death and a fatal cardiac arrest.

This patient had not been in areas of *P. falciparum* endemicity for the last 20 years and did not live near an international airport. A definite diagnosis of transfusion-transmitted malaria was made when one of the four blood donors was found to be positive for *P. falciparum*: blood obtained 7 days after the death of the patient was positive by serology (1/600; positive above 1/40), thick film (3 trophozoites per 2 µl), and polymerase chain reaction (PCR). The frozen blood sample taken at donation by this donor was positive by serology and PCR. Further tests confirmed that the molecular *P. falciparum* patterns were identical by detecting the same mutation in the donor and recipient (mutation *Pf*CRT K76T, molecular marker of chloroquine resistance).

The donor was a 19-year-old African woman who had been living in France for 4 years. She convincingly denied having returned to sub-Saharan Africa during those 4 years and was asymptomatic. At the time of donation, in compliance with French blood donation guidelines, she had been considered a safe blood donor requiring no additional laboratory tests since she reported no clinical malaria episodes during her life and had been asymptomatic for more than 3 years spent continuously in France. One month after the diagnosis of *P. falciparum* malaria, she was still asymptomatic, with a positive blood PCR for *P. falciparum*, but a negative thick film. She was finally treated successfully with a course of proguanil-atovaquone in October, 2002, and she was strictly asymptomatic until the last visit in May, 2003, where PCR and thick film were negative.

In industrialized countries, the estimated incidence of transfusion-transmitted malaria is less than one case per million blood units collected, similar to that of hepatitis C virus or human immunodeficiency virus since the introduction of nucleic acid-testing techniques [1]. The diagnosis of transfusion-transmitted malaria is difficult and, when *P. falciparum* is the cause, is often delayed until severe malaria develops [2]. In a study from the United States, mortality was as high as 11% and was highest in older patients and in those with *P. falciparum* [3].

No laboratory tests for routine malaria screening of donated blood have been approved in industrialized countries, so that prevention rests on exclusion of potentially infected donors based on the donor interview. About one-third of cases of transfusion-transmitted malaria occur despite adherence to guidelines [3, 4]. Before this case, the French guidelines for blood donation recommended *Plasmodium* serology only for blood donors who have spent time in a malarious area in the past 3 years. As a result of this case, in order to reduce the risk of transfusion-transmitted malaria, the French health authorities decided in September, 2002, to implement systematic *Plasmodium* serology for every blood donor born in an endemic area, whatever the duration of stay in France. In addition, the infected donors have been coded to prevent further donations of components for transfusion.

The infected donor in our case had had asymptomatic *P. falciparum* infection for at least 4 years. A few well-documented similar cases have been reported, mainly in foreign-born residents, including four cases in the largest study of transfusion-transmitted malaria in United States, and three more cases in Canada [3, 5, 6].

Asymptomatic falciparum malaria is common in adults living in areas of high endemicity who, as a result of frequent infection, have become semi-immune to malaria and can experience long periods of asymptomatic parasitemia. Other factors associated with asymptomatic malarial infection include hemoglobinopathies (sickle cell trait, glucose-6-phosphate dehydrogenase deficiency) and other host-resistance factors presumably leading to inhibition of parasite growth (polymorphisms in the promoter region of TNF gene, mutation in the promoter region of nitric oxide synthase-2, mutation in ICAM-1 gene) [7]. On the other hand, the pathophysiology of prolonged asymptomatic *P. falciparum* infection in areas of non-endemicity remains to be clarified. The presumed hypotheses include persistent partial immunity, immunologic equilibrium between the host and a single genotype of *P. falciparum*, persistence of latent merozoites in the capillaries or in the lymphatic network, or unrecognized protective genetic polymorphisms [3, 5, 7].

In conclusion, the diagnosis of transfusion-transmitted malaria must be considered routinely in a patient with unexplained fever within a few weeks after a blood transfusion.

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