Fatal Transfusion Malaria

By Marion H. Brooks and Kevin G. Barry

In 1884 Gerhardt demonstrated that malaria could be transmitted to healthy subjects through administration of blood from individuals harboring the parasite. Although this mode of transmission has been used extensively in the treatment of central nervous system syphilis, accidental transmission of malaria by blood transfusion is uncommon. Since the original report of Woolsey in 1911, approximately 49 cases of accidentally induced malaria have been described in non-endemic areas. Plasmodium malariae (23 cases) and Plasmodium vivax (17 cases) have been the causative agents in the majority of instances whereas transmission of Plasmodium falciparum (6 cases) and Plasmodium ovale (1 case) by transfusion is rare. In two cases the species of plasmodium was not specified.

The purpose of this report is to emphasize the potential hazard of this complication by describing a patient who died as a result of Plasmodium falciparum infection contracted by transfusion of whole blood. To our knowledge only one other fatal case of transfusion malaria has been reported. This is the first instance in which falciparum malaria has been accidentally transmitted by blood obtained from a donor residing in a non-endemic area for more than two years.

Case Report

J. R., a 56-year-old male, received 4 units of whole blood during surgery for laryngeal carcinoma. Seventeen days after the last transfusion his temperature abruptly increased to 104 F. and remittent fever persisted for one week. On the fourth day of fever the patient had a grand mal seizure and became comatose. Neurologic examination revealed findings compatible with thrombosis of the right middle cerebral artery. Lumbar puncture disclosed an opening pressure of 7 cm. saline, protein 78 mg./100 ml., and cell count 34/mm³ (24 neutrophils and 10 lymphocytes). Cerebrospinal fluid culture was negative. A routine blood film obtained on the sixth day of fever revealed numerous trophozoites of Plasmodium falciparum. At this time hepatosplenomegaly was noted and the patient had become hypotensive (BP 90/50 mm. Hg) and moderately dehydrated.

Dexamethasone (3 mg. I.M. every six hours) was started immediately because of severe cerebral manifestations and the patient regained consciousness within 24 hours. Anti-malarial therapy was initiated with 900 mg. of chloroquine phosphate and 50 mg. of...
FATAL TRANSFUSION MALARIA

Fig. 1.—Hospital course during the last 10 days of life. Fever developed 17 days after the last transfusion (day 31) but the diagnosis of malaria was not established until 6 days later. Sustained diuresis was used to prevent renal failure. Although the hematocrit decreased 18 volumes per cent, no abnormalities of renal function developed.

pyrimethamine via nasogastric tube. Quinine hydrochloride, 600 mg. intravenously every eight hours, was started simultaneously. An additional 900 mg. of chloroquine and 75 mg. of pyrimethamine were given during the next two days. Despite vigorous anti-malarial therapy, parasitemia persisted until death.

Hypovolemia (BP 90/50 mm. Hg; C.V.P. 4 cm. saline) and dehydration also required immediate therapy. Plasma volume expansion with 50 Gm. of albumin and one liter of 5 per cent dextrose in 0.45 per cent saline promptly increased the blood pressure to 140/90 mm. Hg. In anticipation of massive hemolysis with its threat of renal failure, diuresis was initiated with 50 mg. of ethacrynic acid intravenously. An alkaline diuresis (urine pH 7.0-7.5) of 230 ml./hour was maintained by sustained hydration with 0.45 per cent saline containing 44 mEq of sodium bicarbonate per liter. Although the hematocrit decreased from 30 to 22 per cent in a six hour period and the concentration of free hemoglobin in plasma increased to 14.9 mg./100 ml. (normal less than 5 mg./100 ml.), no abnormalities of blood urea nitrogen or serum creatinine developed. Administration of 800 ml. of packed cells over a 24 hour period restored the hematocrit to normal without elevating the central venous pressure above 10 cm. of saline. Fluid intake and urine volume averaged 266 and 232 ml./hour respectively, during the remainder of the hospital course (Fig. 1).

Although there was no evidence of fluid retention, renal impairment or cardiac abnormalities, the patient developed pulmonary edema on the third day of therapy and expired. The most significant findings at autopsy were markedly congested, edematous lungs (1900 Gm.) and bilateral pleural effusions (300 ml.). Microscopically there was severe pulmonary edema, capillary congestion, thickened alveolar septa, focal hyaline mem-
brane formation and scattered areas of intra-alveolar hemorrhage. The heart weighed 310 Gm. and was unremarkable except for moderate arteriosclerosis of the left anterior descending coronary artery. The brain was edematous and congested. Parasitized erythrocytes were demonstrable in the cerebral capillaries but there were no foci of hemorrhage.

Investigation of Blood Donors

It is unlikely that the infection of this patient was naturally-acquired since he had always resided in Washington, D.C. area, had not travelled beyond the continental United States, and studies of his serum were negative for fluorescent antibodies against all species of plasmodia. Three of the donors gave no history of malaria or unexplained fever and their sera were likewise negative for anti-malarial antibodies. The fourth donor, a Nigerian student, gave no history compatible with malaria and a physical examination was normal. Although multiple thick and thin blood smears were negative, rare Plasmodium falciparum trophozoites were present in his peripheral blood 24 hours after a 500 ml. phlebotomy. The fluorescent antibody titer of this donor's serum was 1:64 against Plasmodium falciparum and 1:16 against Plasmodium vivax. This individual had resided in the United States continuously for 32 months before donating blood, had received no blood transfusions, did not use narcotics, and was fully qualified as a donor under the current recommendations of the American Association of Blood Banks.18

DISCUSSION

The rapidly lethal course of this patient emphasizes the potential hazard of transfusion malaria and the necessity for prompt diagnosis and therapy of falciparum infections. In the majority of cases, diagnosis of transfusion malaria has been delayed by failure of the physician to consider this uncommon complication. Since a variable incubation period is necessary, diagnostic accuracy could be improved by systematically excluding malaria in any patient with onset of unexplained febrility several days after transfusion.

To our knowledge only one other fatal case of transfusion-induced malaria has been reported.4 This low mortality rate probably reflects the infrequency of Plasmodium falciparum infections rather than a loss of virulence by the parasite as suggested by Nabarro and Edward.4 The role of host resistance in determining the outcome is more difficult to evaluate. Interestingly, the majority of patients have recovered despite underlying malignant disease or other severe illness.

Persistence of Plasmodium falciparum parasites in the donor for more than 32 months should be emphasized. Although clinical attacks of falciparum malaria seldom recur after 12–15 months,19,20 there is little information about the duration of asymptomatic parasitemia. Since the infective donor in the present report had not visited an endemic area for 32 months, had received no blood transfusions and was not a drug addict sharing a common syringe it is probable that his infection was of long duration and acquired before entering the United States. The mechanism of plasmodial persistence in this case is difficult to assess. Since Plasmodium falciparum has no recognized exo-erythrocytic cycle,21 it is probable that extremely low levels of parasitemia were constantly present and that clinical expression of the disease was prevented by the host's immune response.

In falciparum infections prompt institution of proper therapy is undoubtedly important in determining the outcome. As illustrated by this case, however, even vigorous therapy may fail to alter the progression of far-advanced in-
fections. Since parasitemia persisted in this patient despite three days of chloroquine therapy, it is possible but not proven that this strain of plasmodium was chloroquine resistant. The emergence of chloroquine-resistant strains of Plasmodium falciparum in many parts of the world should influence the selection of anti-malarial therapy for any patient with falciparum malaria. Since chloroquine resistance is usually established by therapeutic failure, we believe that a combination of anti-malarial drugs should be employed routinely unless the responsiveness of the particular strain in question is well established. This recommendation, based upon reported experience in the treatment of chloroquine-resistant malaria, may be especially important in future cases of transfusion malaria since thousands of potential blood donors are returning to the United States annually from Vietnam where chloroquine-resistant falciparum malaria is common.

The American Association of Blood Banks currently recommends that individuals with a history of more than one attack of malaria be permanently rejected as donors and that persons who have been in malarious areas be rejected as donors for two years after termination of exposure. This case illustrates that these measures will not entirely eliminate the risk of transfusion-induced falciparum malaria. This serious complication will remain until techniques are developed which can rapidly and accurately identify individuals with asymptomatic parasitemia.

**Summary**

This report of fatal falciparum malaria emphasizes an unusual but potentially hazardous complication of blood transfusion. To our knowledge this is the first instance of fatal Plasmodium falciparum infection transmitted by this means. The source of infection was an asymptomatic donor who had resided outside an endemic area for more than 30 months. This is the longest interval thus far recorded that falciparum malaria has remained latent before transmission by transfusion.

**Sommario in Interlingua**

Iste reporto de un caso mortal de malaria a Plasmodium falciparum trahe attention a un inusual sed potentialmente hasardose complication de transfusion de sanguine. In tanto que nos lo sape, isto es le prime reporto de un infection lethal con P. falciparum transmitite per transfusion. Le fonte del infection esseeva un donator asymptomatic qui haveva residite foras de territorio endemic durante plus que 30 menses. Isto es le intervallo le plus longe reportate usque nunc de latentia de malaria a P. falciparum ante su transmission per transfusion.

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