

CASE REPORT

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Malaria Deaths in the United States: Case Report and Review of Deaths, 1979–1998

ABSTRACT: Malaria is the world's most important parasitic disease, accounting for an estimated 300 to 500 million new cases and between 1.5 and 2.7 deaths annually. The majority of these deaths occur in sub-Saharan Africa where malaria is endemic and are the result of infection with *Plasmodium falciparum*. The number of deaths in the United States due to malaria is comparably much lower and involves so-called "imported" cases in which U.S. travelers acquire the infection upon travel to endemic areas and subsequently return to the United States or in which infected foreign citizens travel to the United States.

There were a total of 118 deaths due to malaria in the United States between 1979 and 1998 with an average of 5.9 deaths per year. Specific epidemiological data provided by the CDC regarding the 40 deaths that occurred between 1992 and 1998 yielded the following results. Deaths occurred in patients ranging from 9 months to 89 years of age (median, 53 years). Thirty-eight (95%) of these were due to *P. falciparum* and two (5%) due to *P. vivax*. Anti-malarial chemoprophylaxis was taken in 40% of cases, not taken in 45% of cases, and unknown in 15% of cases. Twenty-four (60%) of the cases involved U.S. travelers to endemic areas, of whom 59% traveled to Africa, 25% to South America, 8% to India, 4% to Haiti, and 4% to unspecified areas. The remaining cases included eleven foreign travelers to the U.S. (27.5%), three induced cases (7.5%), and two undetermined cases (5%). Thirty-nine (98%) of the cases were diagnosed antemortem and only one case was known to have come to the attention of the medical examiner/coroner.

An illustrative case report demonstrates many of the features associated with fatal malaria infections in the United States. The case involves a U.S. student who was studying in Africa and who, by report, had not taken antimalarial chemoprophylaxis. Despite seeking medical attention, the patient was not diagnosed with *P. falciparum* infection and cerebral malaria until the time of medico-legal autopsy, where the classic gross and microscopic features of cerebral malaria were identified.

This case represents one of the few cases of *P. falciparum* infection in the United States not diagnosed antemortem. Given the worldwide prevalence of the disease, increasing international travel, and rapidly developing drug resistance, malaria will continue to be an important disease and should be considered in cases of sudden, unexplained deaths. By reviewing the major epidemiological features of malaria-related deaths in the United States and by presenting the major gross and microscopic features of cerebral malaria, an attempt is made at raising the awareness of the forensic community to the potential of malaria-related deaths.

KEYWORDS: forensic sciences, malaria, *Plasmodium falciparum*, deaths

Malaria is the world's most important parasitic disease, accounting for an estimated 300 to 500 million new cases and between 1.5 and 2.7 million deaths annually (1,2). Most deaths occur in sub-Saharan Africa and are the result of *Plasmodium falciparum* infection (2). In the United States, however, the number of deaths due to malaria is comparably much lower. These represent so-called "imported" cases in which U.S. travelers acquire the infection upon travel to endemic areas and subsequently return to the United States or in which infected foreign citizens travel to the United States. In the vast majority of these cases, the malarial infection is diagnosed and well documented in the clinical, antemortem setting, and therefore most such deaths do not come to the attention of the medical examiner/coroner. In an effort to raise awareness to the potential of malarial infection in the forensic setting, we review the deaths due to malaria in the United States between 1979 and 1998 and report a case of *P. falciparum* infection diagnosed only at the time of medico-legal autopsy in rural New England.

Case Report

The Office of the Chief Medical Examiner was notified on November 11, 2000 regarding the death of a 24-year-old woman at a local college. The deceased had spent the previous semester studying in Africa (Ghana) and returned to the United States approximately 18 days prior to her death. On approximately November 7, 2000 she became ill with flu-like symptoms that included a dry cough, nausea, vomiting, and diarrhea. In addition, she was found to have a urinary tract infection for which she was started on oral Amoxicillin. On November 11, 2000 she was found unresponsive in her dormitory bed, after having last been seen alive in the evening of November 10, 2000. Scene examination revealed the decedent in bed on her right side under average bedding, with water, juice, and the prescribed Amoxicillin bottled next to the bed. By report, the decedent had not taken anti-malarial chemoprophylaxis.

Autopsy Findings

The major gross finding was that of a diffusely dusky, gray-red discolored brain that weighed 1480 g (Fig. 1). Microscopic exami-

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nation of the brain revealed extensive engorgement of capillaries and venules with red blood cells. Many of the red blood cells were arranged in a rosette-like fashion at the endothelial surface, and many contained parasitic forms and/or birefringent pigment granules (Fig. 2). Although less prominent, similar histologic features were seen in the capillaries and venules of the major visceral organs (Fig. 3). Blood smear examination revealed extensive parasitemia with many atypical ring forms resembling *P. falciparum*

(Fig. 4). Immunoassay directed against parasite lactate dehydrogenase (Optimal[®]) was positive and indicative of *P. falciparum*.

Results

Our review of deaths in the United States due to malaria that were reported to the Centers for Disease Control (CDC) between 1979 and 1998 revealed a total of 118 deaths and an annual aver-

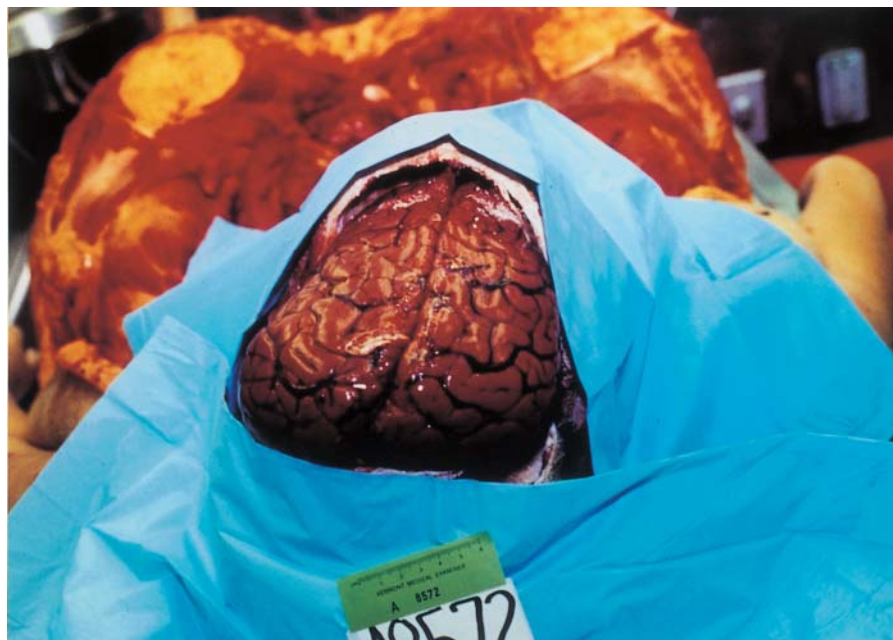


FIG. 1—Dusky gray-red discoloration of brain in cerebral *Plasmodium falciparum* infection.

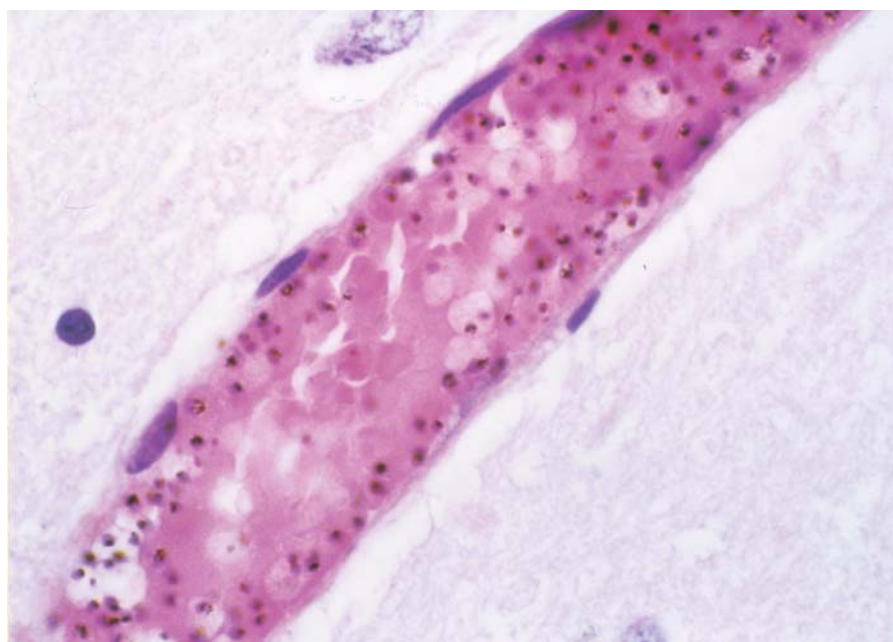


FIG. 2—Engorged cerebral blood vessels with red blood cells containing parasitic forms of *Plasmodium falciparum* (H&E, 1000X).

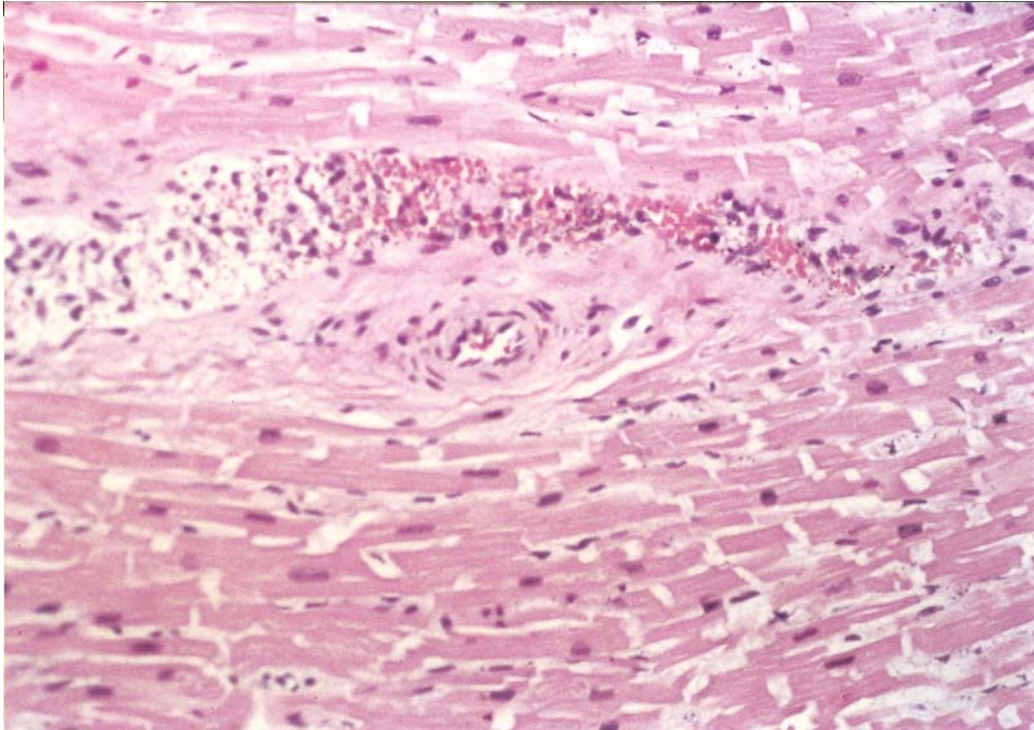


FIG. 3—Cardiac blood vessels showing engorgement with infected red blood cells (H&E, 400X).

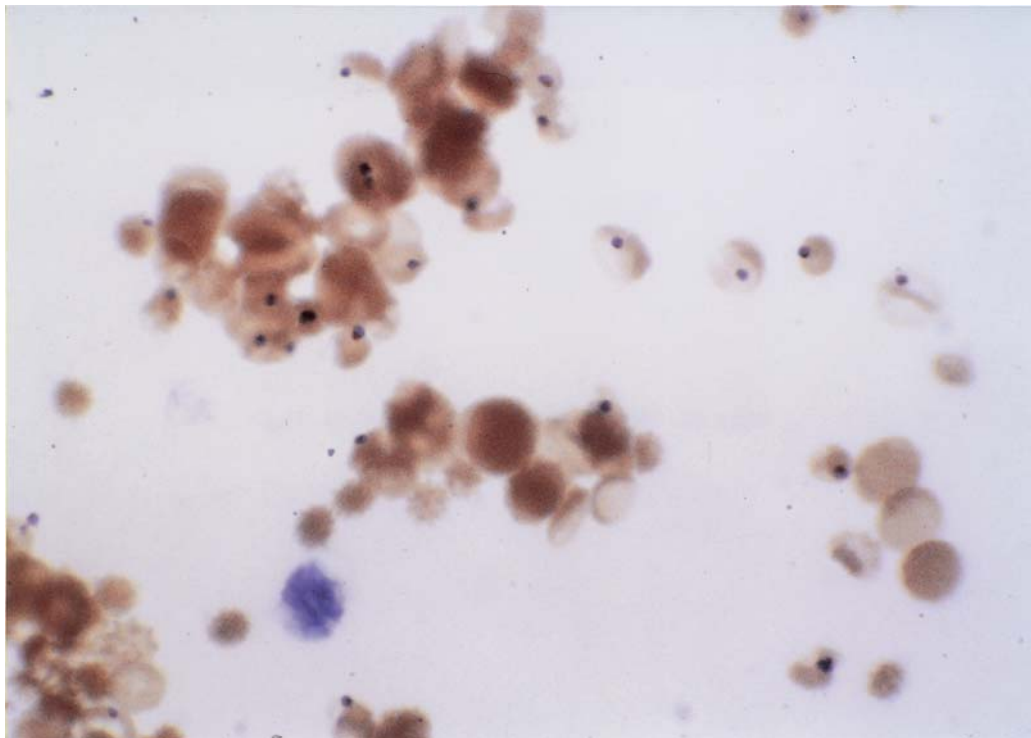


FIG. 4—Postmortem peripheral blood smear showing atypical ring forms of *Plasmodium falciparum* in red blood cells (Giemsa, 1000X).

age of 5.9 (3.4). Specific information regarding the deaths between 1992 and 1998 obtained from the CDC (personal and electronic communication with E. Smith, M.D. and S. Kachur, M.D.) (5) reveals that a total of 40 malaria-associated deaths occurred in patients ranging from 9 months to 89 years of age (median, 53 years). Of these, 38 (95%) were due to *P. falciparum*. The remaining deaths were both cardiac in etiology in individuals who had concurrent *P. vivax* infection and, although contributory, the malaria infection was not felt to have directly caused their deaths. Thirty-nine of the cases (98%) were diagnosed antemortem (Table 1). Two additional cases involved individuals who died in the hospital after blood smears were made but before the diagnosis was discovered or the treatment initiated. In both cases, blood smears obtained in the emergency room revealed *P. falciparum*; however, it is unclear as to whether either of these cases fell under medial examiner/coroner jurisdiction. Anti-malarial chemoprophylaxis was used in 40% of the cases and not used in 45% of the cases. The chemoprophylaxis status of the remaining six cases (15%) is not known. Twenty-four cases (60%) involved U.S. travelers to endemic regions. The remaining cases included eleven foreign travelers to the U.S. (27.5%), three induced cases (7.5%), and two undetermined cases (5%). Of the 24 U.S. travelers to endemic areas, 59% traveled to Africa, 25% to South America, 8% to India, 4% to Haiti, and 4% to unspecified areas.

Discussion

Deaths in the United States due to malaria are relatively rare. Those that come to the attention of the medical examiner/coroner are even more so. The present case illustrates many of the features associated with fatal malaria infections in the United States. First, as malaria is nonendemic in the United States, all U.S. cases are considered imported and the majority involve travel to endemic areas. In an earlier publication, Greenberg and Lobel reviewed all fatal cases of *P. falciparum* malaria in the United States between 1959 and 1987 (6). They found that, of the 68 deaths from imported *P. falciparum* during that time period, 61 (90%) were in travelers. They do not specify whether this percentage involves only U.S. travelers to endemic areas or includes foreign travelers to the United States. If the latter were the case, the percentage would be quite comparable to the 87.5% found in our review. Additionally, our review showed that most travel-related deaths due to malaria involve travel to Africa (59%) or South America (25%), which is similar to the 84% Greenberg and Lobel identified from these regions combined.

Next, *P. falciparum* is the malaria species most associated with mortality. Our review showed that 95% of malaria deaths resulted from *P. falciparum* infection. The morbidity of *P. falciparum* is owed to its unique ability to invade red blood cells. This ability to invade and the subsequent red blood cell cytoadherence to endothelial cells is the basis for the microvascular pathology seen in cerebral *P. falciparum* malaria (7). The present case demonstrates many of the typical gross and microscopic findings related to the pathophysiology of *P. falciparum* infection. In a recent report on the postmortem diagnosis of cerebral malaria, Peoc'h reviewed many such findings (8). These include the dusky gray-red discoloration of the gross brain resulting from a combination of vascular congestion and intraerythrocytic malaria pigment (hemozoin), the microscopic, birefringent hemozoin pigment resulting from the parasitic degradation of hemoglobin, and, finally, the extensive parasitized erythrocyte sequestration in the cerebral microvasculature. The petechial hemorrhages, ring hemorrhages, and Durks' granulomata described by Peoc'h and others (9) were not seen in our case.

Chemoprophylaxis is another important factor in deaths due to malaria. Our review showed that chemoprophylaxis was taken in 45% of fatal cases and was not taken in 40% of cases. These findings are substantially different from the lack of prophylaxis of 77% reported previously by Greenberg and Lobel. Although our review shows that not taking chemoprophylaxis is associated with more deaths, the relative increase in deaths in which prophylaxis was used likely reflects an increasing *P. falciparum* drug resistance. With the extensive use of chloroquine as a primary chemoprophylactic agent, chloroquine-resistant *P. falciparum* has been recognized in nearly all parts of the world (2) and extensively throughout the African continent (Fig. 5). Coupled with increasing international travel, both current and emerging drug resistance will continue to be an important factor in the mortality associated with *P. falciparum*. This ongoing concern is illustrated in a recent report by the CDC describing two malaria deaths in the U.S. in January-March of 2001. The deaths involved U.S. travelers to known chloroquine-resistant areas of Africa, both of whom had taken inappropriate chemoprophylaxis (10).

One important difference between the present case and most other malaria-associated deaths we reviewed is that the current case represents one of the few cases that was not diagnosed antemortem. In our review of deaths due to malaria between 1992 and 1998 only one other case was not diagnosed prior to death. That case involved a 24-year-old U.S. citizen who was volunteering in the jungles of Guyana. Although specific details as to this illness, hospital ther-

TABLE 1—Malaria deaths in the United States, 1992–1998.

Year	Number of Deaths	Number Diagnosed Premortem, (%)	Organism		Chemoprophylaxis		
			<i>P. falciparum</i>	<i>P. vivax</i>	Yes	No	Unknown
1992	7	7 (100)	7	...	4	2	1
1993	8	7 (87.5)	7	1 *	3	5	...
1994	4	4 (100)	3	1 *	...	4	...
1995	6	6 (100)	6	...	1	3	2
1996	5	5 (100) †	5	3	2
1997	6	6 (100)	6	...	4	1	1
1998	4	4 (100) †	4	...	4

* Both deaths associated with *P. vivax* were cardiac related with concurrent malaria infection.

† One case in 1996 and one case in 1998 involved individuals who died in the hospital after blood smears were made, but before diagnosis was made or treatment initiated.

