Babesiosis in Patients with AIDS: A Chronic Infection Presenting as Fever of Unknown Origin

Matthew E. Falagas and Mark S. Klempner

Babesiosis is a malaria-like, tick-transmitted zoonosis caused by protozoa of the family Piroplasmorida, which includes Babesia and Theileria species. In the United States, the infection is endemic in the Northeast and upper Midwest, although cases have recently been described in California and Washington State. We report a case of babesiosis in a patient infected with HIV who presented with a prolonged fever of unknown origin; the patient had not undergone splenectomy. Parasitemia persisted despite initial clinical improvement after treatment with quinine and clindamycin. Babesiosis was controlled with a maintenance regimen consisting of clindamycin, doxycycline, and high-dose azithromycin, but the infection was not eradicated. Babesiosis should be considered in the differential diagnosis of HIV-infected patients with fevers and/or anemia in areas where the infection is endemic. HIV-infected patients who are severely immunosuppressed, even those without a history of splenectomy, may present with severe manifestations of babesiosis and develop a chronic infection, which may require therapy to prevent relapse of disease.

Case Report

A 42-year-old homosexual male was found to be infected with HIV in 1986 and began receiving treatment with antiretroviral agents. He was well until July 1993, when he presented to the hospital with a 2-week history of fever. Tests of liver function revealed mildly elevated values of transaminases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and a laboratory test revealed a CD4 cell count of 27/mm³; however, the cause of the fever was uncertain. Empirical treatment with clarithromycin was given for possible Mycobacterium avium-Mycobacterium intracellulare infection.

The patient did well until November 1993, when he complained of worsened fevers, night sweats, dyspnea on exertion, dry cough, and weight loss despite a normal appetite. The results of blood cultures (including special media for mycobacteria) and cultures of bronchoalveolar lavage fluid were negative, as were stains. The patient’s symptoms worsened in February 1994; he had fever (temperature to 40.5°C), daily drenching night sweats, and further weight loss. The patient frequently visited Nantucket Island in Massachusetts. He did not recall any tick bites. His overseas travel consisted of a short trip to St. John in the U.S. Virgin Islands in early February 1994. He did not have a history of blood product transfusion.

Physical examination revealed a temperature of 39°C, splenomegaly, and hepatomegaly without lymphadenopathy. Laboratory investigations revealed pancytopenia (hematocrit, 22%; WBC count, 1,900/mm³; platelet count, 90,000/mm³) and elevated results of liver function tests (AST, 132 U/L; ALT, 42 U/L). Examination of bone marrow specimens obtained by aspiration and biopsy did not reveal any abnormalities. Examination of peripheral blood smears revealed intraerythrocytic parasites with occasional intraerythrocytic tetrads (figure 1). Reexamination of blood smears from blood specimens that had been taken after December 1993 verified the presence of rare intraerythrocytic parasites. Serology for Lyme disease and western blot were negative. On the basis of epidemiologic and clinical findings and the morphological characteristics of the intraerythrocytic parasites, the diagnosis of babesiosis was made.

The patient’s clinical course, parasitemia level, hemoglobin level, and the regimen used for treating the acute episodes of babesiosis as well as for suppressing the infection are shown in figure 2. In brief, quinine and clindamycin were successfully used to treat all of the patient’s symptoms, to eliminate the pancytopenia, and to normalize the levels of AST and ALT.
The patient was educated about the areas in which he was at risk of reexposure and was told how to protect himself against possible reinfection with treatment. While he was receiving treatment for the second episode of symptomatic babesiosis, the patient had an allergic reaction manifested by severe rash that was temporally related to quinine; therapy with quinine was therefore discontinued, and treatment with oral doxycycline (200 mg/d), high doses of azithromycin (2,000 mg/d), and clindamycin (1,800 mg/d) was initiated. The patient’s symptoms were well controlled while he was receiving this regimen.

Subsequently, the infection was controlled for 9 months by continuous treatment with clindamycin, doxycycline, and azithromycin, with a gradual decrease in the dosages of these drugs (figure 2). While the patient was receiving therapy with clindamycin (600 mg/d), doxycycline (100 mg/d), and azithromycin (500 mg/d), he noted the recurrence of low-grade fevers; laboratory tests revealed that these fevers were accompanied by a mild decrease in the hemoglobin level, a mild elevation in the levels of ALT and AST, and a mild increase in the level of parasitemia. The patient’s symptoms in the third symptomatic episode of babesiosis were controlled by increasing the doses of these three drugs.

**Review and Discussion**

Babesiosis is an emerging vector-borne infection that is endemic in the United States in the Northeast and upper Midwest, where most reported cases are nonfatal infections caused by *Babesia microti* in patients who have not undergone splenectomy. In contrast, most reported cases of babesiosis in Europe are fatal infections in splenectomized patients and are caused by *Babesia divergens* [1–3]. A recently identified *Babesia*-like organism that is phylogenetically closer to *Babesia gibsoni* (a canine pathogen) and *Theileria* species than to *B. microti* or *B. divergens* was the cause of a febrile illness in four splenectomized patients from northern California [4]. Except in rare cases of transfusion-associated infection [7, 8], babesiosis is a zoonotic infection and requires transmission from an animal reservoir to humans via a tick vector. In the Northeastern region of the United States and the Midwest, rodents (usually the white-footed mouse) are the reservoir of *B. microti*. Babesiosis is transmitted to humans via *Ixodes scapularis*, the deer tick that also transmits Lyme disease. This explains the high frequency of positive serological tests for Lyme disease in patients with *B. microti* infections [9].

Although seroprevalence studies of babesiosis have shown that the seropositivity rate is high in areas of endemicity, prospective surveillance studies have not been done to determine the incidence of acute symptomatic babesiosis in these areas [10]. Patients with symptomatic babesiosis usually complain of nonspecific symptoms; fever, chills, fatigue, headache, and myalgias are frequently reported, while arthralgias, abdominal pain, nausea, and vomiting are infrequently reported. Fever may be sustained or intermittent. Some patients complain of sore throat, photophobia, pigmenturia, or emotional lability. Patients rarely have a persistent dry cough that prompts evalu-
tion for a pulmonary infection. Most patients do not recall a tick bite. Physical examination of patients with babesiosis sometimes reveals splenomegaly and/or hepatomegaly. Patients with babesiosis may have hemolytic anemia, mild neutropenia, and/or mild elevations in the levels of lactate dehydrogenase, AST, ALT, and bilirubin. The diagnosis of babesiosis is usually made by microscopic examination of a stained blood specimen (Giemsa stain or Wright’s stain), which reveals intraerythrocytic parasites. Babesiosis may be differentiated from malaria by noting where the patient lives and works and where he or she has traveled as well as by noting the subtle morphological characteristics of the RBCs and the intraerythrocyte parasites. In our case there were rare intraerythrocytic tetrads of Babesia organisms (“Maltese cross”), a finding that is specific for babesiosis. In cases of diagnostic uncertainty, serological tests (available through the Centers for Disease Control and Prevention) should be performed or infected blood should be injected into hamsters [11]. Detection of Babesia species with use of a PCR-based test has been reported [12-14].

The pathogenesis and natural history of babesiosis are not well understood. The spleen appears to play an important role in the host defense since infection is more common and severe in splenectomized patients [15, 16]. Cellular immunity may play a critical role in this infection. Nude mice or mice treated with serum with antibodies to T lymphocytes develop higher levels of parasitemia [17]. The interactions between Babesia or Theileria organisms and the immune system are interesting. An increase in T suppressor/cytotoxic lymphocytes is noted in patients with babesiosis [18]. Theileria species cause pharmacologically reversible lymphoproliferation in cattle [19]. A chronic carrier state has been described in animals infected with Babesia or Theileria species [20]. It is likely that chronic subclinical infection is common in humans with babesiosis. In a recent study, persistence of Babesia-specific DNA was found in blood samples from patients with unrecognized babesiosis [21]. An exoerythrocytic stage, relatively protected from immune surveillance, may be associated with persistent infection as with infection due to some species of Plasmodium.

These observations and experimental studies may explain the persistence and severity of babesiosis in patients infected with HIV. Chronic babesiosis is likely in this setting, making long-term treatment with agents to prevent relapse of disease necessary. There are three reported cases of babesiosis in HIV-infected patients. Two of these cases occurred in splenectomized hosts and required RBC exchange and chemotherapy (quinine and clindamycin) for control of symptomatic babesiosis [22, 23]. In one of these cases, continuous treatment with quinine and doxycycline led to suppression of babesiosis during 8 months of follow-up. In the second case, no recurrence of babesiosis was noted during 1 year of follow-up after the patient had received 6 months of maintenance therapy with quinine, clindamycin, and doxycycline. In the third case, the patient had an intact spleen. This patient had two episodes of acute babesiosis (8 months apart) that were treated with quinine and clindamycin. He had no evidence of recurrence of babesiosis while he was receiving these agents (the follow-up period was not reported) [24].

The combination of clindamycin (600 mg) and quinine (650 mg), both given orally every 8 hours for 7 days, is the treatment of choice for patients with acute babesiosis [1, 2]. Patients with babesiosis have occasionally been treated with doxycycline or pentamidine with or without trimethoprim-sulfamethoxazole [2, 24, 25]. In chemotherapeutic trials in hamsters, chloroquine, metronidazole, primaquine, tetracycline (50 mg/kg·d), and sulfadiazine in combination with pyrimethamine had no effect on the course of parasitemia, while pentamidine, dimenazene aceturate, and high doses (500 mg/kg·d) of minocycline and tetracycline had antiparasitic activity [26]. Recent preliminary data from hamster studies have shown that high doses of atovaquone offer some promise in the treatment of babesiosis [27].

It is not known whether more prolonged treatment is beneficial in HIV-infected patients. However, it seems prudent to start continuous therapy for preventing relapse of babesiosis immediately after the end of treatment for the acute episode. The optimal agents and dosage for this purpose are not known. In our case, a severe allergic reaction to quinine prohibited the use of this agent as a long-term treatment for preventing relapse of babesiosis. However, prolonged suppression of the infection was accomplished with the combination of clindamycin, doxycycline, and azithromycin. In experimental babesiosis, use of high doses of azithromycin has led to suppression of parasitemia [28]. It is possible that clarithromycin, another macrolide antibiotic given to our patient for possible M. avium-M. intracellulare infection, suppressed babesiosis for several months.

The probability of completely and permanently clearing Babesia organisms after subclinical, self-limited, or successfully treated infection is unknown both in immunocompetent and immunocompromised hosts. Thus, whether and when to stop treatment to prevent relapse of disease in cases of undetectable parasitemia are unknown. It is reasonable to gradually decrease the doses of agents to prevent relapse of disease as long as patients are closely observed and the level of parasitemia is frequently determined, although we do not think that permanent clearance of Babesia parasites is likely in HIV-infected patients with severe immunosuppression. Educating patients to recognize symptoms consistent with recurrent babesiosis at an early stage in the course of their disease and performing surveillance for parasitemia and anemia are important.

Conclusion

Babesiosis should be considered in the differential diagnosis of HIV-infected patients with fevers and/or anemia in areas in the United States where the infection is endemic, such as the Northeast and upper Midwest. The infection may present with severe manifestations in HIV-infected patients and may lead to chronic infection that requires therapy to prevent relapse of
disease in HIV-infected patients who are severely immunosuppressed, even those who do not have a history of splenectomy. Besides quinine and clindamycin, doxycycline and azithromycin may be useful agents in the treatment of acute babesiosis as well as in the long-term suppression of the infection. The increasing number of HIV-infected patients in the United States combined with ecological changes that lead to expansion of areas where babesiosis is endemic and the recent recognition of Babesia-like pathogens in the western United States are expected to gradually increase the incidence and prevalence of babesiosis in HIV-infected patients. Clinicians need to have increased awareness of babesiosis, and further studies are needed to clarify the optimal management of this infection in HIV-infected patients.

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References