CLINICAL PROBLEM-SOLVING

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A Chilly Fever

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In this Journal *feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.*

A 30-year-old graduate student presented to the emergency department in March reporting fevers associated with shaking chills and severe headaches. He had been well until 1 week before presentation, when he began to have daily fevers, with temperatures as high as 103.0°F (39.4°C) and with associated chills, nausea, and headaches. The fevers were most notable in the evening; by morning, the patient was afebrile and felt well enough to attend class. He had been taking acetaminophen, without symptom relief.

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Fevers associated with many conditions are worse in the evening owing to the circadian rhythm of body temperature; consequently, this pattern need not imply a true "periodic fever." Although fever with acute onset in an otherwise healthy young adult is usually viral in origin, the presence of shaking chills suggests the possibility of bacteremia; potential sources include pyelonephritis, infection of the biliary tree, and pneumonia. Other considerations include endocarditis, salmonella infection, typhoid fever, and tularemia. The patient should be asked about any use of injection drugs and about recent travel, contact with animals, and ingestion of untreated water or unpasteurized milk or milk products. Although the shaking chills suggest bacteremia, viral illness (e.g., acute infection with the human immunodeficiency virus [HIV]) and noninfectious causes of fever (e.g., cancer or rheumatologic disease) must also be considered. A sexual history should be taken to identify behaviors associated with an increased risk of HIV infection, with information obtained regarding the number of sex partners and a history of sex in exchange for money or illicit drugs or of sex with men.

The patient reported no neck stiffness, arthralgias, morning stiffness, gastrointestinal illness, or weight loss but noted sweats with his fevers. There had been no alterations in mental status. His medical history was notable only for knee arthroscopies; he had no internal fixation device. The only medication he was taking was acetaminophen. He had not received the influenza vaccine and had a history of rash on treatment with cephalosporins. The patient lived in the Boston area with his wife, who was his only sexual partner, and there was no history of a sexually transmitted disease. He did not smoke or use illicit drugs, and he drank one to two alcoholic beverages on social occasions. He had spent several days in Cape Cod, Massachusetts, 3 weeks before presentation. His only overseas travel was a trip to Uganda 2 years earlier. He had received appropriate vaccinations before that trip and reported excellent adherence to malaria prophylaxis.

Given the recent trip to Cape Cod, tickborne illnesses with an incubation period of 1 to 6 weeks must be considered. In the Cape Cod area, the predominant tickborne

illnesses are Lyme disease, anaplasmosis, and babesiosis, all of which can cause a nonspecific flu-like illness with fever, malaise, myalgias, and headache. Although the peak incidence typically occurs from May through August, infections can occur at any time of year. Lyme disease is characteristically manifested as erythema migrans, a macular, erythematous rash with central clearing (known as a bull's-eye rash). In early localized Lyme disease, the rash develops at the site of the bite within a few weeks after the bite; multiples of such lesions, which can be seen in early disseminated Lyme disease, may develop weeks to months after infection. Although many patients do not notice the rash, patients for whom there is a suspicion of Lyme disease should nevertheless be questioned about any recent rash. Clinicians should also inquire about activities associated with tick exposure, such as walking in grassy fields, wooded areas, or brush.

This patient's travel to Uganda merits consideration for infections that can be acquired in East Africa and are manifested long after acquisition. These diseases include malaria, tuberculosis, filariasis (although this infection is unlikely after short-term travel), visceral leishmaniasis, and Q fever. Malaria relapses are more likely to begin with rigors than are primary infections. The physical examination should focus on the liver and spleen (since hepatosplenomegaly can develop in association with malaria, visceral leishmaniasis, or Q fever), the lungs (particularly the upper lobe, which is often involved in tuberculosis), the heart (since pericardial rubs or murmurs can be detected in association with Q fever), and the extremities and the scrotum (since lymphangitis and lymphedema can develop in association with filarial fevers).

At presentation, the patient's temperature was 98.0°F (36.7°C), his heart rate 90 beats per minute, blood pressure 121/57 mm Hg, and oxygen saturation 97% while he was breathing ambient air. He appeared fatigued but was not in acute distress. There was no scleral icterus or conjunctival pallor. His oropharynx was clear and without erythema or exudates. The neck was supple. The jugular venous pressure was 5 cm of water. The heart rate was regular, with no murmurs, gallops, or rubs, and the lungs were clear to auscultation. The abdomen was soft and nontender, with normal bowel sounds. There was no hepatomegaly. A nontender spleen tip was palpable at the left costal border. There was no peripheral edema and no cervical, axillary, or inguinal lymphadenopathy. The distal pulses were 2+ bilaterally. Scattered petechiae were present on the anterior shins and both feet. The neurologic examination was within normal limits.

The examination is notable for splenomegaly and petechiae, findings that should be considered in the context of the patient's reported fever. Petechiae may occur with a variety of viral infections and with sepsis from meningococcal or pneumococcal infections. Noninfectious causes of fever and petechial rash include thrombotic thrombocytopenic purpura, a condition in which fever and petechial rash are accompanied by renal failure, neurologic symptoms, and hemolytic anemia. In the presence of splenomegaly, however, the petechiae may represent the hemostatic consequences of splenic sequestration of platelets. The differential diagnosis of splenomegaly and fever includes hematologic cancers, collagen vascular diseases, and multiple infectious causes, with infectious mononucleosis being the most likely cause of infection in a young adult. Although cervical lymphadenopathy, which is commonly associated with mononucleosis, is not present, mononucleosis remains a possibility; a finding of atypical lymphocytosis on a complete blood count would support this diagnosis. Other infectious causes of fever and splenomegaly include viral hepatitis, babesiosis, cytomegalovirus infection, bacterial endocarditis, and malaria.

The basic metabolic panel and liver-function tests were normal. The white-cell count was 5400 per cubic millimeter, with 80% neutrophils, 7% lymphocytes, and 5% monocytes. The hemoglobin level was 11.9 g per deciliter, the hematocrit 35.1%, and the platelet count 50,000 per cubic millimeter. Mean corpuscular volume was 84.4 fl. The prothrombin time was 16.3 seconds (normal range, 12.2 to 14.6), partial thromboplastin time 34.7 seconds (normal range, 23.8 to 36.6), and the international normalized ratio 1.3 (normal range, 0.9 to 1.1). The urinalysis was normal. The lactate dehydrogenase level was elevated at 283 U per liter (normal range, 135 to 225). Rapid screening of a nasal swab for influenza viruses was negative.

The normal white-cell count makes severe bacterial infection unlikely. Mild anemia and moderate

thrombocytopenia may occur with a variety of viral and parasitic infections. The slight elevation in the lactate dehydrogenase level is a nonspecific marker that can be seen in a variety of conditions, including hemolytic anemia, cancer, and infectious mononucleosis. Among the tickborne illnesses, babesiosis and anaplasmosis remain considerations. Babesiosis can cause hemolytic anemia, thrombocytopenia, and splenomegaly, but it is also often reflected in abnormalities on liver-function tests. Anaplasmosis causes leukopenia and anemia, thrombocytopenia, and liver-function abnormalities. Malaria can cause anemia, thrombocytopenia, and splenomegaly. It would be helpful to obtain a peripheral-blood smear, which might reveal intraerythrocytic parasites (such as those present in babesiosis and malaria), intracytoplasmic inclusions (morulae are seen in 20 to 80% of neutrophils in patients with anaplasmosis), or abnormal myelocyte or lymphocyte lineages (suggesting hematologic cancer).

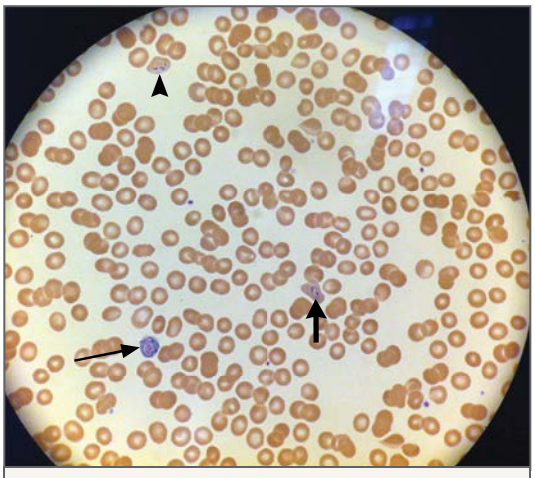

Figure 1. Thin Smear of Peripheral Blood.
The smear shows an enlarged red cell with Schüffner's dots (intracytoplasmic granulation) and an intraerythrocytic ring form (short arrow), an ameboid trophozoite in an enlarged red cell (long arrow), and a gametocyte with pigment (arrowhead).

A peripheral-blood smear revealed intraerythrocytic parasites.

Intraerythrocytic parasites are seen in both malaria and babesiosis. Although *Babesia microti* is endemic in Cape Cod, infection in late winter or early spring is unusual. The patient's travel history places him at risk for exposure to malaria, and his clinical presentation could be explained by a malaria relapse. The peripheral-blood smear should be examined carefully to distinguish between these infective agents.

Plasmodia metabolize heme to form an intracellular crystallized pigment, hemozoin. Although hemozoin is not invariably identified in cases of malaria, its presence reliably distinguishes malaria infection from babesia infection. Malaria parasites can be distinguished from *B. microti* by the presence of recognizable gametocytes (characteristically banana-shaped in *Plasmodium falciparum* and round, with a granular appearance, in nonfalciparum species). The gametocytes are precursors of the sexual forms of the malaria parasite. In addition, intracellular vacuoles and extracellular merozoites are unusual in malaria but common in babesiosis, and the classic "Maltese cross" (a tetrad of parasites budding at right angles) is unique to babesia species.

When malaria is diagnosed, the species should be identified. Given the patient's delayed presentation, years after presumed exposure, *P. falciparum* can be ruled out, since it does not give rise to relapses. The morphologic features of the parasites and the infected erythrocytes make it possible to differentiate between two other species, *P. vivax* and *P. ovale*, both of which can cause relapse months or years after initial infection.

On further examination of the peripheral-blood smear, Schüffner's dots (intracytoplasmic granulation caused by the maturation of *P. vivax* or *P. ovale* within a cell) could be seen, in addition to intraerythrocytic ring forms. More mature ameboid trophozoites (Fig. 1) were also detected, as were pigment-containing, rounded gametocytes, the presence of which is consistent with *P. vivax*. The parasite burden was low at 0.4%.

Parasitemia exceeding 5% is correlated with severe infection. This patient's low parasite burden is characteristic of *P. vivax*. The treatment of malaria is guided by anticipated drug susceptibility. Whereas *P. falciparum* from many parts of the world is chloroquine-resistant, nonfalciparum infections from most regions respond well to chloroquine; *P. vivax* infections acquired in Uganda would be expected to be chloroquine-sensitive. Whereas chloroquine should effectively end this relapse by eliminating parasitemia, it will not prevent future relapses, since it does not affect

the latent forms of *P. vivax* (hypnozoites) in the liver. A 2-week course of primaquine should also be prescribed to clear the hepatic reservoir of malaria, thus preventing future relapses. Given the risk of hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency who receive treatment with primaquine, the patient should be tested for G6PD deficiency.

The patient was given 1 g of chloroquine phosphate, followed by 500 mg at 6, 24, and 48 hours. The fevers and headaches resolved within 12 hours after initiation of treatment. A repeat blood smear at 24 hours showed only two gametocytes per smear. A test for G6PD deficiency was negative. After receiving the four doses of chloroquine, the patient was directed to take 30 mg of primaquine daily for 14 days. At a 2-week follow-up visit, he remained afebrile and had no residual symptoms except for some mild fatigue. A repeat peripheral-blood smear obtained at that time showed no indication of parasitemia.

COMMENTARY

In hindsight, it is tempting to refer to the patient's fever as cyclic, given the classic association of cyclic (periodic, or relapsing) fever with malaria. Although the differential diagnosis for periodic fever is different from that for randomly recurring fever,[1] many febrile illnesses follow a pattern of nightly fevers with morning defervescence. In malaria, the febrile pattern is initially irregular but subsequently regularizes if a dominant brood of synchronously replicating parasites develops. Typically, the periodicity of fever is 72 hours with *P. malariae* and 48 hours with other species. However, any fever in a patient who has had possible exposure to malaria should prompt consideration of this diagnosis.

In clinical practice, malaria is often categorized as falciparum versus nonfalciparum (which includes *P. vivax*, *P. ovale*, and *P. malariae*). *P. falciparum* carries the highest risk of death. Among the nonfalciparum species, *P. vivax* accounts for the greatest number of cases, and among all species it has the widest geographic range. *P. vivax* occurs widely in the tropics, is present in some temperate areas, and occurs only rarely in sub-Saharan Africa.[2,3] In the United States, the annual incidence of malaria is approximately 1500 cases.[4] In 2010, a total of 1691 cases were reported to the Centers for Disease Control and Prevention (CDC), the largest number reported since 1980; *P. falciparum*, *P. vivax*, *P. malariae*, and *P. ovale* were identified in 58%, 19%, 2%, and 2% of cases, respectively.[5]

The malaria life cycle at initial infection is identical across species, beginning with inoculation by a feeding female anopheles mosquito of immature malaria parasites (sporozoites) that migrate through the host's bloodstream to the liver, where they invade hepatocytes and replicate by means of schizogony (asexual division into multinucleated cells called schizonts that contain many merozoites). Mature schizonts rupture the hepatocyte, releasing tens of thousands of merozoites into the bloodstream, where they invade erythrocytes and undergo another round of schizogony, forming trophozoites (the form taken during the feeding stage of the parasite).[3] Trophozoites develop into blood-stage schizonts that usually contain up to 24 merozoites, which, upon rupture of the erythrocyte, enter the bloodstream and infect other erythrocytes. Fever, rigors, and other symptoms of the malaria paroxysm are the consequence of red-cell rupture and release of merozoites.[3]

In the case of *P. vivax* and *P. ovale*, some sporozoites do not replicate immediately when they invade hepatocytes but remain dormant (as hypnozoites) for prolonged periods before undergoing schizogony and giving rise to a clinical relapse,[6] as occurred in this case. The average time to relapse is approximately 9 months, but it can range from weeks to years. The interval to relapse depends on the strain (earlier with tropical strains and later with temperate strains), the initial inoculum, and host factors (e.g., febrile illnesses can trigger relapse associated with *P. vivax*).[7] None of the commonly used prophylactic agents (chloroquine, mefloquine, doxycycline, or atovaquone–proguanil) eliminate hypnozoites. Primaquine, the only effective drug against dormant hypnozoites, has not been approved by the Food and Drug Administration for primary prophylaxis,[8] but the CDC endorses its use for prophylaxis in Latin American countries where *P. vivax* predominates, because the drug can prevent both primary attacks and relapses caused by all species that are a source of malarial infection.[9] It is unlikely that this patient had received primaquine for malaria prophylaxis. Instead, his prophylactic therapy protected him from a clinically apparent initial infection but did not prevent dormant infection in his liver.

In regions where malaria is endemic, the risk of disease can be reduced by limiting mosquito bites; it is helpful to wear protective clothing, apply repellents such as N,N-diethyl-3-methylbenzamide (DEET) or picaridin to skin and permethrin to clothing, sleep under insecticide-treated bed nets, and avoid outdoor activities during peak biting times (in most areas, between dusk and dawn).[10] Even with these measures, chemoprophylaxis is essential for travelers to areas in which the disease is endemic. Owing to the widespread resistance of *P. falciparum* to chloroquine, the main agents for chemoprophylaxis are mefloquine and doxycycline, which are active against bloodstream parasites and prevent clinical disease, and atovaquone–proguanil, which is active against parasites in the liver and the bloodstream but not against hypnozoites. The choice of drug must take into account the travel destination and duration of stay, concurrent medical conditions, adverse-event profile, and cost.

In patients with acute or recurrent malaria infection, treatment depends on the species and the resistance status in the area where the infection was acquired. *P. falciparum* is resistant to chloroquine in most regions in which it is endemic and resistant to mefloquine in parts of Southeast Asia. In contrast, nonfalciparum malaria parasites do not have substantial resistance to mefloquine, and the distribution of chloroquine-resistant *P. vivax* malaria is limited, occurring primarily in Indonesia and Papua New Guinea.[11] After treatment is initiated, peripheral-blood smears should be obtained daily for 4 days (parasitemia is typically eliminated by day 4), on days 7 and 28 to confirm eradication, and at any time symptoms recur, suggesting treatment failure.[10]

In areas other than those with known chloroquine resistance, chloroquine, followed by a 14-day course of primaquine to prevent subsequent relapses, remains the standard treatment for *P. vivax* parasitemia.[2] Among patients with a contraindication to primaquine therapy (e.g., pregnant women or persons with G6PD deficiency), treatment with chloroquine alone carries a 20% risk of relapse[12]; extended chloroquine prophylaxis can be offered to patients who have frequent relapses.

This case highlights the importance of travel history (recent and remote) in constructing the differential diagnosis of a febrile illness. Although babesiosis was a possibility in this patient, since he had traveled only 3 weeks before presentation to an area in which the disease is endemic, consideration of the possibility of relapse of *P. vivax* malaria years after initial exposure prompted careful review of the blood smear and led quickly to the correct diagnosis and appropriate therapy.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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