A 73-Year-Old Man with Febrile Illness

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What's the Take Home?

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Introduction. A previously healthy 73-year-old man was brought to Temple University Hospital in Philadelphia, PA by family members after experiencing anorexia and persistently elevated fevers for 4 to 5 days.

Patient history. The patient denied pains other than muscle aches symmetrically in his hands, arms, shoulders, and neck. There was no chest or abdominal pain. His appetite was poor, with little intake of foods and liquids.

His personal medical history includes being a long-time cigarette smoker, but he has no known significant medical conditions. That said, he has rarely had regular medical testing or care. He works on a landscaping crew, which is currently in its busiest season (late spring and early summer). Due to his condition, the patient has not worked for the past week.

His physical examination shows an ill-appearing man weighing 58 kg (127 pounds) who is responsive but lethargic. The patient presented with fever, mild tachycardia, and normotensive vital signs, alongside laboratory abnormalities. The physical examination was notable for dry mucous membranes, mild expiratory wheezes without rales or consolidation, a soft, non-tender abdomen, non-focal neurologic findings, and dry skin without rash on thorough inspection. (Table 1).

Table 1. Vital signs and laboratory findings on presentation

Test or Measurement	Result	Reference Range
Blood pressure (supine), mm Hg	100/70	90–120 / 60–80
Heart rate, beats/min	108	60–100
Respiratory rate, breaths/min	16	12–20
Temperature, °F	103.8	97.0–99.5
Hemoglobin, g/dL	10.9	13.5–17.5 (male)
MCV, fL	86	80–100
WBC count, $\times 10^3/\mu L$	2.7	4.5–11.0
ANC, $\times 10^3/\mu L$	1.7	1.5–8.0

Platelet count, $\times 10^3/\mu L$	76	150–400
Creatinine, mg/dL	2.6	0.6–1.2
BUN, mg/dL	30	7–20
EKG	Sinus tachycardia	Normal sinus rhythm
Chest radiograph	Hyperinflation; no infiltrates	Clear lung fields

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Correct answer: C. Obtain thin blood smears for professional examination by a hematologist or pathologist

Although this was a challenging diagnosis, with the patient presenting with an array of serious symptoms and findings that were non-specific in nature, the ultimate finding is babesiosis. The patient's symptoms included subacute onset of significant malaise and fatigue but without a dominant finding of localized pain, rash, cough, shortness of breath, or any clues for the "trigger" of a sepsis syndrome. Additionally, there was onset of a very high and hectic fever, perhaps a clue in the differential but a very weak one.

Still, there were clues in the patient's history, along with findings and pace of the illness that warrants going deeply enough into a differential to consider babesiosis. This will be the third case in 3 years in which this article featured once rare illnesses (dengue, vibriosis, and babesiosis) as these diseases continue to expand their range due to, among other factors, changes in climate.

Babesiosis is on the ever-expanding roster of tickborne diseases now including Lyme (by far the most common), anaplasmosis, and rickettsia. These tickborne diseases have essentially doubled their incidence within the last 20 years.[1,2] Although protozoal in nature, babesiosis is a tickborne disease requiring time in tick salivary glands and a mammalian blood meal (the tick bite) to complete its life cycle. The specific tick carrier is *I. scapularis* (known as the deer tick), which endemically infects deer and wood mice. The specific babesiosis species that causes most human babesiosis is *B. microti*. Tick activity and the risk of human exposure increase between spring and late summer (April through October), a pattern supported by the seasonal behavior of their primary hosts, such as deer and mice, whose population dynamics influence tick abundance.

The geographic epicenter of human babesiosis was originally in New England, where it was once referred to as Nantucket fever.[3,4] However, due to climate change, increasing human encroachment, and greater interaction with vector species, the range of babesiosis has expanded to much of the northeastern and northcentral United States. In certain highly endemic areas of New England, the incidence of babesiosis has approached that of Lyme disease. Additionally, because of its incubation period of 1 to 4 weeks, babesiosis can be transmitted via blood transfusion from asymptomatic donors.[3,4]

Regarding pathophysiology, babesia is a protozoan and requires a 1-4 week of incubation post-tick bite to manifest illness in humans. In fact, an overwhelming majority of *B. microti*. infestations are either asymptomatic or subclinical in nature. In the 25% who develop clinical disease, there is a clear picture of reduced immunity allowing this to happen. Thus, the following groups are at risk for developing illness: (1) patients who have undergone a splenectomy—a significant risk factor; (2) those with associated comorbidities such as cancer, hemoglobinopathies; (3) patients using immunosuppressive medications such as the biologicals (e.g. Rituxamab); (4) patients who are 50 years of age or older.[3,4]

In clinical case series, the following non-specific symptoms and signs have been reported in more than half of patients with confirmed babesiosis: fever, fatigue, sweats, myalgias, headache, chills, and anorexia.[4] However, several features may help differentiate babesiosis from other non-specific febrile illnesses. First, the fever associated with babesiosis is often high-grade, commonly exceeding 103°F to 104°F, which is unusual for many adult infections. Second, patients with a history of splenectomy—or, conversely, those with splenomegaly on physical examination—are at increased risk and should prompt consideration of babesiosis.[4] Third, recent travel to or residence in endemic regions during high-risk months, or occupational exposure such as landscaping (as in the present case), further strengthens suspicion. Such exposure histories often initially raise concern for Lyme disease; however, in the absence of rash, babesiosis should be strongly considered.

Therefore, when a clinician suspects Lyme disease, but there is no rash, babesiosis should be in the differential. Once babesiosis is established in a human, especially in high-risk patients, about 20% become ill enough to require hospitalization and are at risk for serious complications such as disseminated intravascular coagulation or acute respiratory distress syndrome. This all translates into a 6% to 9% overall mortality rate in hospitalized cases with a 21% mortality rate in the immunosuppressed subpopulation.[3]

Babesiosis should be included in the differential diagnosis of any unexplained febrile illness in patients residing in or recently traveling to endemic areas between May and October. It should also be considered when Lyme disease is suspected but no rash is present, particularly if a sepsis-like syndrome persists despite broad-spectrum antibiotic therapy and no obvious source is identified.

The patient described in this case meets all three key clinical criteria warranting suspicion for babesiosis. Confirmatory diagnosis remains pathological, requiring identification of *Babesia* organisms on Wright- or Giemsa-stained peripheral blood smears examined by a hematologist or pathologist.[3,4] An important aspect of the smear examination is that it allows for quantification of parasitemia, defined as the percentage of red blood cells (RBCs) infected with *Babesia*. This measurement is both prognostic and therapeutic, as higher levels of parasitemia are associated with increased severity and mortality. Specifically, parasitemia greater than 10% is considered a threshold for initiating red blood cell exchange transfusion, a blood bank procedure used to physically remove infected RBCs.[3,4]

Additional indications for exchange transfusion includes the development of hypoxia, acute renal failure, or significant anemia. As we are in the era of molecular and biologic medicine, there is now a PCR assay for *B. microti*. DNA. But this test takes time whereas another added advantage to the "old fashioned" professional smear exam is its availability and speed.

There are very effective therapeutics for human babesiosis. Strong studies have shown the combination of the anti-protozoan drug atovaquone with azithromycin is effective in essentially all cases to the same extent as atovaquone and quinine with far less side effects and need for discontinuation of therapy. The usual duration of therapy is 7 days to 10 days.[5] If there is parasitemia greater than 10%, significant anemia and/or development of pulmonary, renal or hepatic failure exchange transfusion is added to the pharmacology.[3]

What's the take home? Babesiosis is a tickborne illness caused by the protozoan *B. microti*. in most human cases and is transmitted by the deer tick. It represents one of the ever-increasing tickborne illnesses being encountered in a growing area of endemic presence in the United States. These illnesses, which include the most common and well-known Lyme disease, have a seasonal timing of May to October and epidemiologic predilection to infestation of persons living in or traveling to the endemic areas, especially the Northeastern quadrant of the United States as well as persons with occupation or hobbies with significant outdoor exposures, e.g. landscapers.

Babesiosis has a 1 to 4-week incubation period and is asymptomatic in most infections or at least not requiring medical attention. In the group who develop symptomatic disease, many non-specific symptoms such as malaise, fatigue, and myalgias ensue. A characteristic finding and clue in severe cases is a high temperature. Roughly 25% of symptomatic cases require hospitalization with a mortality rate of 6% to 9% overall but up to 20% in patients who are immunocompromised. Although PCR assays are now available, the excellent, efficient, and prompt method of diagnosis in suspect cases remains professional examination of blood smears. Treatment involves 7 to 10 days of atovaquone and erythromycin. In high-risk situations (parasitemia more than 10%, severe anemia, pulmonary/renal/hepatic failure) RBC exchange transfusion can quickly reverse the process.

Patient follow-up. The presentation of a patient with an extreme temperature and volume depletion prompted the thought of sepsis. Indeed, the patient received vigorous IV hydration with normal saline with improvement in hydration status and renal function. He also received broad spectrum antibiotics and had several sets of blood and urine culture. At 36 hours, the hydration status and renal laboratory tests were improved and all cultures were negative. Yet, he continued to show high temperatures, some in excess of 104 °F.

With hydration, the patient's initial hemoglobin level of 10.9 reduced to 7.7 and the neutropenia and thrombocytopenia worsened as well by about 25%, such that attention was paid toward the causation for these significant cytopenias with a hematology consultation. As is routine with all hematology consults, the team reviewed a Wright-stained smear and observers appreciated what appeared to be intracellular inclusions. The smear was sent to pathology, where the hematopathologist prepared a Giemsa-stained thin smear, which confirmed the presence of the pleiomorphic intra-erythrocytic and extra-erythrocytic

organisms with ringed forms typical of babesiosis. Parasitemia was estimated at 3% to 4%. (This was subsequently reviewed by the Centers for Disease Control and Prevention, which confirmed the findings as babesia organism).

Since the patient was significantly anemic and still with hectic fevers, the decision was made to perform a complete red blood cell exchange transfusion, which was performed without any complications. The patient was started on atovaquone and erythromycin, which manifested prompt subjective and objective improvement. Indeed, the patient's temperature returned to normal levels 48 hours later, which was Day 4 at the hospital. He also showed ongoing improvement in all laboratory parameters.

The patient was discharged to home care in good condition with outpatient atovaquone 750 mg PO twice daily and erythromycin 500 mg PO twice daily for a total of 10 days. He was afebrile and feeling well at his 2-week outpatient follow-up appointment.

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