

One man, three tick-borne illnesses

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SUMMARY

A 70-year-old man presented to the emergency department with fevers, ankle edema and nausea following a presumed insect bite on his ankle 1 month prior. On examination, he was febrile and had left leg pain with passive range of motion. Laboratory studies revealed anemia, thrombocytopenia, acute kidney injury and elevated aminotransaminases. Due to his recent travel to the Northeastern United States, he was suspected of having a possible tick-borne illness. Serologies were positive for *Borrelia burgdorferi*, *Anaplasma phagocytophilum* and *Babesia microti*, and the patient was diagnosed with Lyme disease, babesiosis and anaplasmosis. He was treated with doxycycline, atovaquone and azithromycin, leading to resolution of symptoms. While co-infection with Lyme disease is common, infection with three tickborne illnesses at one time is relatively rare.

BACKGROUND

Cases of tick-borne illnesses are increasing yearly. Lyme disease remains the most common tick-borne disease, and co-infection, most commonly with babesiosis, can occur with up to one-third of *Borrelia* infections. Several factors raise suspicion for co-infection, including laboratory abnormalities and prolonged duration of symptoms despite appropriate treatment. Physicians must maintain a high level of suspicion for co-infection, as untreated disease can result in long term and sometimes life-threatening sequelae.

CASE PRESENTATION

A 70-year-old Caucasian man with a history of prostate cancer status post-prostatectomy presented to the emergency department (ED) reporting of fevers at night for several weeks, as well as bilateral ankle edema and nausea. The patient reported that he had been in his usual state of health until 1 month prior to admission. At that time, he noticed a small raised red lesion on his left ankle which he believed to be an insect bite sustained during his work as a residential electrician in the Philadelphia area. The ankle became erythematous and swollen, and he applied hydrocortisone cream to the area without improvement. Two days after noting this ankle lesion, the patient noticed an erythematous rash on his neck and chest. He presented to his primary care provider's office at that time, and was prescribed an antihistamine as well as a 7-day course of trimethoprim-sulfamethoxazole.

The patient's chest rash resolved after 5 days of antibiotic therapy, but he reported ongoing ankle pain and swelling. At an office visit 1 week later, he underwent ankle radiograph, which showed mild

degenerative changes. Over the next 2 weeks, the patient continued to report pain in his left ankle as well as his left hip, and was diagnosed with sciatica and prescribed gabapentin. He reported taking two trips to visit family in Boston, Massachusetts, USA, during the summer (May and July) and had spent time in a heavily wooded area, though did not recall any tick bites. In late July, 2 weeks prior to presentation to the ED, the patient began experiencing fevers at night, nausea, bloating and bilateral lower extremity edema, and reported an 8 pound weight gain in the week prior to ED presentation.

In the ED, the patient was febrile to 39°C and otherwise hemodynamically stable. His physical examination was normal except for pain with movement of the left leg; there was no evidence of edema or rashes.

INVESTIGATIONS

Investigations including chest radiograph and ECG were negative for acute pathology. Complete blood count revealed a hemoglobin of 118 g/L and platelet count of 92×10^9 /L. White blood cell count was 5.1×10^9 /L with 21.7% monocytes (normal 1%–12.5%) and an otherwise normal differential. Comprehensive metabolic panel was notable for a creatinine of 1.56 mg/dL (baseline 0.6), alkaline phosphatase of 118 IU/L, aspartate transaminase of 188 IU/L and alanine transaminase of 281 IU/L. His urinalysis showed 2+ protein, 1+ bilirubin, trace blood and 1+ ketones. A troponin I, lactic acid and thyroid stimulating hormone were within normal limits. His HIV and hepatitis A, B and C serological tests were negative. Two sets of blood cultures were obtained, and were negative for bacterial growth.

The patient was admitted to the medical service, and due to his presenting symptoms, lab findings and history of travel to the Northeastern United States, he was suspected of having a possible tick-borne illness and was started on doxycycline. The infectious diseases (ID) team was consulted, and ordered a Lyme ELISA, *Babesia*, *Anaplasma*, *Ehrlichia* and *Rickettsia* IgM and IgG antibodies by indirect fluorescent antibody (IFA), as well as sedimentation rate (ESR), C reactive protein (CRP) and creatine kinase. Creatine kinase was normal, and ESR and CRP were elevated at 57 mm/hour and 6.1 mg/dL, respectively. Due to his musculoskeletal and gastrointestinal problems, a CT scan of the patient's abdomen and pelvis was ordered, which did not demonstrate musculoskeletal pathology, but did show evidence of anasarca. The patient was discharged from the hospital with planned clinic follow-up with ID, and 2 days after discharge his labs returned positive for *Borrelia burgdorferi*, *Anaplasma phagocytophilum* and *Babesia microti* serologies. Total Lyme antibodies were positive at



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3.55 LIV, and the patient's *Bo. burgdorferi* IgM and IgG were reported positive with >5 bands present on western blot. *A. phagocytophilum* IgM titre was 1:64 with an IgG titre of 1:320. *B. microti* IgM titre was >1:320 with an IgG titre of >1:256. Although PCR for *Babesia* was not performed and a peripheral blood smear was negative for atypical cells or inclusion bodies, the patient did not experience improvement in his symptoms until he was also treated for babesiosis with atovaquone and azithromycin.

OUTCOME AND FOLLOW-UP

The patient remained on doxycycline for treatment of Lyme disease and anaplasmosis; atovaquone and azithromycin were added for the treatment of babesiosis. He reported significant improvement in his leg pain and swelling 2 days after starting treatment with atovaquone and azithromycin. The patient returned to the Philadelphia area, where he followed up with his primary care provider. One year after this episode, he reports symptoms of neuropathy at the site of his presumed insect bite.

DISCUSSION

Ticks were first discovered to be vectors for disease transmission in 1906, when Dr Howard T. Ricketts identified the *Dermacentor andersoni* wood tick as responsible for the transmission of Rocky Mountain spotted fever. The Gram-negative spirochete responsible for Lyme disease, *Bo. burgdorferi*, was first identified in 1982. Lyme disease has remained the most common tick-borne disease since that time. In USA, Lyme disease is transmitted by the *Ixodes* spp ticks, found in the Northeast, upper Midwest and Pacific Coast.¹ The hallmark of infection with Lyme disease is the pathognomonic erythema migrans rash, which was not described in our patient. While the most common initial presentation of Lyme disease is a solitary erythema migrans rash,² the next most common reported symptoms are fever and headache. Infection with Lyme disease rarely causes lab abnormalities.³ If Lyme disease is not recognized and treated in the early stage, patients may progress to early and late disseminated disease, with cardiac, neurologic and rheumatologic sequelae (heart block, aseptic meningitis, facial palsy, oligoarthralgias). Appropriate screening tests for screening include Wright-stained peripheral blood smear, darkfield microscopy for spirochetes and ELISA IFA. The diagnosis is confirmed with western immunoblot and PCR assay. Treatment consists of a 10–14-day course of doxycycline or a 14–21-day course of amoxicillin.⁴

Anaplasmosis, formerly known as human granulocytic ehrlichiosis, is caused by a Gram-negative obligate intracellular bacterium which infects leukocytes. The causative agent, *A. phagocytophilum*, is also transmitted by the *Ixodes* tick, with regional distribution again including the Northeastern United States, upper Midwest and northern California. The most common presenting symptoms of anaplasmosis include fever, malaise, myalgias and headache 1–2 weeks after tick bite; anaplasmosis is rarely associated with rash. Anaplasmosis causes multiple laboratory abnormalities, including leukopenia, thrombocytopenia and elevated transaminases. Recommended diagnostic tests include Wright-stained peripheral blood smear (which may show characteristic intracytoplasmic aggregates in neutrophils) followed by PCR assay and IFA.¹ Recommended treatment is a 10-day course of doxycycline.⁵

Babesiosis is a tick-borne protozoal infection which can lead to prolonged parasitemia in humans. The term 'babesiosis' refers to two types of infection in humans. Infection with *Babesia divergens* occurs in immunocompromised human hosts,

mainly in cattle-ranching regions during summer months. The more common cause of babesiosis is infection with *B. microti*. *B. microti* is transmitted to humans by *Ixodes* ticks, and distribution of disease parallels that of Lyme disease. Co-infection with Lyme disease occurs in two-thirds of cases.⁶ Young healthy patients with babesiosis are often asymptomatic. When symptoms occur, the patient may experience a self-limited influenza-like febrile illness with anorexia, malaise and lethargy. Complications can include hemolytic anemia, jaundice and acute respiratory failure.¹ Lab abnormalities include anemia and thrombocytopenia.⁶ Diagnosis is made with Giemsa-stained thin smear followed by testing for IgM antibodies and PCR-based assays. Blood smear may show intraerythrocytic ring forms as well as clumped extraerythrocytic forms. Treatment is based on severity of infection. Mild to moderate disease is treated with azithromycin and atovaquone, as in our patient's case, whereas life-threatening infections are treated with quinine and clindamycin.¹

In patients who are receiving adequate treatment for Lyme disease but remains febrile for more than 24 hours, investigation for co-infection with other tick-borne illnesses is recommended. Testing for co-infection is also recommended in patients with unexplained thrombocytopenia and/or anemia, as was present in our patient.³ In one paper examining rates of co-infection with tick-borne illnesses published in *Clinical Infectious Diseases*⁷ in 2002, 39% of patients were co-infected with more than one organism. The most common co-infection was Lyme disease with babesiosis (81% of co-infections), and only 5% of patients had three infections (Lyme, anaplasmosis, babesiosis).⁶ Patients with co-infection tend to have more severe and prolonged symptoms, including high fever, sweats and rigors. Symptoms tend to be more severe in older patients and patients with splenectomies.³

Learning points

- ▶ Tick-borne illnesses should be suspected when patients present with fever, fatigue, myalgias and diaphoresis with a history of travel or residence in an endemic region.
- ▶ Co-infection with Lyme disease and another tick-borne illness is common, and testing for co-infection should be performed in patients with >24 hours of symptoms despite appropriate treatment, as well as unexplained laboratory abnormalities.
- ▶ Both Lyme disease and anaplasmosis are treated with doxycycline, but treatment for mild to moderate babesiosis includes azithromycin and atovaquone.

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