



Triple Tick Attack

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Introduction

Tick borne diseases are frequently seen in tick endemic areas. Lyme disease is the most common tick-borne illness. However, co-infection with other pathogens is not uncommon and can present with nonspecific symptoms complicating the diagnosis. We present a case of triple infection with babesiosis, Lyme disease, and anaplasmosis treated with antibiotics and RBC exchange (Erythrocytapheresis).

Case Presentation

A 74-year-old female with past medical history significant for Chronic Obstructive Pulmonary Disease (COPD) and hypertension, who was an avid gardener, presented with one week of progressive dyspnea, cough with mucoid expectoration, and fatigue. On presentation, she was hypotensive to 85/49 mm of Hg and tachycardia to 150 beats per minute without fever, requiring 6 L of oxygen to maintain saturation. General examination was significant for altered mental status, dyspnea, pallor, and peripheral edema. Exam showed flat neck veins, an irregular heart rate with no audible murmurs or gallops, and bibasilar pulmonary crackles. The remainder of the physical examination was normal.

Pertinent laboratory findings were significant for hemolytic anemia (9.9 g/dL) and thrombocytopenia (34 K/uL). A peripheral blood smear revealed the presence of intracytoplasmic parasites consistent with *Babesia*. The patient was started on azithromycin and atovaquone. Doxycycline was added empirically for Lyme disease which was later confirmed by serology. In addition, *Anaplasma* titers were positive. Further investigation revealed that the parasitic load of 9.04% and RBC exchange was performed for severe babesiosis. Repeat labs demonstrated an inadequate reduction in parasitic load (6.54%) requiring a second round of erythrocytapheresis. Antimicrobials were changed to clindamycin and quinine with doxycycline for a total of fourteen days. The patient's anemia and thrombocytopenia improved along with her clinical status.

Discussion

Lyme disease is the most frequently diagnosed tick-borne disease; however, patients in endemic areas should be screened for co-infection in cases with nonspecific symptoms and lack of response to therapy within 48 hours. A 10-day course of doxycycline is usually sufficient for Lyme disease and anaplasmosis while babesiosis usually responds to atovaquone and azithromycin. Erythrocytapheresis should be considered in severe babesiosis as it may prevent further complications including severe hemolytic anemia, DIC, respiratory failure, and renal failure.

A 74-year-old female with a past medical history of Chronic Obstructive Pulmonary Disease (COPD), Hypertension, Depression and Glaucoma and Retinal detachment presented to the hospital with one week of progressively worsening dyspnea and fatigue. The patient was asymptomatic until a week before the presentation when she started experiencing dyspnea on exertion with household tasks including gardening. She also endorsed a cough productive of yellowish mucoid sputum accompanied with fatigue impacting her daily activities. The patient denied any chest pain/discomfort, palpitations, pre-syncope, syncope, orthopnea or Paroxysmal Nocturnal Dyspnea (PND). She also denied any fevers, arthralgia, myalgia, or rashes. Her social history was remarkable for active smoking, 75 pack year smoking history without any history of alcohol or other illicit drug use.

In the Department of Emergency, the patient was a febrile, blood pressure of 85/49 mm of Hg with a heart rate of 150 and respiratory rate of 22 per minute with oxygen saturation of 94% on 6 Liters of oxygen *via* nasal cannula. The patient was oriented to person but appeared lethargic, and

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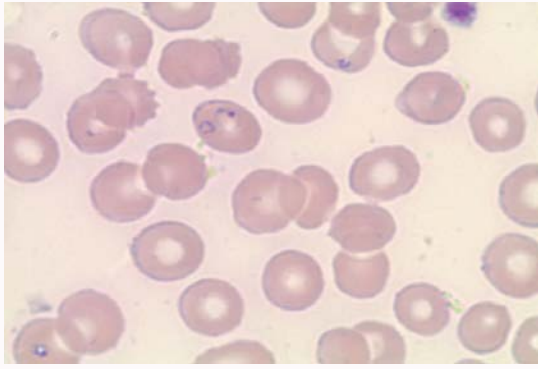


Figure 1: Peripheral blood smear showed intracytoplasmic parasites.

was using accessory muscles of respiration. General examination was remarkable for pallor with anicteric sclera, and no palpable lymph nodes were present in the cervical, axillary, or inguinal regions. Her right pupil was 3 mm reactive to light. Left pupil was noted to be chronically adducted and downward secondary to retinal detachment. Oral mucosa appeared dry with thickly coated tongue. Neck veins were flat. Heart Examination was remarkable for fast, irregular heart rate, variable first heart sound, normal second heart sound without any murmurs or gallops. Lung examination was significant bilateral mid to late inspiratory crackles. The abdomen was soft, distended, non-tender with normal bowel sounds. Extremities were noted to be cold and clammy, with 1+ pitting edema. The neurological examination had decreased muscle strength throughout with normal sensations. Deep tendon reflexes were noted to be symmetric.

Routine laboratory investigations revealed WBC count of 7.5 (4.0 k/uL to 10.5 k/uL), Hemoglobin of 9.9 (12.5 g/dL to 16 g/dL) and hematocrit 32.3 (37% to 47%). Her baseline hemoglobin concentration was around 15 g/dL. Platelet count was 34 (150 K/uL to 450 K/uL) with elevated Mean Platelet Volume (MPV) of 12.4 (7.4 fL to 11.4 fL). A peripheral blood smear showed intracytoplasmic parasites suspicious for *Babesia* along with reduced platelets (Figure 1). The parasitic level was found to be at 9.04%. Lactate Dehydrogenase (LDH) was 1,544 U/L (125 U/L to 220 U/L), Haptoglobin was <6 mg/dL (27 mg/dL to 139 mg/dL), Total bilirubin 5.4 mg/dL (0.3 mg/dL to 1.0 mg/dL) with direct fraction 3.5 mg/dL (0.0 mg/dL to 0.2 mg/dL). AST was 202 U/L (5 U/L to 40 U/L), ALT 90 U/L (7 U/L to 52 U/L), with albumin of 2.3 g/dL (3.5 g/dL to 5.0 g/dL). BUN was 51 mg/dL (7 mg/dL to 17 mg/dL) with normal Creatinine of 0.8 mg/dL, Sodium 129 (135 mmol/L to 145 mmol/L), Potassium 4 (3.5 mmol/L to 5.1 mmol/L), Chloride 103 (98 mmol/L to 107 mmol/L), serum Bicarbonate 19 (24 mmol/L to 32 mmol/L) and calcium of 7 (8.4 mg/dL to 10.2 mg/dL). Electrocardiogram showed atrial fibrillation with a rapid ventricular response.

Chest x-ray was remarkable for cardiomegaly with small right pleural effusion and small airspace opacity within the right lower lobe. Given her presentation, we started intravenous fluids along with empiric antibiotic coverage for community-acquired pneumonia with Ceftriaxone and Azithromycin. We also started doxycycline and atovaquone as *Babesia* on peripheral smear raised the suspicion of co-infection with Lyme. She received around 10 Liters of intravenous fluids with a downtrend in lactic acid from 2.8 mmol/L to 2.0 mmol/L. However, she continued to remain hypotensive and required Norepinephrine to maintain her blood pressure. Given her severe disease and parasitic load, erythropheresis was done. Following

erythropheresis, on day three there was a mild improvement in her parasitic load to 5.54%, and due to her continued septic shock state, we added Clindamycin to the regimen. Her renal function worsened secondary to pigment induced nephropathy from hemolysis. Given inadequate response and development of Acute Kidney Injury, we repeated erythropheresis resulting in a reduction in parasite load to 1.75%. At this point, Lyme IgM immunoblot was found to be positive, with IgG being negative. *Anaplasma* titers also showed recent/current infection, with IgG >1:1,024 (reference <1:64) and IgM 1:80 (reference <1:20). These results prompted discontinuation of Atovaquone and Azithromycin and addition of quinine. Her hemodynamic status improved and she came off of pressor support along with improvement in respiratory status. Her Hemoglobin reached a nadir of 9.1 g/dL, but platelets improved to 35 cells/L \times 10⁹ cells/L and creatinine returned to baseline. She received a total of 14 days of antibiotic therapy. Her liver enzymes trended down, with improvement in her hemoglobin and platelet count throughout her inpatient stay.

Lyme Borreliosis (LB) is the most common tick-borne disease in the United States. It is caused by the bacteria *Borrelia burgdorferi* spread by the tick *Ixodes scapularis*. This tick is known to carry at least seven human pathogens in the United States and Europe, including *Anaplasma phagocytophilum* and *Babesia* spp. [1,2]. It is common for patients to have co-infection with two pathogens but the incidence of three pathogen infection is rare [1,3,4]. Individuals staying in endemic tick areas such as the North-Eastern United States are at increased risk. This risk is higher in certain professions such as farmers, gardeners or foresters. Our patient lived in an endemic tick area and spent most of the time outside her home doing gardening.

Typical clinical presentation of Lyme disease includes characteristic rash known as Erythema migrans, intermittent or persistent arthritis and certain neurologic manifestations such as subtle encephalopathy or polyneuropathy. Also, individuals may have evidence of meningeal irritation, migratory musculoskeletal pain, hepatitis, generalized lymphadenopathy, splenomegaly, sore throat, nonproductive cough, or testicular swelling [5]. *Anaplasma* and *Babesia* usually have nonspecific symptoms such as fever, malaise, myalgia, headache, and chills. Some patients may develop nausea, vomiting, cough, and arthralgia. Clinical manifestations of *Babesia* are mainly due to hemolysis because of parasite-mediated lysis of erythrocytes. Mild hepatosplenomegaly may be present, but thrombocytopenia, leukopenia, and anemia are frequently detected.

Cases with severe anemia (Hemoglobin <10) and high parasitic load (>10%) are classified as severe babesiosis and are at increased risk of complications such as acute respiratory failure, disseminated intravascular coagulation, congestive heart failure, and renal failure [3]. Low threshold for suspicion should be held for co-infection when patients present with a presentation which would be atypical for single pathogen exposure. Delay in diagnosis can lead to prolonged disease duration and increases the comorbidities associated with the infectious state [3,4,6]. Our patient presented with non-specific symptoms of shortness of breath and fatigue without typical signs and symptoms of any of the tick-borne diseases but had a *Babesia* parasitemia level of 9% with hemoglobin of 9.8 g/dL, as well as evidence of acute respiratory and renal failure. These all subsequently improved with antibiotics and erythropheresis.

Various methods are available for diagnosis such as blood smear, Polymerase Chain Reaction (PCR) assay, and serological

examinations but, none of these methods have 100% sensitivity or specificity. Lyme is diagnosed by a Two-step testing with Enzyme Immune-Assay (EIA) and western blot testing; If the EIA is reactive, separate IgM and IgG western blot can be obtained for confirmatory testing. If symptom duration is more than four weeks, IgG western blot alone is highly sensitive [2]. In our patient, Lyme IgM immunoblot was positive with negative IgG consistent with duration of illness less than four weeks. Anaplasmosis can easily be diagnosed by presence of morulae in neutrophils on thin smear. PCR and serological testing is also available, which are more sensitive than thin smear. Our patient had *anaplasma* titers of IgG >1:1,024 (reference <1:64) and IgM 1:80 (reference <1:20). Titers >1:640 are diagnostic of acute infection with culture as the most sensitive method [7]. The blood smear is the gold standard for diagnosis of *Babesia*, however, if the patient has a low level of parasitic load, PCR is more sensitive [7-9].

Our patient's initial thin blood smear had a characteristic intracytoplasmic appearance such as rings and Maltese cross. We obtained multiple blood smears to assess the response to therapy by trending parasitic load. Serological detection of antibodies is also an option, however, is not employed routinely. IgG titers more than 1:1,024 suggests active or recent infection. Positive IgM titers suggest infection and must be accompanied by positive IgG titers for diagnosis [10]. Blood smear may be negative if the patient has a low level of parasitic load. In these cases, if suspicion is high, molecular techniques such as PCR should be used to confirm the diagnosis [10].

Individuals diagnosed with any tick-borne disease, as well as cases from endemic tick areas, should always be screened for other tick-borne pathogens especially if there is an atypical presentation or a lack of response to initial treatment modalities [8]. A multiplex PCR is available for screening of all three tick-borne pathogens with one PCR reaction. Treatment may be delayed if an accurate diagnosis is not established [11].

Lyme can be treated with doxycycline, amoxicillin, and cefuroxime, and macrolides are considered second-line agents. Treatment duration of a total of ten days has been shown to be highly effective in treating both Lyme disease and human granulocytic anaplasmosis [12,13]. In contrast Mild to moderate babesiosis effectively respond to a 7 to 10 day course of oral azithromycin and atovaquone which has been found to be superior to clindamycin and quinine due to the tolerability profile [14]. Various other drug combinations have also been used for treatment such as atovaquone, azithromycin, and clindamycin or atovaquone, clindamycin and artemisinin although none of these regimens have been shown to be superior in comparison to each other [15]. In the case of immunocompromised individuals who are at risk relapsing *Babesia*-treatment for a total of six weeks is preferred including a period of two weeks after parasites are no longer visible on thin smear [15].

Partial or complete Erythropheresis (red blood cell exchange) should be considered in patients with high-grade parasitemia (>10%) with active hemolysis (Hb<10). 90% reduction should be targeted by exchanging 2.5 times the patient red blood cell volume. Cases with severely complicated babesiosis such as pulmonary, renal or hepatic dysfunction should also receive early erythropheresis as it may prevent further complications such as DIC, acute renal failure or acute respiratory failure [16]. After initial erythropheresis, our patient did not have an adequate response with only a 40% reduction in parasitic load, therefore, requiring a second session with significant improvement in her parasitic load as well as her symptoms. Patients

diagnosed with any one of the tick-borne pathogens should always be screened for other tick-borne illness especially if there is no significant response to treatment within 48 hours or if cases have unexplained leukopenia, thrombocytopenia, and anemia. Early treatment should include doxycycline to cover Lyme and anaplasmosis empirically. Atovaquone and azithromycin can be added if the patient has mild to moderate uncomplicated babesiosis. Early erythropheresis should be considered for individuals with severe babesiosis or concomitant pulmonary, renal or hepatic dysfunction.

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