CASE REPORT

Pancytopenia in Lyme disease

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SUMMARY

We present a 49-year-old man with subacute onset of fever, weakness, shortness of breath, unilateral lower extremity oedema and pancytopenia who was found to have positive serology for Lyme disease. The patient presented with an intravascular haemolytic pattern on laboratory findings where an extensive infectious disease and haematological workup ruled out ehrlichiosis, anaplasmosis, babesiosis, Rocky Mountain spotted fever, HIV, hepatitis B and other parasitic infections. This left a very atypical presentation of Lyme disease.

BACKGROUND

Lyme disease is a tick-borne illness due to an infection with *Borrelia burgdorferi*, a spirochetal bacterium that is transmitted by a cutaneous tick bite, specifically *Ixodes scapularis* or 'deer tick'.¹ In order for infection to occur, the tick must typically remain attached to the skin for more than 36–48 h.^{1 2}

B burgdorferi is the most common vector-borne illness in the USA, with incidence peaking in the summer months of May through August.^{2–6} Geographically, the predominance of cases occur in northeastern USA, though other coastal areas have reported cases of infection.^{3 6 7}

There are three stages of clinical manifestations in Lyme disease.^{1 3 4 8 9} Stage 1 occurs within weeks after infection and patients often report a 'flu-like' illness, lymphadenopathy and the classical erythema migrans (EM) rash, that is, an erythematous patch with a central clearing.^{1 7 10–12} Stage 2 occurs within weeks to months after infection and presents with more systemic involvement; patients may experience migratory arthralgias, myalgias, cranial nerve palsies and atrioventricular-node heart block, along with general systems of fatigue, malaise and multiple EM lesions.^{1 8 9 11 13–15} Stage 3 occurs months to years after infection and classically presents with a recurrent monoarthritis or oligoarthritis of the large joints, polyneuropathy, neurological manifestations and an acrodermatitis chronica atrophicans skin rash.^{1 8 10 11 13}

Despite the fact that patients may present with diffuse symptoms as described above, pancytopenia, haemolytic anaemia and lower extremity oedema are very rare manifestations of Lyme disease.

We present a 49-year-old Caucasian man who presents with a subacute course of fatigue, shortness of breath, weakness and unilateral lower extremity oedema, who was found to have pancytopenia, with positive serology for Lyme disease.

In this case study, we are aiming to acknowledge and establish an association of pancytopenia with Lyme disease and ultimately provide a medical

framework for both the diagnosis of this condition with an atypical initial presentation and inclusion of this rare correlation in the formulation of the differential diagnosis.

CASE PRESENTATION

A 49-year-old man with a medical history significant for alcohol abuse was brought in by ambulance to the emergency department (ED) with 10 days of constant fevers, chills, generalised weakness and unilateral lower extremity swelling over the preceding week. The patient had been experiencing fevers as high as 104 F along with nausea and vomiting that had occurred intermittently. He endorses feeling confused with dizziness and decreased 'endurance', describing how it takes him nearly 40 min to walk a distance that he could previously walk in 10 min at his baseline level of functioning. He also has noticed that his urine has appeared 'whiskey-coloured' during this time but with no increased or painful urination. His last drink of alcohol was the night prior to admission when he drank close to 10 cans of beer.

The patient had been recently admitted to the intensive care unit (ICU) the week prior to this admission with symptoms of fevers and pancytopenia, but left against medical advice the next day, after being transferred to the general medicine floor.

On presenting to the ED, his vitals showed a temperature of 102.6 F, pulse 100 bpm, respiratory rate 20/min, blood pressure 96/58 mm Hg and oxygen saturation 98% on room air.

His family history was not significant. Social history was significant for alcohol abuse, close to 12 cans of beer per day. The patient denied any recreational drug use, but did endorse smoking close to 1/2 pack of cigarettes per day. He also denied any sick contacts or recent travel, though he admits that he has spent a considerable amount of time in the woods, often remaining there for a significant portion of the day before returning home.

Physical examination was significant for dry mucous membranes, an II/VI systolic murmur at the left lower sternal border without radiation that increased on expiration, and 1+ pitting oedema of left leg to the mid-calf. The lung fields were clear to auscultation bilaterally with no signs of respiratory distress or accessory muscle use. There was slight splenomegaly appreciated on abdominal exam, with splenic tip palpated in right-lateral decubitus position. Dorsalis pedis and radial pulses were 2+ bilaterally, with skin warm and well perfused. Cranial nerves II–XII were intact with no sensory deficits. Strength was 5/5 for upper and lower extremities bilaterally. The patient

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demonstrates a constricted affect with intact perception, speech and cognition.

Investigations

An EKG, chest X-ray and non-contrast head-CT were obtained in the ED, and the patient was given vancomycin 1000 mg intravenously once and Zosyn 3.375 g intravenously once. He also received acetaminophen 650 mg once and 1 L intravenous normal saline. A urine toxicology screen was carried out and found to be negative. Blood and urine cultures were also obtained in the ED and were negative. The patient's haemoglobin and haematocrit was found low at 7.2 g/dL and 22.1% and he was typed and screened and given 1 unit of packed red blood cells (RBCs) with an appropriate response. Mean corpuscular volume was found to be elevated at 99, with normal B₁₂, folate and thyroid-stimulating hormone on prior admission.

EKG findings include sinus tachycardia, borderline left axis deviation and QTc 491. Lactic acid was found to be elevated at 2.8 mmol/L along with elevated aspartate aminotransferase (255 U/L) and alanine transaminase (302 U/L). Given the presence of two positive SIRS criteria (temperature >100.4 F and heart rate >90) in the presence of lactic acidosis and relative hypotension, the patient was transferred to the ICU.

While in the ICU, the patient responded to fluids resuscitation and his lactic acidosis resolved. The fever did not resolve with one-time dose of both Zosyn and vancomycin. Therefore a CT of the chest/abdomen/pelvis was obtained to rule out occult infection. An infectious disease consult was also consulted, and given the patient's history of spending a significant time in the woods, a workup for possible parasitic cause of haemolysis and fever was recommended and initiated.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis at this point includes Lyme disease, Rocky Mountain spotted fever, ehrlichiosis/anaplasmosis, babesiosis, leptospirosis, reactivation of parvovirus secondary to excessive alcohol use and immunocompromised state, severe malnutrition, infective endocarditis and congestive heart failure.

OUTCOME AND FOLLOW-UP

The patient began to spike fevers within the next few days following admission. Chest CT demonstrated bilateral pleural effusions, bibasilar atelectasis and diffuse pattern of interstitial disease in lower lobes. CT of abdomen and pelvis showed ascites and bowel wall oedema with portal and pericholecystic fluid. A transthoracic echocardiogram was also performed to rule out endocarditis, but did not show any valvular vegetation. Given the patient's asymmetric lower extremity oedema, a bilateral Doppler ultrasound was ordered, but showed no evidence of deep vein thrombosis.

His initial haematocrit was 22.1% on admission. An anaemia workup was begun, showing normal serum iron (84 µg/dL), decreased total iron binding capacity (232 µg/dL), normal transferrin saturation (36%) with a decreased transferrin (169 mg/dL), elevated lactate dehydrogenase (627 U/L), reticulocytosis (6.9%), elevated erythrocyte sedimentation rate (86 mm/h), low haptoglobin (<10 mg/dL) and increased urobilinogen (4 mg/dL).

White cell count was initially $2.3 \times 10^3/\mu\text{L}$, but trended up to normal values at discharge. RBC blood cell distribution width was elevated at 17.3% on admission and remained elevated. Platelets were low throughout the hospital course but increased to a normal value of $211 \times 10^3/\mu\text{L}$ on discharge. Haematocrit trended up to 30.8% on discharge.

Given likely suspicion for tick-borne illness per the history and anaemia labs, further laboratory studies and serologies were ordered. Laboratory results were significant for positive Lyme ELISA, a negative Babesia smear, positive Parvovirus IgG, negative Ehrlichiosis/Anaplasmosis serology and negative HIV 1 and 2 antibody. A Lyme western blot was ordered, along with serology for Babesia.

The patient was started on doxycycline 100 mg orally twice daily, given positive Lyme serology and negative blood smear for Babesia. His symptoms significantly improved on day 2 of Doxycycline; he expressed being able to walk down the hospital corridor without any significant fatigue, although remarking he was not yet back to his baseline level of functioning. His haematocrit steadily increased over the course of the next few days. Lyme western blot returned as positive with three bands present on IgM. Babesia serology was positive for IgG.

After confirming the diagnosis of Lyme disease, the patient was given treatment with doxycycline for a total of 14 days, and ultimately his symptoms all resolved, as did his laboratory values. He was scheduled to follow-up with a haematologist within a week of discharge.

DISCUSSION

Despite the well-documented haematological finding of haemolytic anaemia as a manifestation of tick-borne illnesses,¹⁶ specifically babesiosis due to infection by *I. scapularis* vector, anaemia and particularly pancytopenia are rare findings associated with Lyme disease. Our case demonstrates a peculiar presentation of a common infection and highlights the inherent difficulty in diagnosing this condition with a vague constellation of signs and symptoms, atypical from the classic course. This certainly provides perspective on clinical decision making, as a pattern of haemolysis would point the clinician down a different diagnostic road, possibly considering other infectious tick-borne diseases such as babesiosis, anaplasmosis and ehrlichiosis as the more feasible aetiology. In our case, the sheer presence of anaemia with an intravascular pattern of haemolysis, and other clinical findings of heart failure, prompted a broader differential diagnosis. As a result, this could have resulted in delayed treatment and further progression of the underlying disease, which could carry a poorer prognosis.

There has been speculation as to whether the infectious agent of Lyme disease, *B. burgdorferi*, houses the potential to induce haemolysis and mimic the normocytic anaemia seen in other tick-borne illnesses. The answer to this question came through the finding of the oxygen-labile haemolysin enzymes present in certain strains of *B. burgdorferi* that are also associated with certain strains of leptospirosis.¹⁷ The presence of a *Borrelia* haemolysin gives credence to its likely involvement in rare cases of haemolytic anaemia in advanced stages of Lyme disease and excludes the need for further explanation of this crucial laboratory finding.¹⁷

Furthermore, there must be a high index of clinical suspicion for coinfection, particularly in endemic areas. Given that the *I. scapularis* vector transmits babesiosis, Lyme disease and human granulocytic anaplasmosis (HGA), a comprehensive workup must be performed to effectively narrow down the aetiological microbe.¹⁸ There have been findings of pancytopenia in the clinical setting of Babesia and Lyme coinfection, with a predominance of anaemia and borderline neutropenia/thrombocytopenia.¹⁸ Also, although the smear was negative in our patient, it does not rule out that he still may have a coinfection with Babesia since blood smears could be negative in cases with low levels of parasitemia. The important question here would have

been to assess the timeframe in which the patient had a potential contact with a vector. However, after several attempts to clarify this, the patient was not able to give us a reliable answer. One particular study examined the significant haematological findings in HGA in patients who were originally, or at some point in the diagnostic workup, considered to have Lyme disease.¹⁸ Despite overlapping features between these two diseases and the shared vector of transmission, HGA was more commonly associated with leucopenia, lymphopenia and thrombocytopenia ($p < 0.01$).¹⁸ However, a significant amount of patients culture confirmed for HGA, ranging from 2.3% to 10% ($p < 0.001$) were simultaneously diagnosed with Lyme disease, making the distinction even more difficult.¹⁹

Consequently, in light of the aforementioned findings and enlightening research on this topic, we stress the inclusion of haematological findings, such as isolated anaemia and ranging to pancytopenia, in the consideration of clinical manifestations of Lyme disease. Further investigations are warranted to establish the definite pathophysiology of this rare complication. Furthermore, it is important to remember that in some cases with Lyme disease, a concomitant infection could also develop and thus complicate the clinical course. A history of tick-bites or recent exposure to tick-carrying animals in the wilderness setting, should always prompt an investigation of these tick-borne illnesses, regardless of symptom presentation, since, as seen in our case, the manifestations can be very atypical.

Learning points

- Lyme disease can present atypically without the classic erythema chronicum migrans rash and have a predominance of non-specific symptoms that mimics other tick-borne illnesses or systemic inflammatory diseases.
- Pancytopenia, though rare, is a possible laboratory finding of Lyme disease.
- In cases of Lyme disease, there must be a high index of clinical suspicion for coinfection, particularly in endemic areas.
- Clinical acumen is crucial in the diagnosis of tick-borne illnesses, as any length of delay in antimicrobial therapy can result in neurological and haematological sequelae that are often difficult to manage and carry a poorer prognosis.

Contributors All authors have seen and approved the manuscript and contributed significantly to the work.

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