A 46-year-old man presented to the emergency department in early September after an episode of presyncope. He had also been experiencing fever, headaches, myalgias, and fatigue for 2 weeks. His medical history was significant for diet-controlled type 2 diabetes. He was not taking any medications or supplements. The patient was from the Upper Midwest and had recently been hiking and camping several times throughout the summer. He endorsed multiple mosquito bites but denied any tick exposure. He had no international travel within the past 10 years and denied any recent travel outside the Midwest.

Vital signs on presentation were as follows: temperature, 98.2°F; blood pressure, 100/56 mm Hg; pulse rate, 32 beats/min; respiratory rate, 14 breaths/min; and oxygen saturation, 99% on room air. On general examination, he was alert and well appearing. Cardiovascular examination revealed bradycardia; no murmurs or peripheral edema was noted. Skin examination revealed 2 homogeneous erythematous patches, one located on the posterior aspect of the right knee and the other in the left axillary region. Pulmonary, abdominal, neurological, and musculoskeletal examinations were unremarkable.

An electrocardiogram (ECG) revealed new complete heart block with a wide QRS escape rhythm with a heart rate of 30 beats/min. Laboratory evaluation revealed the following (reference ranges presented parenthetically): hemoglobin level, 13.9 g/dL (13.2–16.6 g/dL); leukocyte count, 9 ((3.4–9.6)×10^9); thyroid-stimulating hormone level, 5.3 mIU/L (0.3–4.2 mIU/L); and free thyroxine level, 1.5 (0.9–1.7 ng/dL). Chest radiography results were normal.

The patient was admitted to the hospital for management of complete heart block.

1. Which one of the following pathological processes is most likely involved in this patient’s complete heart block?
   a. Tick-borne infection
   b. Sarcoidosis
   c. Myocardial ischemia
   d. Age-related fibrosis of the conduction system
   e. Native valve infective endocarditis

This patient is relatively young and had no history of cardiac disease. He had a history of multiple hiking trips in a Lyme disease endemic area; thus, the most likely pathological process causing complete heart block is a tick-borne infection. Lyme disease is the most common tick-borne disease in the United States. It is caused by the spirochete *Borrelia burgdorferi*, which is mostly transmitted to humans by the *Ixodes scapularis* tick. On physical examination, the patient had 2 homogeneous erythematous lesions consistent with erythema migrans (EM), which is the most common sign of Lyme disease observed in 85% of patients. Many patients with Lyme disease do not recall a tick bite. A thorough examination of the patient’s skin is essential to help make the appropriate diagnosis. Although EM lesions are classically described to have central clearing, as many as two-thirds of the lesions are uniformly erythematous and may not have the “classic” central clearing bull’s-eye appearance. Erythema migrans usually begins as a small macule or papule approximately 1 to 2 weeks after the tick bite at the site of attachment. Approximately 80% of patients develop 1 skin lesion. However, the bacteria can disseminate hematogenously to other skin sites and multiple EM lesions can be present as seen in this patient.

Sarcoidosis involves deposition of noncaseating granulomas typically in the lungs,
though it can affect any organ system. In the United States, it is more common in Black individuals. Cardiac involvement is found in 25% of patients, and the clinical presentation depends on the location of granuloma deposition, either in the conduction system or in the myocardium. This patient did not have systemic features to suggest sarcoidosis, such as hilar lymphadenopathy or hypercalcemia, and the presence of EM is not characteristic of sarcoidosis. Sarcoidosis should always be considered in the differential diagnosis of a young patient presenting with complete heart block once other causes such as Lyme disease are excluded.4

Myocardial ischemia is less likely in a young patient who is an active hiker with no history of cardiac disease or exertional chest pain. His main cardiac risk factor is type 2 diabetes. He had no history of hyperlipidemia, smoking, or recreational drug use. This diagnosis is less likely in the setting of constitutional symptoms and rash. Age-related fibrosis of the conduction system would be a more likely cause of complete heart block in an older patient, in whom age-related scarring and/or calcification would be the most common cause. Congenital heart block is also in the differential diagnosis for complete heart block. It is however highly unlikely in this case given the age of the patient and the lack of genetic disease history.

Native valve infective endocarditis is uncommon, with an incidence of 2 to 10 cases per 100,000 person-years. The patient did have intermittent fever, which would only fulfill 1 minor clinical criterion from the modified Duke criteria. He did not have a heart murmur or any vascular or immunological phenomena that could be seen with endocarditis. Additionally, complete heart block would be an infrequent complication of infective endocarditis resulting from paravalvular extension of infection.5

On the basis of his clinical presentation, medical history, and environmental risk factors, the leading differential diagnosis for this patient’s complete heart block was Lyme carditis. To evaluate for any structural heart disease, the patient had a transthoracic echocardiogram, which revealed normal biventricular systolic function with no regional wall abnormalities. He also had no valvular disease.

2. Which one of the following tests is most likely needed to secure the diagnosis?
   a. Borrelia burgdorferi blood culture
   b. Urinary antigen testing
   c. Two-tier testing with enzyme-linked immunosorbent assay (ELISA) and Western blot
   d. Polymerase chain reaction (PCR) to detect serum borrelial DNA
   e. Polymerase chain reaction testing of skin biopsy

Recommendation for testing in Lyme disease is based on the stage of disease and clinical pretest probability. Available tests can be subdivided into direct and indirect methods of detection. Direct methods include PCR and Borrelia culture, which detect the spirochete. Indirect methods include ELISA and Western blot, which detect antibodies.1 Borrelia burgdorferi blood culture is not a routinely available diagnostic method for Lyme disease; it has low sensitivity and long incubation period and requires a special growth medium. Ability to grow B burgdorferi is present in select research laboratories.6

Urinary antigen testing is not a recommended test for the diagnosis of Lyme disease. The accuracy and clinical utility have not been established.6

Antibody testing in the early localized stage of Lyme disease is insensitive as IgM antibodies can take 1 to 2 weeks to develop, followed by IgG antibodies in 2 to 4 weeks. This patient however presented in the early disseminated stage of Lyme disease, evidenced by cardiac disease manifesting as complete heart block. At this stage, the recommended testing is 2-tier testing with ELISA and Western blot, which detect various anti-Borrelia antibodies.

Polymerase chain reaction to detect serum borrelial DNA may be helpful in early infection before antibody response develops or in the setting of reinfection as antibodies may persist for a period of time after...
infection. The sensitivity of PCR for detection of borrelial DNA varies with the source of the sample. Polymerase chain reaction testing is most helpful in patients with Lyme arthritis as PCR of the synovial fluid has a sensitivity of up to 80%. Polymerase chain reaction testing of the serum has a much lower sensitivity.

Polymerase chain reaction testing of skin biopsy of an EM lesion is also possible with a sensitivity of approximately 70%. These methods would not be recommended in this patient who would be expected to have mounted an antibody response. The standard 2-tier testing would be the test of choice. The patient’s screening ELISA test was positive for Lyme disease. A confirmatory Lyme disease Western blot was positive for IgM antibodies.

3. Which one of the following is the most appropriate initial antibiotic choice and appropriate time to initiate treatment for this patient?
   a. Azithromycin after confirmatory laboratory testing
   b. Intravenous (IV) ceftriaxone before confirmatory laboratory testing
   c. Intravenous ceftriaxone after confirmatory laboratory testing
   d. Doxycycline before confirmatory laboratory testing
   e. Doxycycline after confirmatory laboratory testing

Borrelia burgdorferi is susceptible to antibiotics from several different classes. The most used include doxycycline, amoxicillin, ceftriaxone, and azithromycin. The antibiotic choice can be based on drug allergy, adverse effect profile, and likelihood of coinfection with other tick-borne illness.

Answer choice "a" would be inappropriate because azithromycin, a macrolide antibiotic, is considered a second line option owing to lower efficacy.7

Intravenous ceftriaxone before confirmatory laboratory testing is the most appropriate for this patient who is hospitalized in the setting of complete heart block. Given the high suspicion for Lyme carditis, treatment should be initiated before confirmatory laboratory testing, which can take several days to result. Answer choice "c" includes the appropriate antibiotic choice but the wrong time to initiate therapy.

In patients with Lyme carditis who are managed in the outpatient setting, initial therapy would be oral antibiotics, preferably doxycycline. Answer choices "d" and "e" are not the best option, as the current guidelines recommend IV ceftriaxone as initial therapy for hospitalized patients. Our patient met the criteria for hospitalization on the basis of having symptomatic complete heart block. He was initiated on IV ceftriaxone on presentation, before any confirmatory laboratory testing.

The recommended duration of therapy for Lyme carditis is 14 to 21 days. Patients who are initially treated with IV antibiotics can be transitioned to oral antibiotics once there is evidence of clinical improvement to complete 14 to 21 days of therapy. This patient was transitioned to oral doxycycline after 4 days of IV ceftriaxone to complete a total of 21 days of therapy.

4. Which one of the following is the best immediate management strategy for this patient?
   a. Antibiotics and outpatient follow-up
   b. Holter monitor, antibiotics, and outpatient follow-up
   c. Placement of a temporary pacemaker and antibiotics
   d. Placement of a permanent pacemaker and antibiotics
   e. Inpatient cardiac monitoring and antibiotics

The current guidelines recommend hospitalization, not outpatient follow-up, for patients with Lyme carditis at risk of severe cardiac complications. This includes individuals with first-degree heart block and PR interval 300 milliseconds or greater, individuals with second- or third-degree block, or clinical manifestations of myopericarditis. Answer choices "a" and "b" are not appropriate as this patient met criteria for hospitalization given third-degree block.
Placement of a temporary pacemaker and antibiotics is the best option. The indications for the placement of a temporary pacemaker in patients with Lyme carditis include high-grade second- or third-degree atrioventricular (AV) block with symptoms and/or hemodynamic instability. This patient presented with symptomatic third-degree or complete heart block, which is an indication to receive temporary pacing by standard transvenous pacing. The appropriate treatment would also include antibiotics to treat the cause of AV block.

Answer choice "d" would be inappropriate as placement of a permanent pacemaker is not indicated as initial treatment of AV block in Lyme carditis. AV block is usually transient in nature and expected to resolve with appropriate antibiotic therapy. Permanent pacing is not warranted unless AV block does not resolve with antibiotics.

Inpatient cardiac monitoring and antibiotics is insufficient treatment for this patient who met criteria for placement of a temporary pacemaker. The patient had a temporary pacemaker placed within 3 hours of admission to the hospital. He was also initiated on IV ceftriaxone for a suspected diagnosis of Lyme carditis.

5. Which one the following is the most likely outcome of this patient’s disease?
   a. Self-limited illness
   b. Persistent arthritis
   c. Posttreatment Lyme disease syndrome
   d. Persistent cardiac disease
   e. Death

Self-limited illness is the most likely outcome for this patient. Most patients with Lyme disease who receive appropriate antibiotic therapy are cured with no residual symptoms.

A manifestation of late disseminated Lyme disease is arthritis, which typically presents as oligoarthritus or monarthritus often affecting the knee, 3 to 6 months after infection. With appropriate antibiotic therapy, joint pain typically resolves. Ten percent to 20% of patients may develop persistent joint pain. This patient did not complain of arthralgias, and he was appropriately treated with antibiotics, so he is unlikely to have persistent arthritis after treatment.

Posttreatment Lyme disease syndrome is characterized by certain lasting symptoms experienced by a subset of patients who had Lyme disease. The diagnostic criteria include documented episode of Lyme disease that has been treated with an appropriate regimen, onset of subjective symptoms within 6 months of the diagnosis that persist for at least 6 months after completion of antibiotic therapy, and symptoms that include fatigue, widespread musculoskeletal pain, and cognitive difficulties. Posttreatment Lyme disease syndrome is not the most likely outcome as only 5% to 10% of patients have persistent symptoms.

Persistent cardiac disease is not likely. High-grade AV block typically resolves within the first 10 days of antibiotic therapy.

The prognosis for treated Lyme carditis is favorable. Death is not the most likely outcome as mortality is rare in patients with Lyme carditis who are treated.

He had a temporary pacemaker placed. Three days later, his ECG revealed first-degree AV block, with very infrequent pacing noted on telemetry. The temporary pacemaker was removed 4 days after placement. An ECG obtained at follow-up 10 days later disclosed complete resolution of AV block. He completed his course of oral antibiotics in the outpatient setting.

DISCUSSION

Lyme disease is the most common vector-borne disease in the United States. It is caused by the spirochete *B. burgdorferi*, which is mainly transmitted to humans by the *Ixodes scapularis* tick (deer tick) when it ingests a blood meal. Most cases occur in the northeastern, mid-Atlantic, and Upper Midwest regions.

The most common sign of Lyme disease is an EM rash. A clinical diagnosis of Lyme disease can be made on the basis of the presence of characteristic rash and history of potential exposure to ticks in an endemic area. Some patients will present later in their disease course with cardiac or neurological symptoms.
manifestations. The standard laboratory testing is ELISA followed by a confirmatory Western blot. Antibody testing may be negative in the early phase of the disease; however, after the development of extracutaneous manifestation, the sensitivity of the test increases.

Lyme carditis is a manifestation of early disseminated infection. Atrioventricular block is the most common presentation seen in approximately 90% of cases. Lyme carditis should be in the differential for patients presenting with complete heart block, especially younger patients with no cardiac history. If a patient in the neonatal period or early childhood, congenital heart block should be suspected. Up to one-third of patients with Lyme carditis require temporary pacing for the management of symptomatic bradycardia or high-risk electrocardiographic features. In most cases, AV block resolves with appropriate antibiotic therapy. The initial recommended therapy for hospitalized patients with Lyme carditis is IV ceftriaxone. Intravenous antibiotics should be continued until there is evidence of clinical improvement. The preferred oral antibiotic for nonpregnant adult patients is doxycycline. The recommended duration of therapy is 14 to 21 days.

Potential Competing Interests: The authors report no competing interests.

REFERENCES

CORRECT ANSWERS: 1. a. 2. c. 3. b. 4. c. 5. a.