A 72-year-old man presented to the emergency department during the summer with a 3-week history of cyclic fever, malaise, and fatigue. During this time, he had temperatures as high as 39.4°C daily, usually in the evening, with associated night sweats and chills. He concurrently experienced diffuse, nonfocal weakness and loss of appetite. He presented to the emergency department after an episode of light-headedness with findings of hypotension (systolic blood pressure of 80 mm Hg) on his home blood pressure system.

His medical history was notable for superficial melanoma of the left cheek treated with a Mohs surgical procedure, diabetes mellitus, chronic kidney disease, hypertension, gout, and primary hyperparathyroidism after parathyroidectomy.

On review of systems, the patient reported no headache, cough, upper respiratory tract symptoms, nausea, vomiting, diarrhea, dysuria, joint pain or swelling, rash, or neck pain. Furthermore, he had no sick contacts, recent travel, or new exposures other than spending more time outside recently. The patient lived in a rural wooded area in the Upper Midwest and had spent a substantial amount of time outdoors for his hobbies over the summer months. Incidentally, he disclosed that he intentionally lost over 45 kg during the past year with an online dieting service.

In the emergency department, he was found to be febrile (temperature of 38.3°C) and mildly tachycardic. Blood pressure was 90/46 mm Hg. There were no focal findings on physical examination with the exception of mild splenomegaly.

Initial laboratory tests revealed the following (reference ranges provided parenthetically): hemoglobin, 11.1 g/dL (13.5-17.5 g/dL); white blood cell count, 2.3×10⁹/L (3.5-10.5×10⁹/L); absolute neutrophil count, 1.79×10⁹/L (1.70-7.00×10⁹/L); platelet count, 57×10⁹/L (150-450×10⁹/L); reticulocyte count, 26.1×10⁹/L (38.1-112.6×10⁹/L); aspartate aminotransferase, 42 U/L (8-48 U/L); alanine aminotransferase, 48 U/L (7-55 U/L); alkaline phosphatase, 103 U/L (45-115 U/L); total bilirubin, 1.1 mg/dL (0.1-1.2 mg/dL); direct bilirubin, 0.5 mg/dL (0.0-0.3 mg/dL); and C-reactive protein, 61 mg/L (≤8 mg/L). On peripheral smear, no organisms or schistocytes were seen.

1. Which one of the following pathologic processes is most likely in this patient?
   a. Viral infection
   b. Fungal infection
   c. Community-acquired bacterial infection
   d. Tick-borne bacterial infection
   e. Autoimmune disorder

The patient’s signs and symptoms include 3 weeks of cyclic fever, chills, and malaise, hypotension, mild splenomegaly, and pancytopenia. The time line and lack of sick exposures, rash, upper respiratory tract symptoms, or focal lymphadenopathy make a viral infection unlikely in this case. Likewise, a fungal infection is unlikely because the organs typically involved (central nervous system with fungal meningitis, respiratory system with Aspergillus or Pneumocystis, skin, sinus, and ocular) were not involved, and the patient did not have sufficient risk factors (human immunodeficiency virus [HIV] infection/AIDS, poorly controlled diabetes, poor hygiene, known immunocompromise) that would place him at risk for a fungal infection. Because there were no focal findings such as respiratory consolidation, focal pain, or rash, a community-acquired bacterial infection is less likely. Furthermore, a community-acquired bacterial infection would not explain the cyclic fever or the systemic symptoms of malaise, fatigue, splenomegaly, and pancytopenia in this case. A tick-borne bacterial infection would be most likely in this case given that the patient had spent more time outside recently and had a cyclic pattern of fevers, night sweats, fatigue, and malaise in combination with his laboratory findings of pancytopenia. With an autoimmune process, a characteristic rash, joint pain, or more...
substantial C-reactive protein elevation would be expected.

Further questioning revealed numerous tick exposures during the past month. A tick-borne disease panel was performed. At Mayo Clinic, exposure to tick-borne illnesses is tested by performing antibody and DNA tests on samples of the patient’s blood. These panels test for Lyme serology as well as Ehrlichia, Anaplasma, and Babesia by default. The results for this patient were negative for Lyme disease screening, Anaplasma phagocytophilum, Babesia titers and polymerase chain reaction (PCR), and Ehrlichia ewingii, Ehrlichia chaffeensis, and Ehrlichia muris—like titers and PCR and positive for Ehrlichia chaffeensis titer and PCR. Ehrlichia is an obligate intracellular gram-negative species of Rickettsiae bacteria. Of note, during the first week of infection, peripheral blood smear may reveal morulae (microcolonies of ehrlichiae) in leukocytes in up to 20% of patients. Although our patient’s peripheral smear did not reveal morulae, this does not rule out the diagnosis.

2. Which one of the following is the most appropriate treatment for the pathologic process in this patient?
   a. Erythromycin
   b. Ciprofloxacin
   c. Streptomycin
   d. Ertapenem
   e. Doxycycline

   Erythromycin is a macrolide antibiotic that is used to treat bacteria responsible for causing infections of the skin and upper respiratory tract including Streptococcus, Staphylococcus, and Haemophilus genera and is often used in persons with penicillin allergies; it is not the most appropriate choice for Ehrlichia. Ciprofloxacin is a fluoroquinolone antibiotic that has gram-negative and weak gram-positive activity and is used broadly for dermatologic, respiratory tract, urinary tract, and gastrointestinal tract infections. It is not the most appropriate choice of treatment for Ehrlichia. Streptomycin is an aminoglycoside best known for its effectiveness against Mycobacterium tuberculosis and Yersinia pestis. It would not be an appropriate choice for treatment of Ehrlichia. Ertapenem is a broad-spectrum carbapenem that is typically used to treat infections caused by multidrug-resistant organisms, and its use would not be appropriate in this case because it would not represent a judicious use of antibiotics. Erythromycin, ciprofloxacin, streptomycin, and ertapenem are not known to be effective against Ehrlichia.

Doxycycline is a tetracycline effective against Ehrlichia. The appropriate treatment duration is a matter of debate in the literature, but most patients should begin responding to the antibiotic in 24 to 48 hours, making a 10-day course effective. There are rare cases of patients requiring 14- to 21-day courses to eradicate the organism, but given that most patients respond in a day or 2, a 10-day course would be the most appropriate choice in this case.

The patient was given a 10-day course of doxycycline and discharged from the hospital. However, he continued to have cyclic fevers with night sweats, and his symptoms of malaise and fatigue did not improve despite completion of the 10-day course. He was readmitted to the hospital because of his ongoing symptoms. A repeated DNA tick panel, including Ehrlichia PCR, yielded negative results, indicating adequate treatment of his ehrlichiosis.

3. At this time, which one of the following would be the most informative test for diagnostic purposes?
   a. Abdominal radiography
   b. HIV testing
   c. Hepatitis serologies
   d. Positron emission tomography—computed tomography (PET-CT)
   e. Mycobacterial testing

Abdominal radiography would yield limited information in this case. It may provide information about bowel distention, but the patient was not complaining of abdominal pain or gastrointestinal symptoms. An HIV test would also yield limited information in that if results are positive, it would only indicate that the patient is at risk for immunocompromise. Further testing would be necessary to determine if an AIDS-defining illness was present. If findings are negative, it would provide no further information. Hepatitis serologies would be useful in this case to rule out hepatitis. The results of the patient’s liver function tests were only mildly elevated.
making acute infectious hepatitis unlikely. In view of the patient’s continuing cyclic night sweats, fevers, and fatigue, notable weight loss, and personal history of melanoma, PET-CT would provide the most information about the presence and extent of an underlying malignant neoplasm. The patient has minimal risk factors for tuberculosis, so the likelihood of identifying a mycobacterial infection is minimal.

The patient underwent outpatient PET-CT. The imaging revealed diffuse enlargement of the spleen and mild fluorodeoxyglucose accumulation. There was also diffuse increased mild fluorodeoxyglucose uptake throughout the axial and proximal appendicular skeleton. Of note, PET-CT results should be interpreted with caution because incidental findings are not uncommon. At this point, the patient continued to be symptomatic with cyclic fevers, chills, and malaise. Further work-up was planned given the findings and the patient’s desire to identify an etiology for his symptoms.

4. Which one of the following is the most appropriate next step in management for this patient?
   a. Bone marrow biopsy
   b. Observation and supportive care
   c. Lymph node biopsy
   d. Extended course of antibiotic coverage
   e. Palliative consultation

   Given the splenic uptake on PET-CT, a lymphoproliferative disorder was suspected. The most appropriate test for work-up would be a bone marrow biopsy. Because the patient was interested in pursuing an etiology for his symptoms, observation and supportive care would be inappropriate. PET-CT did not identify any suspicious areas of lymphadenopathy other than the spleen and axial skeleton, nor had any been defined on previous physical examinations. A lymph node biopsy would be difficult to perform, and the diagnostic yield would likely be low. The patient had completed a 10-day course of doxycycline. Continuation of the antibiotic would be inappropriate because the repeated tick-borne disease panel had confirmed eradication of the Ehrlichia DNA. Palliative consultation would also be inappropriate because the patient expressed interest in further work-up of his disease process.

   Bone marrow biopsy results for this patient were not concerning for lymphoma or leukemia. Given his ongoing symptoms and PET-CT findings, the decision was made to pursue a diagnostic splenectomy.

5. As a result of undergoing splenectomy, which one of the following immunization regimens is most important for this patient?
   a. Hepatitis A and hepatitis B
   b. Hepatitis A, hepatitis B, and influenza
   c. Pneumococcal, meningococcal, and Hae-mophilus influenzae
   d. Herpes zoster
   e. Pneumococcal and influenza

   Hepatitis A and B vaccines are important parts of pediatric vaccine schedules and should also be provided for people at high risk of contracting these viruses. Because hepatitis A is spread by the fecal-oral route, risks include travel and work in the food industry. Adults at risk for the hepatitis B virus include individuals with multiple sexual partners, health care workers, and intravenous drug users. Our patient did not have these risk factors and had received these immunizations previously. It is important that individuals receive the influenza vaccine on a yearly basis, especially people with chronic illness, immunocompromise, or employment in health care facilities. Our patient had already received this vaccine, and it is important around the time of splenectomy. However, hepatitis vaccines would be unnecessary. Patients with asplenia are at risk for pneumococcal, meningococcal, and H influenzae infections because of impaired opsonization. Immunization against encapsulated bacterial organisms decreases the incidence of serious postsplenectomy infections such as sepsis. Therefore, the most important immunizations for this patient include pneumococcal, meningococcal, and H influenzae vaccines to reduce this risk. The herpes zoster vaccine is helpful in individuals older than 65 years to reduce the risk of shingles and subsequent postherpetic neuralgia. However, it is not the most appropriate choice around the time of splenectomy. Pneumococcal and influenza vaccines would be appropriate around the time of splenectomy, but meningococcal and Hae-mophilus vaccines would also be required.
The patient was given meningococcal, *H influenzae*, and pneumococcal vaccines. He had previously been vaccinated against influenza. He underwent an uncomplicated diagnostic laparoscopic splenectomy. Of note, laparoscopic splenectomies are now more frequently performed than open splenectomies because of reduced blood loss, shortened duration of hospital stays, and reduced cost. Pathologic examination of the surgical specimen revealed an immunophenotypically distinct lymphocytic population replacing the splenic white pulp and infiltrating the red pulp, consistent with a final diagnosis of splenic marginal zone lymphoma (SMZL). Flow cytometric immunophenotyping revealed monotypic (cytoplasmic) λ light chain, positive CD19 and CD20, and negative CD5, CD10, and CD23 expression. The patient’s symptoms subsequently resolved.

**DISCUSSION**

*Ehrlichiosis* is a broad term that is used generally to describe multiple bacterial diseases that may affect animals and humans. It presents with a constellation of symptoms that may include cyclic fevers, chills, malaise, myalgia, nausea, vomiting, diarrhea, and pancytopenia. Rash is more commonly seen in children than in adults and is more common with *E chaffeensis* infections. The constellation of symptoms and severity of the disease course vary from person to person, which makes diagnosis challenging. Notably, symptoms typically emerge 1 to 2 weeks after exposure.

According to the Centers for Disease Control and Prevention (CDC), cases of ehrlichiosis can occur throughout the year, but June and July are the most common months in which cases are reported. The prevalence of reporting in June and July may be due to the fact that the primary vector of the bacteria (*E chaffeensis*, *E canis*, and *E ewingii*), the Lone Star tick (*Amblyomma americanum*), is in an active life stage during the summer so is more likely to come into contact with and bite a host. In addition to a higher incidence of illness in the summer months, the CDC-reported cases indicate that males, particularly those over 50 years, are more likely to experience ehrlichiosis. Based on CDC data, the estimated case fatality is 1.8%, with immunocompromised patients having higher risk of severe outcomes. In addition to the *Ehrlichia* genus, *Anaplasma phagocytophilum* (human granulocytic anaplasmosis), *Neorickettsia sennetsu*, and a newly described *E muris*—like species have been noted to cause this constellation of symptoms.

Of note, it is possible to contract multiple tick-borne diseases simultaneously because many of the risk factors are similar to those described for *Ehrlichia*. In addition, vector organisms can carry and transmit multiple pathogens. *Babesia microti* infections, in particular, can present similarly to *Ehrlichia*. Patients may not have any symptoms or may experience fever, chills, night sweats, loss of appetite, and malaise, like the patient in this case. *Babesia* infects red blood cells and can also cause a hemolytic anemia presenting with jaundice and dark urine. Serious infections may also present with hypotension, thrombocytopenia, and consumptive coagulopathies. Clearly, there is overlap between these diseases; microbiological and molecular testing are important in determining definitive disease etiology. Of importance in this case as well, the patient would be at increased risk for subsequent infection with *Babesia* after splenectomy because the spleen helps to destroy infected red blood cells. Counseling of risks of subsequent exposure is important in these patients.

Drugs of choice for the treatment of ehrlichiosis are doxycycline or minocycline. Rifaxampin is a second-line alternative treatment option. Notably, the dose and duration of tetracycline needed to treat ehrlichiosis have not been found to cause staining of permanent teeth; therefore, the tetracyclines are the first-line course of treatment regardless of age. Although evidence from randomized controlled trials is lacking, a 10- to 14-day treatment course is generally recommended, with treatment response typically occurring within 48 to 72 hours. Conveniently, doxycycline treatment would also cover other tick-borne illnesses such as Rocky Mountain spotted fever and anaplasmosis.

Another important consideration in this case is the utility of diagnostic splenectomy in fever of unknown origin (FUO). A retrospective analysis of 54 patients undergoing splenectomy for FUO in China revealed that a diagnosis was made in 72.2% of patients. Another analysis of 15 patients with FUO from a hospital in Mexico undergoing diagnostic laparotomy revealed a diagnosis in 66% of patients, and the procedure helped to rule out other intra-abdominal pathology in 4 additional patients. A larger retrospective US study analyzed over 2000 patients...
with splenomegaly in order to determine etiology.7 The study reported that hematologic disorders were the most prevalent cause of splenomegaly in this population. The most common hematologic association was chronic leukemia. The remaining contributing pathologic processes included infectious diseases (19%), hepatic diseases (11%), congestive or inflammatory disorders (9%), and primary splenic disorders or unknown causes (4%).7

In our patient, SMZL was diagnosed after a diagnostic splenectomy. Splenic marginal zone lymphoma is a rare, indolent B-cell lymphoma in which patients can present with splenomegaly and absent lymphadenopathy, as in our patient. Characteristic features in this case included the presence of systemic B symptoms (Ann Arbor staging) and the lack of bone marrow findings, which are typically found with SMZL. An association has been reported between mantle cell lymphoma and Borrelia infection.8 Likewise, SMZL has been associated with certain infectious agents, including hepatitis C virus, Epstein-Barr virus, and malaria; however, there is no established relationship between lymphoma and ehrlichiosis in humans.9

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**REFERENCES**


**CORRECT ANSWERS:** 1. d. 2. e. 3. d. 4. a. 5. c