65-Year-Old Man With Persistent Fever

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A 65-year-old man was transferred to our institution for evaluation of fever. His symptoms included subjective fever, cough productive of creamy white sputum, and nasal congestion of 3 months’ duration. He denied dyspnea, hemoptysis, weight loss, or night sweats. Approximately 10 days before admission, he had been seen by his primary care physician for worsening of symptoms and was treated empirically with an undefined antibiotic. Subsequently, palpitations and severe fatigue developed, and the patient was admitted to a local hospital, where he was noted to be febrile and hypoxic with pulse oximetry readings in the high 80% range. Acute coronary syndrome was excluded, and ceftriaxone and moxifloxacin were initiated empirically. Computed tomography (CT) of the chest without intravenous contrast was performed. Compared with chest CT performed 4 years earlier, no new pulmonary infiltrate was evident; however, both the superior and the lateral aspect of the right hilum were more prominent than in the previous study and were suspicious for adenopathy. The patient was transferred to our institution approximately 2 days later for further evaluation.

On admission, the patient’s main symptoms were fever, fatigue, palpitations, mild chest discomfort, cough, and nasal congestion. Findings on the rest of the systems review were unremarkable. The patient had a history of asthma, chronic sinusitis, seasonal allergic rhinitis, aspirin intolerance, nasal polyposis with multiple prior polypectomies, and benign prostatic hypertrophy. His medical regimen consisted of omeprazole, atorvastatin, doxazosin, irbesartan-hydrochlorothiazide, montelukast, and fluticasone-salmeterol. His family history was notable for lung cancer of 37.9 °C, heart rate of 95 beats/min (regular), blood pressure of 149/74 mm Hg, respiratory rate of 18 breaths/min, and pulse oximetry of 94% while breathing 3 L of oxygen via nasal cannula. He appeared comfortable and had palpable anterior cervical chain and submandibular lymph nodes, jugular venous distension 3 cm above the clavicle, faint inspiratory crackles at both lung bases, and a grade 2/6 systolic murmur best heard at the apex. Findings on the rest of the physical examination were normal. Laboratory results are listed in the Table.

1. Which one of the following is the least likely explanation for the patient’s fever based on clinical presentation?
   a. Infection
   b. Connective tissue disease
   c. Sarcoidosis
   d. Malignancy
   e. Drug-induced fever

Infection was suspected because of the patient’s prolonged fever, pulmonary symptoms, hilar enlargement, leukocytosis, elevated inflammatory markers, and elevated hepatic test results. Infections mainly presenting with subacute or chronic symptoms were considered, including infective endocarditis, histoplasmosis, tuberculosis, *Mycoplasma* and *Chlamydia* infection, and rickettsial infections.

Patients with systemic lupus erythematosus (SLE) can present with fatigue, fever, anemia, thrombocytopenia, renal insufficiency, and elevated hepatic test results. Systemic lupus erythematosus does not commonly present with lymphadenopathy (seen in 2%-12% of patients with SLE at diagnosis), and our patient had no cutaneous or articular manifestations of SLE. Antineutrophil cytoplasmic antibody vasculitides may present with chronic respiratory symptoms, fever, and renal insufficiency and was suspected as a potential etiology of our patient’s symptoms. Sarcoidosis is less likely, given that it typically manifests before the age of 40 years in 70% to 90% of patients and usually presents with bilateral hilar adenopathy; reticular pulmonary infiltrates; and skin, joint, or eye lesions. Malignancy, especially hematologic malignancies, can present as a febrile illness with renal and hepatic dysfunction. Lymphoma was suspected given the patient’s history of prolonged fever, anemia, thrombocytopenia, and right hilar abnormality. His family history is notable for lung...
cancer, which can present with hilar enlargement; however, fever of unknown origin is not a common presentation.

Antimicrobials, particularly β-lactams, and anticonvulsants are responsible for most cases of drug-induced fever. After a medication has been initiated, the median time of onset of fever is 8 days, but it can vary from less than 24 hours to many months.3 Our patient’s symptoms started 3 weeks after the medication had been started, which is within the expected time frame for drug-induced fever.

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Blood cultures and a detailed autoimmune panel were negative. Chest CT with intravenous contrast showed no pulmonary embolism or evidence of a lung mass or cavitary lesion but revealed bilateral hilar and paratracheal adenopathy. Right hilar transbronchial lymph node biopsy was negative for malignancy.

Additional history was obtained. The patient had a 12-pack-year history of cigarette smoking but had quit 30 years ago. He raised beef cattle in Wisconsin and had exposure to horses, dogs, and cats, as well as exposure to sheep several years previously. The patient did not consume unpasteurized dairy products or uncooked meat. He had no known exposure to tuberculosis or recent ill contacts. The patient had not traveled outside the United States in the past several years, nor had he recently traveled to the southwestern part of the United States.

3. Which one of the following infections is least likely on the basis of the exposure history?

a. Influenza
b. Q fever
c. Histoplasmosis
d. Paracoccidioidomycosis
e. Tuberculosis

Influenza can present with cough, shortness of breath, and hypoxia, but the presence of mediastinal and hilar adenopathy makes it less likely. Acute Q fever may present with an influenza-like illness, pneumonia, or hepatitis and may cause anemia, thrombocytopenia, and lymphadenopathy.4 Chronic Q fever is a more indolent infection, lasting more than 6 months, and is typically manifested by endocarditis.4 Histoplasmosis is endemic in the Ohio and Mississippi river valleys and is the most common cause of hospitalization among the endemic mycoses.5 Patients with disseminated histoplasmosis often present with pancytopenia, hepatosplenomegaly, hepatic enzyme elevation, and oropharyngeal or gastrointestinal lesions. Paracoccidioidomycosis is a fungal infection endemic to Central and South America that is caused by Paracoccidioides brasilensis. It characteristically produces a primary pulmonary infection that is often asymptomatic and subsequently disseminates to form ulcerative granulomas of the oral, nasal, and occasionally, gastrointestinal mucosa.6 Our patient did not travel to Central or South America and thus was not at risk for this infection. Tuberculosis could explain our patient’s symptoms; however, he had no known tuberculosis contacts and did not previously live in an endemic area.

A swab specimen to test for influenza by polymerase chain reaction was negative. Serologic testing for phase II IgM antibodies was positive for Q fever, whereas tests for phase II and phase I IgG antibodies were negative. Skin
testing for tuberculosis was negative. Serologic tests for Histoplasma, Anaplasma, Ehrlichia, Chlamydia pneumoniae, and Mycoplasma pneumoniae were also negative.

4. Which one of the following therapeutic measures is **most appropriate** in this patient?

   a. Doxycycline  
   b. Penicillin G  
   c. Caspofungin  
   d. Isoniazid  
   e. Acyclovir

Doxycycline is the drug of choice for treating Q fever. This bacteriostatic agent acts by inhibition of protein synthesis. Penicillin G is active against some gram-positive bacteria, anaerobes, and selected gram-negative cocci (mainly Neisseria and Haemophilus). It has no activity against Coxiella burnetii. Caspofungin is an antifungal agent that inhibits fungal cell wall synthesis. It is used to treat aspergillosis and candidiasis. Isoniazid inhibits synthesis of mycolic acid, which is found in mycobacterial cell walls, and is first-line treatment of tuberculosis. Acyclovir blocks viral DNA synthesis and is used to treat infection due to herpes simplex virus 1 and 2.

Acute Q fever is the most probable diagnosis given the patient’s exposure to cattle; his presentation with fever, thrombocytopenia, transaminitis; and the presence of phase II IgM antibodies. Although a phase II IgG antibody would also be expected to be present after 3½ months of symptoms, it is possible that acute Q fever developed when the patient began to feel ill 10 days before admission. In that case, the phase II IgG antibody would be expected to be negative since IgM antibodies are first to appear early in the course of illness.

Treatment was initiated with 100 mg of doxycycline twice daily, for a total course of 14 days. Echocardiography was performed before dismissal to rule out Q fever endocarditis and showed normal findings. At 1-month follow-up, the patient was feeling much better; the alanine aminotransferase level had decreased to 47 U/L, aspartate aminotransferase to 38 U/L, alkaline phosphatase to 96 U/L, and erythrocyte sedimentation rate to 4 mm/h.

5. Which one of the following options would be **most helpful** to minimize chance of reinfection?

   a. Whole-cell vaccine for Q fever  
   b. Acellular vaccine for Q fever  
   c. Education on sources of infection  
   d. Test family members for C burnetii  
   e. Doxycycline prophylaxis

Whole-cell vaccine has been efficacious in preventing infection in abattoir workers in Australia. To be eligible for immunization, all workers must have negative skin and serologic test results for Q fever and have no history of Q fever. Acellular vaccine, available in the United States, is used primarily for individuals engaged in research with pregnant sheep or live C burnetii. Patients should also have negative skin and serologic test results for Q fever before receiving acellular vaccine. Educating patients who already have Q fever on sources of infection is the most effective method of preventing the spread of infection. This includes appropriate disposal of birth products and aborted fetuses from facilities that house sheep and goats, consumption of only pasteurized milk and milk products, routinely testing animals for C burnetii infection, and quarantine of imported animals. Individuals at high risk of complications of Q fever, including patients with cardiac valvulopathy, pregnant women, and vascular graft recipients, should avoid contact with livestock. Q fever is not transmitted human-to-human, and testing patient’s family members is unnecessary. Chemoprophylaxis with doxycycline should be initiated as soon as possible after exposure and before symptom onset; therefore, our patient would not be a candidate.

Before dismissal from the hospital and at the 1-month follow-up visit, our patient was educated on the prevention of Q fever.

**DISCUSSION**

Q fever is a zoonosis caused by the organism C burnetii, an obligate intracellular gram-negative bacterium. The designation Q fever (from Query) was coined in 1935 after an outbreak of febrile illness in an abattoir in Queensland, Australia. Although previously classified as a rickettsial organism, C burnetii has been placed into the subdivision of the Proteobacteria, which are closer to Legionella and Francisella than to Rickettsia. The most commonly identified sources of human infection are farm animals such as cattle, goats, and sheep.

Clinical signs of Q fever are often mild or absent. Symptomatic illness can be divided into acute and chronic forms. Of patients with acute Q fever, 40% to 60% have hepatitis; 20%, pneumonia plus hepatitis; 14% to 17%, pneumonia; and 17%, fever alone. Hepatitis develops more often in younger people, and pneumonia more often in older people, usually immunocompromised patients. Fibrin-ring granulomas, which have been associated with Q fever, may rarely be seen in the liver and bone marrow and may appear “doughnut-like” because of a lipid vacuole surrounded by a fibrinoid ring. Chest radiography can show normal findings or pleural-based opacities, effusions, atelectasis, and, rarely, hilar adenopathy. Results of laboratory studies are usually normal except for mild elevations in the peripheral white blood cell count (30% of patients); thrombocytopenia is noted in 25% of patients. The erythrocyte sedimentation...
tation rate is usually moderately elevated. Liver enzymes are elevated in almost three-fourths of patients. Q fever is principally diagnosed by serologic methods. The presence of phase I IgM and/or IgG antibodies indicates recent infection, whereas a phase I IgG antibody titer greater than 1:800 indicates chronic infection.

Chronic Q fever may develop within a year or as long as 20 years after the initial infection. It occurs primarily in patients with previous valvular heart disease, immunocompromised patients, and pregnant women. Mortality rates can be as high as 30% to 60%. Q fever endocarditis is identified on the basis of the modified Duke criteria, and a single positive blood culture for *C. burnetii* or a *C. burnetii* anti–phase I IgG titer of greater than 1:800 is considered a major criterion for diagnosis.

The treatment of choice for acute Q fever is doxycycline, 100 mg twice daily, for 15 to 21 days. Fluoroquinolones are also efficacious and may be used. In pregnant women, trimethoprim-sulfamethoxazole can be used as long as the neonate is monitored for potential hyperbilirubinemia. However, given the potential toxic effects of treatment, most therapies are purely to control infection, with curative therapy initiated after the patient has been delivered of her newborn.

Once acute Q fever has been diagnosed, transthoracic echocardiography should be performed to look for valvulopathy; if present, treatment should be initiated for infective endocarditis. If valve lesions are not present, then repeated serologic testing should be performed at 3- and 6-month follow-up. If phase I IgG is elevated, which implies chronic Q fever infection, both transesophageal echocardiography and serum polymerase chain reaction screening for *C. burnetii* should be performed; the latter has been reported to have up to a 100% specificity in some studies of cases of untreated Q fever endocarditis. Treatment of patients with chronic Q fever should include a combination of doxycycline and hydroxychloroquine for at least 18 months; alternative treatment regimens include doxycycline plus either a fluoroquinolone or rifampin for at least 3 to 4 years. Surgery is needed in some cases. Postexposure prophylaxis could be considered after exposure to birthing products from cattle, sheep, and goats or exposure to unpasteurized milk or milk products from these animals. Prophylaxis should be initiated within 8 to 12 days after exposure and should be continued for 1 week.

**REFERENCES**


Correct answers: 1. e, 2. e, 3. d, 4. a, 5. c