

CLINICAL PROBLEM-SOLVING

Ring around the Diagnosis

Maria-Fernanda Bonilla, M.D., Daniel R. Kaul, M.D., Sanjay Saint, M.D., M.P.H., Carlos M. Isada, M.D., and Daniel J. Brotman, M.D.

In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.

A 71-year-old retired schoolteacher from rural Ohio presented to his local hospital with a two-week history of malaise, fever, anorexia, chills, and sweats. He had not had a cough or symptoms involving the upper respiratory, gastrointestinal, or urinary tract.

The patient's symptoms are most likely infectious in origin, but they could be due to an inflammatory or neoplastic condition, particularly lymphoma. Elderly patients may not have localizing signs of infection; for example, cholecystitis may develop without right-upper-quadrant pain. Endocarditis is always a concern in an elderly patient with a prolonged, nonlocalizing fever. Depending on this patient's activities, living in rural Ohio may also have put him at risk for endemic fungal, rickettsial, or other zoonotic diseases.

The patient had undergone coronary-artery bypass surgery six years earlier but had not had recent chest pain or dyspnea. His activities included heavy yard work such as cutting down trees with a chainsaw. He had a distant history of hepatitis A virus infection, but no other serious infections. He was taking atenolol, atorvastatin, and an aspirin daily. Three months before his illness, his wife had had an influenza-like febrile illness that left her bedridden for two weeks; she had recovered fully. The patient had had no other recent exposure to sick persons, no known exposure to tuberculosis, and no tick bites; he reported no travel outside the Midwest. He owned a fish, but no other pets.

Coronary artery disease may be accompanied by valvular disease, which could predispose a person to endocarditis. Yard work in the central Midwest might have exposed this patient to endemic fungi (e.g., histoplasma) or rickettsial diseases. An aquarium, particularly if it is saltwater, can harbor *Mycobacterium marinum*, but infection with this organism is generally confined to the skin. The distant history of infection with hepatitis A virus is not relevant to his current illness. Drug fever is unlikely, given his medication regimen.

The patient was 180 cm tall and weighed 95 kg. He appeared diaphoretic. The blood pressure was 113/58 mm Hg, the heart rate 66 beats per minute, and the respiratory rate 18 breaths per minute and not labored. The temperature was 38.4°C orally. The lungs had no wheezes or crackles, and the heart sounds were normal. The abdomen, skin, and arms and legs also appeared normal. A random measurement of blood glucose revealed a level of 128 mg per deciliter (7.1 mmol per liter). The serum creati-

From the Departments of Internal Medicine (M.-F.B.) and Infectious Disease (C.M.I.), Cleveland Clinic Foundation, Cleveland; the Division of Infectious Disease, Department of Internal Medicine (D.R.K.), University of Michigan, Ann Arbor; Health Services Research and Development Center of Excellence, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, Mich. (S.S.); and the Department of Medicine, Johns Hopkins Hospital, Baltimore (D.J.B.). Address reprint requests to Dr. Brotman at the Hospitalist Program, Johns Hopkins Hospital, Jefferson 242, 600 N. Wolfe St., Baltimore, MD 21287, or at brotman@jhmi.edu.

N Engl J Med 2006;354:1937-42.

Copyright © 2006 Massachusetts Medical Society.

nine level was 1.1 mg per deciliter (97 μmol per liter), and the urea nitrogen level was 14 mg per deciliter (5.0 mmol per liter). The white-cell count was 5400 per cubic millimeter (58 percent neutrophils, 26 percent lymphocytes, 14 percent monocytes, and 1 percent eosinophils). The hematocrit was 37.3 percent, the mean corpuscular volume 88.6 μm^3 , and the platelet count 168,000 per cubic millimeter. A urinalysis was positive for ketones, glucose (+), protein (++) , and bacteria (moderate, with 0 to 3 leukocytes per high-power field). Tests for nitrites and leukocyte esterase were negative. Radiographs of the chest showed no infiltrates.

The patient's vital signs do not suggest the presence of sepsis. Given his temperature elevation, he has a relative bradycardia, but it is probably due to atenolol. The finding of bacteria in the urine without associated pyuria argues against a urinary tract infection. His normal white-cell count does not rule out infection; the absence of eosinophilia makes drug reactions and helminthic diseases (e.g., strongyloidiasis) less likely than other causes. No evidence of pneumonia was seen on chest radiographs. I would be interested in the results of his liver-function tests, since conditions such as cholecystitis and infiltrative disease in the liver may result in fever and may not be accompanied by abdominal pain. Endocarditis or infection involving the biliary system or other abdominal organs is possible, as are fungal, parasitic, and other, less common infections. Inflammatory conditions (e.g., temporal arteritis), neoplastic disease, and drug reactions remain diagnostic considerations.

The patient was admitted with a presumptive diagnosis of urinary tract infection and was treated with intravenously administered ampicillin-sulbactam. On the day after admission, the following values were obtained: aspartate aminotransferase, 150 U per liter (normal range, 5 to 33); alanine aminotransferase, 188 U per liter (normal range, 30 to 65); alkaline phosphatase, 130 U per liter (normal range, 50 to 136); total bilirubin, 1.0 mg per deciliter (17 μmol per liter) (normal range, 0.1 to 1.2 mg per deciliter [2 to 21 μmol per liter]); conjugated bilirubin, 0.2 mg per deciliter (3 μmol per liter) (normal range, less than 0.4 mg per deciliter [7 μmol per liter]); and albumin, 3.0 g per deciliter (normal range, 3.5 to 5.0).

Urinary tract infection is a common misdiagnosis in patients admitted with nonlocalizing febrile syndromes, and this is probably what occurred in this case. I hope that blood was obtained for cultures before the initiation of antibiotic therapy, since the results of blood cultures are often negative in patients with endocarditis when the blood is drawn after the initiation of antibiotic therapy. In the case of a febrile patient in stable condition, it is preferable to defer the administration of antibiotics as the search for the diagnosis proceeds. In this case, the abnormally elevated liver enzymes may be an important clue; imaging of the abdomen should be performed to rule out structural lesions such as hepatic abscess. Biliary tract infection is unlikely, since the levels of alkaline phosphatase and bilirubin remained normal.

Despite continued antibiotic therapy, the patient's clinical status deteriorated during the ensuing two weeks. Computed tomography (CT) of the abdomen showed no intraabdominal abscess, lymphadenopathy, or hepatic abnormalities. The fever persisted, and the creatinine level increased to 2.9 mg per deciliter (260 μmol per liter). Although the aminotransferase elevations remained stable, the total bilirubin level increased to 6.0 mg per deciliter (100 μmol per liter) and the conjugated bilirubin level increased to 5.3 mg per deciliter (91 μmol per liter). The international normalized ratio, which was 1.4 when first measured on the fifth hospital day, rose to 1.7 during the next few days. The albumin level dropped to 1.4 g per deciliter during the first two weeks of hospitalization, while the leukocyte count increased to 18,000 per cubic millimeter (82 percent neutrophils, 10 percent lymphocytes, 5 percent monocytes, and no eosinophils) and the platelet count increased from 168,000 to 563,000 per cubic millimeter. Results of arterial blood gas studies showed a pH of 7.43, a partial pressure of carbon dioxide of 39 mm Hg, a partial pressure of oxygen of 74 mm Hg, and a bicarbonate level of 26 mEq per liter while the patient was breathing 5 liters of supplemental oxygen per minute by nasal cannula.

The findings on abdominal CT make common diseases such as sepsis due to diverticular abscess unlikely. Although the systemic illness that brought the patient to the hospital may account for his progressive multiorgan dysfunction, it is possible that he acquired an infection in the hospital that

was unrelated to the original cause of his fever, such as a central-catheter infection or hospital-acquired pneumonia. Remaining diagnostic possibilities include endocarditis, an occult intra-abdominal infection, or other infection (e.g., histoplasmosis or rickettsial disease).

The results of serial blood and urine cultures were negative, as were serologic tests for hepatitis A, B, and C viruses; cytomegalovirus (CMV); and Epstein-Barr virus (EBV). A purified protein derivative (PPD) skin test was nonreactive; no control was placed. Tests for antinuclear antibodies, anti-smooth-muscle antibodies, antineutrophil cytoplasmic antibodies, and antimitochondrial antibodies were also negative. CT of the chest revealed either bibasilar infiltrates or atelectasis and small, bilateral effusions (Fig. 1). Examination of a biopsy specimen of the liver revealed acute and chronic hepatitis with scattered epithelioid granulomas and mild fatty changes; no acid-fast bacilli or fungi were seen.

The findings on liver biopsy are intriguing and suggest a number of diseases that could explain this patient's illness. Disseminated tuberculosis is often difficult to diagnose, and neither the PPD test nor stains for acid-fast bacilli are sensitive enough to rule out this disease. Fungal infections such as histoplasmosis and cryptococcosis are not ruled out by the negative fungal stain on the liver-biopsy specimen. *Coxiella burnetii* (the cause of Q fever), brucellosis, lymphoma, and certain illnesses caused by viruses such as CMV and EBV may also cause hepatic granulomas with sepsis-like presentations. Because of the results of diagnostic tests and the patient's fulminant course, other causes of hepatic granulomas (such as sarcoidosis, toxoplasmosis, metastatic cancer, Wegener's granulomatosis, Crohn's disease, hepatitis C, autoimmune hepatitis, and drug-induced adverse effects) are unlikely. The hepatic granulomas could be a red herring that is unrelated to this patient's current illness.

Since the patient's condition continued to deteriorate, he was transferred to a referral hospital. At that time, additional history was elicited; during the prior six months, he and his wife had made multiple visits to the farms of friends and relatives in Kentucky and Ohio, during which they were exposed to goats, sheep, and cats.

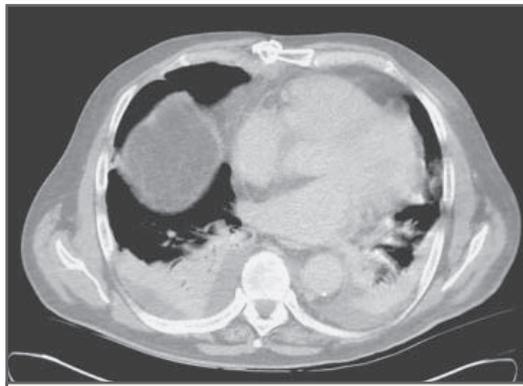


Figure 1. CT Scan of the Chest Showing Small, Bilateral Effusions and Either Bibasilar Infiltrates or Atelectasis.

No clinically significant lymphadenopathy was apparent in the hilum or mediastinum on the other CT images.

On arrival at the referral hospital, the patient appeared jaundiced, dyspneic, and delirious. He was febrile (temperature, 38.7°C), and his blood pressure was 106/83 mm Hg. His respiratory rate was 22 breaths per minute, and pulse oximetry demonstrated an oxygen saturation of 96 percent while he was receiving 5 liters of oxygen per minute by nasal cannula. The white-cell count was 26,900 per cubic millimeter, with 96 percent neutrophils, and the total bilirubin level was 11.5 mg per deciliter (197 μ mol per liter). Broad-spectrum antibiotic therapy (piperacillin-tazobactam) was continued, and treatment with liposomal amphotericin B was started because of the concern about a possible disseminated fungal infection. However, serologic and urinary tests were negative for histoplasmosis, as were serologic tests for blastomyces, aspergillus, and coccidioides. Serologic tests for bartonella and brucella species, *Toxoplasma gondii*, *Rickettsia rickettsii*, and human immunodeficiency virus were also negative. Abdominal ultrasonography showed no abnormality. Although the patient had no focal neurologic symptoms, vision changes, or temporal tenderness, a temporal-artery biopsy was performed on the basis of his persistent fever in the setting of granulomatous inflammation. There was no pathological evidence of arteritis.

I suspect that this patient has an untreated disseminated granulomatous disease. His exposures put him at risk for zoonotic diseases and endemic fungi. Brucella can be acquired by drinking unpasteurized dairy products on a farm, but the

negative serologic tests in this case make this diagnosis unlikely. Serologic tests for histoplasmosis vary in quality, but the combination of a negative serologic test and a negative test for urinary antigens in the setting of disseminated disease makes the diagnosis of histoplasmosis unlikely. Serologic tests for blastomycosis have a low sensitivity, but liver disease, as seen in this case, would be an unusual characteristic of this infection. Q fever may cause granulomatous hepatitis; given the patient's exposure to animals, a serologic test for Q fever should have been performed. Patients with leptospirosis can present with hyperbilirubinemia and multiorgan disease, but piperacillin should have been effective against leptospirosis, and this infection would not cause hepatic granulomas. The hepatic granulomas and the absence of rash are not characteristic of Rocky Mountain spotted fever. Tuberculosis remains a diagnostic possibility. Also, idiopathic granulomatous hepatitis may occur without other evidence of sarcoidosis.

The three most likely diagnoses at this point are disseminated tuberculosis, idiopathic granulomatous hepatitis, and Q fever. Given the patient's deteriorating condition, I would begin treatment with antimycobacterial therapy, doxycycline for possible Q fever, and glucocorticoids for possible granulomatous hepatitis. In the setting of appropriate treatment with antimicrobial agents, short-term administration of glucocorticoids should not be detrimental, even in a patient with a serious infection. Antifungal therapy should be continued pending further culture data. A bone marrow biopsy or bronchoalveolar lavage, with mycobacterial and fungal cultures of the specimens obtained, would be reasonable.

Examination of a bone marrow–biopsy specimen revealed scattered epithelioid and giant-cell granulomas. No malignant cells were seen. Acid-fast and Gomori's methenamine silver stains were negative for mycobacteria and fungi, respectively. In several areas, the granulomatous reaction had a ring formation around a central lipid vacuole—the so-called fibrin-ring, or “doughnut,” granuloma (Fig. 2); pathological review of the liver-biopsy specimen obtained previously revealed similar lesions (Fig. 3).

Fibrin-ring granulomas are usually associated with Q fever, but they may also occur with CMV, EBV,

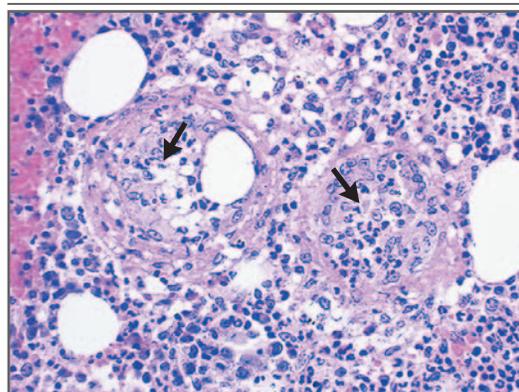


Figure 2. Bone Marrow–Biopsy Specimen Showing Two Granulomas (Arrows) Surrounded by Fibrin Rings (Hematoxylin and Eosin).

The granuloma on the left also has a central lipid vacuole.

and mycobacterial infections; lymphoma; vasculitis; and typhoid fever. Q fever is the most likely diagnosis, given this patient's exposure to farm animals, the absence of lymphadenopathy on CT, the lack of evidence of a neoplasm on biopsy specimens of the liver and bone marrow, the negative viral and fungal serologic tests, and the normal results of the temporal-artery biopsy.

In a blood specimen drawn five days after the bone marrow biopsy, antibody titers to *C. burnetii* were strongly positive (IgG phase 1, 1:16; IgG phase 2, 1:1024; IgM phase 1, 1:1024; and IgM phase 2, 1:256) and thus were diagnostic of Q fever. The patient's clinical status improved dramatically within days after the initiation of doxycycline, and he was discharged home to finish a three-week course of this drug.

Two months after hospitalization, the patient had no symptoms. His wife consented to testing and was found to have positive phase 1 and 2 IgG antibody titers to *C. burnetii*. In retrospect, she recalled that her febrile illness had developed two weeks after visiting a relative's sheep farm.

Humans generally contract Q fever through the inhalation of *C. burnetii*, often by exposure to infected animals or their birth products. Because antibodies against this microorganism persist for years, it is impossible to know precisely when the patient's wife was infected, but it appears likely that Q fever also accounted for her recent illness.

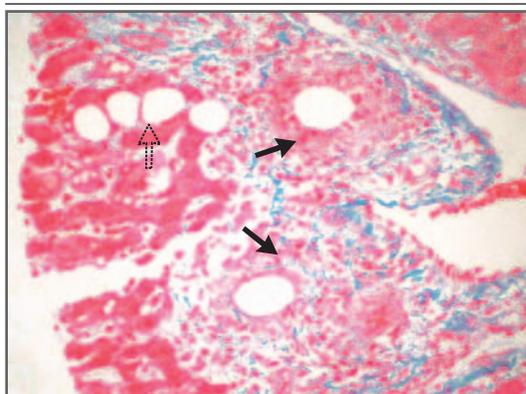


Figure 3. Biopsy Specimen of the Liver Showing Two Granulomas (Solid Arrows) with Central and Adjacent Fat Globules (Open Arrow), Indicating Fatty Infiltration (Hematoxylin and Eosin).

COMMENTARY

Fever of unknown origin (FUO) was defined in 1961 as a temperature of more than 38.3°C on several occasions for at least three weeks, with the diagnosis remaining uncertain after one week of hospitalization.¹ Since then, other definitions have been proposed. The initial evaluation of FUO typically involves a thorough history taking, physical examination, routine blood chemical tests, blood counts, cultures of urine and blood, and abdominal CT. Further testing is generally more invasive, and its pace depends on the patient's condition. In our patient, rapid clinical deterioration mandated an aggressive strategy.

In this case, the evidence directed the team toward a potentially risky diagnostic procedure, a liver biopsy in a patient with mild coagulopathy.²⁻⁴ Although the abnormal elevation of liver enzymes might have been interpreted as a non-specific complication of sepsis, mild abnormalities were present before the patient's clinical deterioration, and therefore, it was thought that a liver biopsy would be helpful in establishing a diagnosis.

A liver biopsy yields a diagnosis in about 15 percent of patients with FUO.⁵ In this case, it changed the diagnostic approach. Finding hepatic granulomas focused the clinicians' attention on conditions associated with granulomatous inflammation. Since granulomatous diseases that affect the liver often involve the bone marrow, a bone marrow biopsy was performed, in the hope that cultures or staining of the specimen might yield a diagnosis. Although the diagnostic

yield of cultures of bone marrow in patients with FUO is usually very low,⁵ the granulomas in this case suggested that a disseminated granulomatous disease was the cause of the illness.

Fibrin-ring granulomas, which have long been recognized in association with Q fever, are an infrequent pathological finding limited to liver and bone marrow specimens.⁶ These granulomas may appear doughnut-like because they contain a lipid vacuole surrounded by a fibrinoid ring.⁷ Q fever accounts for most reports of fibrin-ring granulomas in bone marrow, but they may be seen in other conditions, including typhoid fever, lymphoma, vasculitis, and EBV and CMV infection.⁶⁻¹²

The name "Q fever" (for query fever) was coined in 1937 to describe a febrile illness seen in Australian slaughterhouse workers.¹³ The causative organism, *C. burnetii*, is a gram-negative intracellular bacterium that cannot be cultured by routine laboratory methods, so serologic testing is required. This zoonotic pathogen is present worldwide.¹⁴ Mammalian reservoirs include sheep, goats, cattle, and occasionally, household pets. In animals, *C. burnetii* exhibits tropism for female reproductive organs, and if present in high levels in the delivered placenta, the organism may aerosolize and infect humans. Infection may also occur through contact with body fluids of animals or the ingestion of infected milk. Finally, ticks may serve as vectors.¹⁵

Acute infection may be manifested as a self-limited influenza-like illness, painless hepatitis, atypical pneumonia, or a prolonged FUO.¹⁵ Multiorgan failure, as was seen in this case, is uncommon and cannot be reliably predicted on the basis of host characteristics. Chronic Q fever, which lasts more than six months, occurs in 1 to 5 percent of infected patients, and these patients commonly have endocarditis.¹⁵ A finding of elevated phase 1 IgG antibody titers ($\geq 1:800$) strongly suggests the diagnosis of Q fever endocarditis, which requires at least two years of treatment. The low phase 1 IgG titer in this case argues against that diagnosis; thus, a typical two-week treatment course should have been sufficient.

Dr. Saint reports having received a Career Development Award from the Health Services Research & Development Program of the Department of Veterans Affairs and a Patient Safety Developmental Center Grant from the Agency for Healthcare Research and Quality (P20-HS11540). No potential conflict of interest relevant to this article was reported.

We are indebted to Drs. Karl S. Theil and Jennifer Brainard for their clinical and pathological insights, and to Dr. Martin Lascano for his comments on the manuscript.

REFERENCES

1. Petersdorf RG, Beeson PB. Fever of unexplained origin: report on 100 cases. *Medicine (Baltimore)* 1961;40:1-30.
2. Tobkes AI, Nord HJ. Liver biopsy: review of methodology and complications. *Dig Dis* 1995;13:267-74.
3. McGill DB, Rakela J, Zinsmeister AR, Ott BJ. A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology* 1990;99:1396-400.
4. Piccinino F, Sagnelli E, Pasquale G, Giusti G. Complications following percutaneous liver biopsy: a multicentre retrospective study of 68,276 biopsies. *J Hepatol* 1986;2:165-73.
5. Mourad O, Palda V, Detsky AS. A comprehensive evidence-based approach to fever of unknown origin. *Arch Intern Med* 2003;163:545-51.
6. Ende N, Gelpi AP. Pathologic changes noted in bone marrow in a case of Q fever. *Arch Intern Med* 1957;100:793-6.
7. Okun DB, Sun NCJ, Tanaka KR. Bone marrow granulomas in Q fever. *Am J Clin Pathol* 1979;71:117-21.
8. Pellegrin M, Delsol G, Auvergnat JC, et al. Granulomatous hepatitis in Q fever. *Hum Pathol* 1980;11:51-7.
9. Hofmann CE, Heaton JW Jr. Q fever hepatitis: clinical manifestations and pathological findings. *Gastroenterology* 1982;83:474-9.
10. Srigley JR, Vellend H, Palmer N, et al. Q fever: the liver and bone marrow pathology. *Am J Surg Pathol* 1985;9:752-8.
11. Travis LB, Travis WD, Li CY, Pierre RV. Q fever: a clinicopathologic study of five cases. *Arch Pathol Lab Med* 1986;110:1017-20.
12. Eid A, Carion W, Nystrom JS. Differential diagnosis of bone marrow granuloma. *West J Med* 1996;164:510-5.
13. Derrick EH. "Q" fever, new fever entity: clinical features, diagnosis and laboratory investigation. *Med J Aust* 1937;2:281-99.
14. McQuiston JH, Childs JE. Q fever in humans and animals in the United States. *Vector Borne Zoonotic Dis* 2002;2:179-91.
15. Maurin M, Raoult D. Q fever. *Clin Microbiol Rev* 1999;12:518-53.

Copyright © 2006 Massachusetts Medical Society.