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# Acute Q Fever Hepatitis Mimicking Autoimmune Hepatitis

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**Abstract:** A 44-year-old previously healthy man presented with 17 days of high-grade fevers, chills, night sweats, nausea, dark urine, and progressive jaundice after returning from a 2-week trip to Mexico during which he had eaten unpasteurized goat cheese daily and had contact with goats, horses, and dogs. Evaluation revealed mixed cholestatic and hepatocellular liver injury, splenomegaly, and significantly elevated inflammatory markers, with negative blood cultures and negative *Brucella* serologies. Strongly positive antinuclear, anti-smooth muscle, and antimitochondrial antibodies, together with a liver biopsy initially interpreted as autoimmune hepatitis, suggested an autoimmune process. Q fever serologies obtained during the diagnostic workup showed phase II IgM and IgG titers of 1:512, and pathology review demonstrated granulomatous hepatitis compatible with Q fever. Convalescent serology at 6 weeks confirmed phase I seroconversion. The patient was diagnosed with acute Q fever complicated by Q fever hepatitis and was treated with doxycycline-based therapy. Granulomatous hepatitis with prominent autoantibodies should prompt exposure history and phase-specific serologies before the findings are attributed to autoimmune disease.

**Keywords:** Q fever; *Coxiella burnetii*; granulomatous hepatitis; fibrin ring granuloma

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## Highlights

- Acute Q fever can present as a febrile granulomatous hepatitis and should be considered in prolonged undifferentiated fever with cholestatic liver injury.
- Unpasteurized dairy products from infected ruminants are a recognized foodborne route of *Coxiella burnetii* transmission.
- Acute Q fever frequently induces autoantibodies, including antinuclear, anti-smooth muscle, and antimitochondrial antibodies.

- Paired phase I and phase II serologies are the diagnostic cornerstone.
- Doxycycline 100 mg twice daily for 14 days is first-line therapy for acute Q fever, followed by serologic surveillance for progression to persistent (chronic) infection.

# 1. Introduction

Q fever is a worldwide zoonosis caused by *Coxiella burnetii*, a small, immotile, obligate intracellular gram-negative bacterium [1,2]. Human infection is acquired principally by inhalation of contaminated aerosols and, less commonly, by ingestion of unpasteurized dairy products from infected ruminants: cattle, sheep, and goats are the animals most often linked to human disease [1–3]. The organism is shed in birth products, milk, urine, and feces of infected animals, resists desiccation, and can remain viable in soil and standing water, which permits windborne transmission at distances of many kilometers from livestock operations [1,2]. In the United States, Q fever is a nationally notifiable but likely under-recognized disease, in part, because roughly half of infections are asymptomatic and symptomatic illness is protean [3,4].

The classic presentations of acute Q fever are a self-limited influenza-like illness, pneumonia, and hepatitis, with the dominant syndrome varying by geographic region [1,2,5]. Q fever hepatitis may present with fever, modest aminotransferase elevation, or frank cholestatic jaundice, and is characteristically associated with fibrin ring (doughnut) granulomas on liver biopsy [1,2]. Because acute infection can also induce a broad array of autoantibodies, hepatic Q fever is readily mistaken for autoimmune liver disease. We describe an illustrative case and review the microbiology, epidemiology, clinical spectrum, diagnosis, and management of acute Q fever.

# 2. Case Presentation

## 2.1. History

A 44-year-old man with hyperlipidemia, noncompliant with atorvastatin, presented to the emergency department with 17 days of illness. His symptoms began with abrupt high-grade fevers accompanied by chills, night sweats, and nausea. Eleven days before admission he was evaluated at an immediate care center for fevers, headache, cough, nausea, and vomiting; testing for SARS-CoV-2, respiratory syncytial virus, and influenza A/B was negative, and he was treated with a 7–day course of amoxicillin/clavulanate and ondansetron. Fevers persisted and 6 days before admission he presented to an express care clinic, where *Helicobacter pylori* testing was negative and liver chemistries were newly abnormal: aspartate aminotransferase 129 U/L, alanine aminotransferase 217 U/L, alkaline phosphatase 283 U/L, and total bilirubin 2.2 mg/dL. He reported dark urine. Fevers and drenching sweats continued, and he presented to the emergency department with fevers, chills, sweats, abdominal pain, nausea, myalgias, and weakness. An outpatient abdominal ultrasound had shown splenomegaly.

On direct questioning, patient endorsed fevers, chills, night sweats, nausea, vomiting, diarrhea, and dark brown urine. He specifically denied joint pain. He had no known drug allergies and no sick contacts. He was married, monogamous, drank alcohol socially, and denied use of tobacco, vaping products or illicit drugs. He had traveled to Mexico 6 weeks prior to admission. During his 2-week trip in Mexico, patient ate unpasteurized goat cheese daily and was exposed to goats, horses, and dogs.

## 2.2. Examination

Initial vital signs showed a temperature of 98.3 °F that subsequently rose to 103.5 °F, heart rate 120 beats per minute, respiratory rate 20, blood pressure 150/83 mm Hg, and oxygen saturation 97% on

room air. Patient appeared ill and diaphoretic on arrival and was visibly jaundiced. The remainder of the examination was unremarkable.

## 2.3. Initial Studies

Selected laboratory results are shown in Table 1. Blood cultures were obtained, *Brucella* serologies were sent given the goat and unpasteurized dairy exposure, ceftriaxone was started, and Infectious Diseases was consulted. Empiric doxycycline and rifampin were initiated for possible brucellosis. Computed tomography of the abdomen and pelvis with contrast showed no acute abnormality and hepatic steatosis; liver ultrasound showed mild hepatomegaly with fatty infiltration and patent hepatic and portal veins.

**Table 1:** Selected Laboratory Results.

| Test | Result | Reference/Comment |
|---|---|---|
| AST/ALT (outpatient, day 11) | 129/217 U/L, respectively | Elevated, with alkaline phosphatase 283 U/L and total bilirubin 2.2 mg/dL |
| Procalcitonin | 2.29 ng/mL | Elevated |
| C-reactive protein | 214 mg/L | Reference < 10 mg/L |
| Ferritin | 687 ng/mL | Elevated |
| Lactate dehydrogenase | 563 U/L | Elevated |
| Lactate | 1.7 mmol/L | Normal |
| Lipase | 58 U/L | Normal |
| Troponin | 5.94 ng/L | Reference < 53 ng/L; normal |
| Antinuclear antibody | Positive | |
| Anti-dsDNA | 36 IU/mL | Reference 0 IU/mL to 9.9 IU/mL |
| M2 antimitochondrial antibody | 92.6 U | Reference 0 U to 20 U |
| Anti-smooth muscle (actin) antibody | 78 U | Reference 0 U to 19 U |
| IgG/IgA/IgM | 2016/346/236 mg/dL, respectively | Polyclonal elevation |
| C3/C4 | 124/23.1 mg/dL, respectively | Normal |

## 2.4. Hospital Course

Fevers and sweats persisted despite empiric therapy. On hospital day 3, the patient developed a cough with bilateral basilar rales, right greater than left; chest radiography showed mild cardiomegaly with linear atelectasis or infiltrate at the right lung base, and ceftriaxone was restarted. Gastroenterology ordered autoimmune and viral serologies, and MRI/MRCP showed no biliary ductal dilatation or obstruction. Rheumatology consultation judged the likelihood of a primary rheumatic or connective tissue disease to be low despite the positive serologies. The broad infectious workup, summarized in Table 2, was unrevealing: serial blood cultures showed no growth, *Brucella* IgM and IgG were negative, and transthoracic and transesophageal echocardiography showed no vegetations.

The HIV-1/2 antigen/antibody screen was indeterminate with an unconfirmed differentiation assay, but HIV-1 RNA was not detected and the CD4 count was normal.

On hospital day 6, a percutaneous liver biopsy was performed, and plasma microbial cell-free DNA sequencing (Karius test) was sent. While biopsy results were pending, the patient completed a course of ceftriaxone and remained on doxycycline and rifampin along with empiric levofloxacin and trimethoprim-sulfamethoxazole. Initial pathologic interpretation of the biopsy was consistent with autoimmune hepatitis.

**Table 2:** Infectious and Cardiac Evaluation.

| Study | Result |
|---|---|
| Blood cultures (serial) | No growth |
| *Brucella* IgM and IgG | Negative |
| SARS-CoV-2, RSV, influenza A/B | Negative |
| Malaria antigen and smear | Negative |
| Urine *Legionella* and pneumococcal antigens | Negative |
| *Leptospira* IgM | Negative |
| Syphilis antibody | Negative |
| Chronic hepatitis panel | Negative |
| CMV quantitative PCR | Not detected |
| EBV quantitative PCR | Positive, <35 IU/mL (low level) |
| HIV-1/HIV-2 antigens/antibodies | Indeterminate; differentiation unconfirmed; HIV-1 RNA not detected; CD4 500 cells/uL |
| Transthoracic and transesophageal echocardiography | No vegetations; normal studies |

## 2.5. Diagnosis and Outcome

Karius testing detected *Coxiella burnetii* and Q fever serologies returned strongly positive, with phase II IgM and IgG titers of 1:512 (reference < 1:16), phase I IgM 1:16, and negative phase I IgG, a pattern diagnostic of acute infection. Dedicated pathology review of the liver biopsy revised the interpretation to granulomatous hepatitis compatible with Q fever hepatitis. Convalescent serology 6 weeks later showed persistent phase II titers of 1:512 with seroconversion of phase I IgM and IgG to 1:512 (Table 3). The final diagnoses were acute Q fever and acute hepatitis secondary to Q fever. The patient completed doxycycline-based therapy with plans for serologic surveillance to exclude progression to persistent infection.

**Table 3:** Paired Q Fever Serologies at Presentation and at 6 Weeks.

| Q Fever Serology (IFA) | At Presentation (Phase I) | 6 Weeks Later (Phase II) |
|---|---|---|
| IgM | 1:16 | 1:512 |
| IgG | Negative | 1:512 |

IFA, indirect immunofluorescence assay. Reference for all titers <1:16.

# 3. Discussion

## 3.1. Microbiology

*C. burnetii* exists in 2 morphologic forms. The small-cell variant is a dormant, environmentally stable form that resists desiccation and disinfectants, survives for prolonged periods outside a host, and is transmitted by inhalation. After entry into host cells, the organism transitions to the large-cell variant, the metabolically active form that replicates within an acidified phagolysosome [1, 5]. The organism also undergoes phase variation: phase I is the highly infectious, full-length lipopolysaccharide form recovered from infected animals, for which a single organism can establish infection, whereas laboratory subculture produces the antigenically truncated phase II form with loss of most lipopolysaccharide side chains, including the O-antigen [1,2,5]. This phase variation is exploited diagnostically, because the antibody response to phase II antigens dominates in acute infection while high-level phase I antibody responses characterize persistent infection [1,2].

## 3.2. Epidemiology and Transmission

Q fever occurs worldwide, with notable endemicity in southern France, Australia, and parts of the Middle East, and is conspicuously absent from New Zealand [1,2]. Cattle, sheep, and goats are the principal reservoirs for human infection, although a wide range of animals, including cats and dogs, can harbor the organism [1,2]. Infected animals shed large quantities of organisms in birth products, milk, urine, and feces, and the desiccation-resistant small-cell variant contaminates soil and dust, with windborne spread documented many kilometers downwind of infected herds [1,2]. Inhalation is the dominant route of human infection; ingestion of contaminated raw milk or fresh unpasteurized cheese is a recognized secondary route. Rare mechanisms include transfusion, tick bite, and exposure to the placenta of an infected woman [1–3]. Occupational risk concentrates among veterinarians, farmers, slaughterhouse workers, and laboratory personnel [3]. In this patient, daily consumption of unpasteurized goat cheese in Mexico, together with direct goat contact, provided classic exposure. The 6-week interval between travel and admission is compatible with the 1– to 5–week incubation period of acute Q fever [1,2].

## 3.3. Clinical Spectrum of Acute Q Fever

Only about half of infected patients develop symptomatic disease; the remainder seroconvert silently [1,2]. Symptomatic acute Q fever most often presents as an abrupt influenza-like illness with fever, headache, myalgias, fatigue, and drenching sweats, and the dominant organ-specific syndromes are pneumonia and hepatitis, in proportions that vary by geography [1,2,6]. Less common manifestations include rash, aseptic meningitis and other neurologic diseases, pericarditis, myocarditis and conduction block, ocular involvement, lymphadenitis, and hemophagocytic lymphohistiocytosis [1,6]. Host factors including sex, age, and underlying valvulopathy modulate clinical expression [7]. Approximately 1% to 5% of patients with acute infection eventually develop persistent focalized infection, classically endocarditis or vascular infection [1,2]. This patient's syndrome of prolonged fever, cholestatic hepatitis, splenomegaly, and a late, mild respiratory component with basilar infiltrates reflects the hepatic-predominant phenotype with overlapping pulmonary involvement.

## 3.4. Q Fever Hepatitis and the Autoimmune Mimic

Q fever hepatitis ranges from asymptomatic aminotransferase elevation to febrile jaundice, and its histologic hallmark is the fibrin ring (doughnut) granuloma, a granuloma with a central lipid vacuole

encircled by a fibrin ring [1,2]. Fibrin ring granulomas are strongly associated with Q fever but are not pathognomonic. In a clinicopathologic series of 23 patients with hepatic fibrin ring granulomas, Q fever accounted for 43% of cases, with visceral leishmaniasis, boutonneuse fever, toxoplasmosis, Hodgkin disease, and allopurinol hypersensitivity among the remaining etiologies [8].

A central teaching point of this case is the serologic and histologic mimicry of autoimmune liver disease. Acute *C. burnetii* infection is well documented to induce autoantibodies, including antinuclear, anti-smooth muscle, antimitochondrial, and anticardiolipin antibodies [1]. This patient had a positive antinuclear antibody (ANA) test, anti-double-stranded DNA of 36 IU/mL, an M2 antimitochondrial antibody more than 4 times the upper reference limit, an anti-smooth muscle antibody 4 times the upper reference limit, and polyclonal hypergammaglobulinemia, and the initial biopsy reading was autoimmune hepatitis. Had corticosteroids been initiated for presumed autoimmune hepatitis, the underlying infection could have progressed unchecked. The combination of compatible animal or dairy exposure, prolonged fever out of proportion to the hepatitis, and granulomatous inflammation on biopsy should prompt Q fever serologies before immunosuppression is considered. The indeterminate HIV screening serology with undetectable HIV-1 RNA in this patient likely represents a further example of the nonspecific serologic reactivity that accompanies acute Q fever [1].

## 3.5. Diagnosis

Serology by indirect immunofluorescence is the diagnostic mainstay [3,9]. Phase II antibodies dominate in acute infection: phase II IgG develops a median of 5 days after symptom onset, with IgM appearing at about the same time. An isolated positive phase II IgM should be interpreted cautiously given the frequency of false positives, and demonstration of seroconversion or a 4–fold rise between acute and convalescent phase II IgG titers remains the gold standard for acute Q fever [1,3]. Because phase II IgG can persist for years, low-level titers of 1:16 to 1:128 may reflect past infection [3]. In persistent (chronic) infection, a very high phase I IgG titer, conventionally 1:512 to 1:800 or greater depending on the laboratory, is the serologic signature, whereas lower phase I titers can accompany treated or resolving acute disease [1,3]. Serologic cross-reactivity with *Legionella*, *Bartonella*, *Chlamydophila* and *Leptospira* is described and warrants correlation with the clinical picture [9]. Polymerase chain reaction test of blood or tissue, next-generation sequencing of plasma microbial cell-free DNA, and immunohistochemistry on biopsy material are useful adjuncts, particularly early in illness before seroconversion. The organism does not grow in routine blood cultures, and cell culture isolation is essentially confined to reference laboratories [1,3,9]. In this patient, phase II IgM and IgG titers of 1:512 at presentation strongly supported acute Q fever, which was subsequently confirmed by the 6-week convalescent panel demonstrating phase I seroconversion, corroborating the diagnosis while providing a baseline for surveillance.

## 3.6. Treatment and Follow-Up

Doxycycline 100 mg twice daily for 14 days is the treatment of choice for acute Q fever in nonpregnant adults [3,10]. Alternatives with supporting data include trimethoprim/sulfamethoxazole, moxifloxacin, and clarithromycin, each for 14 days; levofloxacin appears effective although data are more limited, and azithromycin is considered less active [1,10]. After acute Q fever, serologic follow-up at 3, 6, and 12 months is recommended to detect evolution toward persistent infection; patients with risk factors, including known or suspected valvulopathy, prosthetic valves, vascular aneurysm or graft, pregnancy, immunosuppression, or age older than 50 years, warrant extended surveillance at 18 and 24 months and then every 6 to 12 months until 5 years have elapsed [1,3,11]. This patient, treated with a doxycycline-containing regimen during his admission, will continue scheduled serologic monitoring.

## 4. Conclusion

Acute Q fever should be included in the differential diagnosis of prolonged fever with hepatitis, particularly in patients with livestock contact or consumption of unpasteurized dairy products. The infection can generate a convincing autoimmune facade, including high-titer ANA, anti-smooth muscle and antimitochondrial antibodies and biopsy findings initially read as autoimmune hepatitis; recognition of this mimicry protects patients from inappropriate immunosuppression. Paired phase-specific serologies remain the cornerstone of diagnosis; doxycycline is the treatment of choice, and structured serologic follow-up is essential to detect the minority of patients who progress to persistent infection.

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