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Case report of Acute Q fever with Hepatitis progressing to Chronic Q fever with Endocarditis

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CASE REPORT

Case Report of Acute Q Fever with Hepatitis Progressing to Chronic Q Fever with Endocarditis

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Abstract

A 35-year-old male greenhouse worker presented with myalgia, fatigue, and fever. Initially, he was thought to have an unspecified viral infection and was treated with conservative therapy. However, the patient's symptoms persisted, and he reported additional symptoms of mild abdominal pain and headaches. Laboratory evaluation was significant for elevated liver enzymes. Due to concern for acute hepatitis and persistent fever the patient was hospitalized. During his hospital course, no infectious etiology was found to explain his symptoms. After discharge from the hospital, additional testing showed positive serology for Q fever IgG phase II antibody (1:8192) and phase II antibody IgM (>1:2048). He was treated with doxycycline and had a good clinical response. Upon follow-up, he had worsening Phase I IgG serologies. Transesophageal echo demonstrated vegetations consistent with endocarditis.

Keywords: Q fever, Hepatitis, Acute Q fever, Chronic Q fever, Endocarditis, Case report

Core tip

Acute Q fever with hepatitis is an extremely rare disease. The clinician must have a high index of suspicion and obtaining a detailed history including occupation helps to determine the etiology of the disease process.

1. Introduction

Q fever is a rare disease caused by *Coxiella burnetii*, an obligate intracellular bacterium that is difficult to culture and highly contagious.[1] Serology is the most common modality used for diagnosing Q fever, and confirmation of disease may take several weeks to months to detect the required 4-fold increase in titer levels for diagnosis.[1] Acute Q fever typically presents as a mild flu-like illness and may have complications such as pneumonia or hepatitis.[2] In the United States (US), the incidence of acute Q fever is 0.36 per million people.[3] Although Q fever infection is rare in the US, awareness of the disease presentation, diagnosis,

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and management are vital as it has been categorized as a potential bioterrorism pathogen by the Centers for Disease Control and Prevention (CDC).[1] Furthermore, an outbreak reported in the Netherlands from 2007 to 2010 demonstrates the potential *C. burnetii* carries in becoming a significant public health issue.[1,4] Therefore, we present a case report on a 35-year-old male with Q fever.

2. Case presentation

A 35-year-old male presents with complaints of myalgia, fatigue, and fever for several days. Past medical history was significant for hyperlipidemia, congenital nystagmus, and herpes simplex virus labialis. No previous surgeries or known significant family history. The patient first experienced symptoms of myalgia, fatigue, and fever for 5 days. He assumed his symptoms may have been related to COVID-19 infection although he had a negative at-home test. Due to concerns of persistent symptoms, he presented to the emergency department (ED) for further evaluation. He was found to be febrile to 39.2 °C and tachycardic at 117 beats per minute. He was swabbed for Influenza A/B and COVID 19, and both were undetected. The patient was treated conservatively in the ED with oral hydration, ibuprofen, and acetaminophen and discharged from the hospital with a diagnosis of an unspecified viral syndrome.

Next day at outpatient follow up, he described persistent fever, myalgia, and fatigue. In addition, he mentioned symptoms of urinary urgency, decreased urinary stream, mild left-sided abdominal pain, epigastric tightness, dark brown urine, and a headache. He described his headache as 3/10 in severity and a mild cough with minimal phlegm production. At home, the patient had been rotating ibuprofen and acetaminophen for fever management.

The patient endorsed decreasing his alcohol intake over the past 1–2 months and was consuming only three alcoholic beverages a week at the time of presentation. Prior to this, the patient had been drinking 15–20 alcoholic beverages a week for the last several years. He admitted to smoking 1 cigar every 2 weeks and denied any substance abuse. He had no reports of travel outside of the United States and was vaccinated for COVID-19 × 2 doses. The patient works at a greenhouse and previously served in the military with no recent deployment.

Patient's labs were significant for transaminitis, leukopenia, small urobilinogen in urine, and a negative viral hepatitis panel (see Table 1). CT of the abdomen and pelvis, ultrasound of the gallbladder and biliary duct was unremarkable. Chest x-ray showed no pneumothorax and no acute airspace disease. The observed transaminitis was suspected to be from the patient's prior alcohol consumption, and his leukopenia was thought to be related to a viral syndrome of unknown origin.

The patient was seen in follow-up on day five in the clinic, at which point his symptoms had persisted for 10 days. Labs were significant for worsening transaminitis, mild electrolyte dysfunction, and elevated inflammatory markers. Given the worsening laboratory values along with the prolonged fever of unknown etiology, the patient was admitted to the hospital for further inpatient workup.

Physical examination was done upon admission to the hospital and the patient was noted to be in no apparent distress but did appear dehydrated. Abdomen was soft, non-distended, non-tender without rebound, guarding or organomegaly. Eyes, neck, respiratory, cardiovascular, extremities, neurologic, psychiatric, skin, musculoskeletal physical examination were all also unremarkable. CT of the head showed no acute intracranial pathology. CT of the abdomen and pelvis demonstrated a small linear wedge-shaped hypodense area within the splenic hilum concerning for acute splenic infarct (Fig. 1). Given the persistent fever and hepatic dysfunction, infectious disease and gastroenterology were consulted. He was noted to have positive Lyme IgM, Q fever IgM and IgG. His Q fever phase I IgG antibody was <1:16, Q fever phase II IgG antibody 1:8192, Q fever phase I IgM antibody 1:1024, and phase II IgM antibody >1:2048. Based on these results, Q fever was felt to be the most likely explanation for his acute hepatitis. The patient was subsequently initiated on doxycycline 100 mg orally

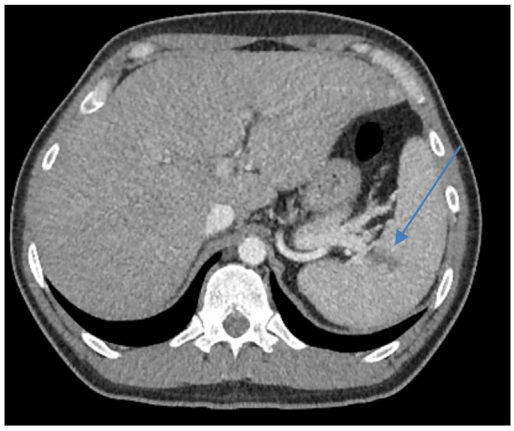

Fig. 1. CT imaging shows acute splenic infarct.

twice daily for a 14-day course. His course of treatment was not initially extended as he had no evidence of endocarditis on a transthoracic echocardiogram and had normalized his hepatic function tests (see Fig. 2).

MR of the abdomen with and without contrast obtained 2 weeks after the abnormal CT scan was done was normal and showed no suspicious splenic lesions.

He had a transthoracic echocardiogram one month after his initial presentation which was normal.

On a follow-up visit five months later, the patient continued to have a poor appetite and occasional lightheadedness without fever. Q fever serology was repeated, which showed increasing Phase I IgG (Table 2). This prompted further evaluation with a transesophageal echocardiogram which showed two new mobile echodensities (2 mm in diameter) at the tips of the noncoronary cusp and right coronary cusp, concerning for mobile aortic valve vegetations.

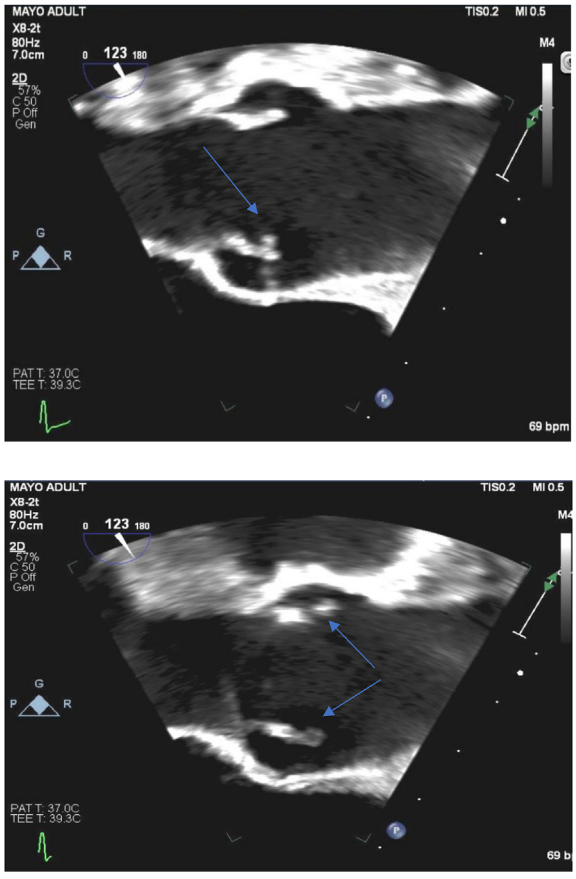

Fig. 2. Mid esophageal Transesophageal Echogram (TEE) of Left ventricular outflow tract and Aortic valve and ascending aorta. The vegetation appears to be associated with both the non-coronary and right coronary cusps. There is no significant insufficiency.

Estimated left ventricular ejection fraction of 60% unchanged from previous echocardiogram.

Considering these findings, the decision was made to treat the patient for Q fever endocarditis. He was started on treatment with doxycycline 100 mg orally twice daily along with hydroxychloroquine 600 mg oral daily for a minimum of 18 months. We will continue to monitor patients' phase I IgG serology to ensure response to treatment with a goal of decreasing his phase I IgG by 4-fold.

He was also followed up at the GI clinic, where his hepatic function normalized, and because of this, a liver biopsy was not pursued.

3. Discussion

Q fever is a rare zoonotic disease caused by the bacteria *C. burnetii*. In the United States, the incidence of acute Q fever is 0.36 cases per million people, and 0.09 per million people for chronic Q fever, according to Cherry et al., in their summary of data provided by the CDC.[3] *C. burnetii* is a gram negative obligate intracellular bacterium that was first reported in Australia by Edward Holbrook Derrick in 1937 (1).[5,6] Q fever is contracted through inhalation of contaminated soil, animal waste, or the placenta of an infected animal.[2,7] It has been found in animals such as sheep, cattle, goats, domestic mammals, marine mammals, reptiles, ticks, and birds.[1,2,7] Our patient presented to our emergency department in the winter which is atypical for Q fever infections. According to the CDC, Q fever infections are more common in late spring and summer months, peaking the months of April and May, correlating with the height of birthing season for goats, cattle, and sheep.[8] Q fever may present acutely as mild febrile illness, hepatitis, pneumonia, meningitis/encephalitis, myocarditis, or chronically as endocarditis, chronic vascular infection, osteomyelitis, osteoarthritis, and chronic pulmonary infection.[2,5,6,9-11]

Patients who are found to have Q fever are predominantly asymptomatic or have a flu-like illness.[2,9,12] If clinical signs and symptoms are present, they typically include fever greater than 10 days, normal white blood cell count, low platelets, abnormal radiographs, elevated liver enzymes, rash (more common in children), and miscarriage or preterm delivery in pregnant patients.[2,13] The most common symptomatic presentation of acute Q fever is a febrile illness with pneumonia or hepatitis.[2] Hepatitis can be due to hepatocellular injury (elevated AST, ALT) or cholestatic disease (elevated alkaline phosphatase, bilirubin).[17,27] As seen with our patient, most common signs of

Table 1. Abnormal initial and subsequent results.

Laboratory examinations			
Test	**Results**		**Reference Range**
Prior to admission			
WBC	3.0 × 10^9/L		3.4–9.6 × 10^9/L
Platelets	123 × 10^9/L		135–317 × 10^9/L
Lymphocytes	0.61 × 10^9/L		0.95–3.07 × 10^9/L
ALT	201 U/L, 522 U/L 4 days later		7–55 U/L
AST	137 U/L, 237 U/L 4 days later		8–48 U/L
Alkaline Phosphatase	131 U/L		40–129 U/L
CRP	61.1 mg/L		≤8.0 mg/dL
ESR	18 mm/1 h		0–22 mm/1 h
PT	15.7 s		9.4–12.5 s
INR	1.4		0.9–1.1
albumin	3.3 g/dL		3.5–5.0 g/dL
Urinalysis	protein	>300 mg/dL	<26 mg/dL
	bilirubin	Small amount	Negative
	urobilinogen	>8.0 mg/dL	0.2–1.0 mg/dL
	WBC	Occ-3 HPF	
During admission			
ALT	281 U/L		7–55 U/L
AST	111 U/L		8–48 U/L
Alkaline Phosphatase	99 U/L		40–129 U/L
Blastomyces EIA antibody	positive		
EBV IgG antibody	positive		
CMV IgG antibody	positive		
Post-discharge			
phospholipid antibody	102.8 GPL		<15.0 (Negative) GPL
Lyme IgM	positive		

hepatic involvement included elevated liver enzymes along with nonspecific signs such as fever, chills, and headaches.[1,13] Patients are rarely jaundiced during the illness course, and when a liver biopsy is done, hepatic granulomas can be observed, which are classically described as "doughnut" granulomas.[1,5] These doughnut granulomas consist of a central fat vacuole, a fibrin ring, activated macrophages, and lymphocytes. In addition, two other "non-typical" granulomas have been described in the literature for patients with acute Q fever infection. First is granuloma with fibrin without the typical ring configuration and the second is with a clear center with no fibrin material. Although, we did not do a liver biopsy for our patient his laboratory results demonstrated elevated AST and ALT with an upward trajectory on repeated laboratory tests. His alkaline phosphates and bilirubin levels were within normal reference range, indicating the type of liver injury in our patient was limited to hepatocellular type of injury.[14-17] In contrast cholestatic liver disease is characterized by an increase in alkaline phosphatase and bilirubin.[27–30] The reason for variation in clinical presentation (whether this may be due to severity of disease) is not very clear and could be an area of future research to evaluate.[17] We ruled out other causes of hepatitis, including viral, autoimmune, and acute alcohol toxicity that may have contributed to his clinical picture. As the more common disorders that cause hepatitis were ruled out, the decision was made to pursue more rare etiologies that could explain his clinical presentation, and hence Q fever serology was sent.

Table 2. Patients Q fever serologies.

Component	Day 0	1 month	4 months
Phase I IgG	<1:16	1:128	1:2048
Phase II IgG	1:8192	1:2048	1:8192
Phase I IgM	1:1024	≥1:2048	≥1:2048
Phase II IgM	≥1:2048	≥1:2048	1:256

Diagnosing Q fever is primarily done with serology due to *C. burnetii* being difficult to culture and requiring a biosafety level 3 laboratory (BSL3).[1] The most commonly available tests are indirect Immunofluorescence assay (IFA), Complement fixation test (CFT), and ELISA.[1,2] The CDC recommends combining PCR with a serologic test for early detection of Q fever infection.[1] *C. burnetii* exists in two distinct antigenic phases (phase I and phase II) due to its varying expression of lipopolysaccharides (LPSs).[5,18,19] Depending on the expression of phase II or phase I antigenicity, it is categorized as either acute Q fever or chronic Q fever, respectively. Currently, there are calls from the international

community to increase the titer levels to classify a patient as having chronic Q fever; however, there has not been a consensus on this, and titer level cutoffs vary depending upon the type of testing used.[20]

The treatment of choice for symptomatic acute Q fever is 100 mg oral doxycycline twice a day for 14 days.[1,12] However, if a patient is unable to take doxycycline, other antibiotics that can be prescribed include moxifloxacin, clarithromycin, trimethoprim-sulfamethoxazole, and rifampin.[1,12,21-23] Currently, asymptomatic patients should not receive treatment but should be monitored for progression to chronic Q fever. They should also be evaluated for risk factors (immunosuppression, pregnancy, vascular and valvular heart defects) that predispose them to severe illness.[1,24] Regardless of risk factors, patients should be reevaluated over a 6- month period to check for possible disease progression.[1] If there is no evidence of disease progression after six months (phase I IgG titer >1:1024, clinical signs), serologic monitoring can be discontinued. Patients who have significant risk factors may need to extend serologic monitoring beyond 6 months as well.[1,5]

Our patient was noted to have increasing Phase I IgG antibodies, which was concerning for the development of chronic Q fever infection. He was also noted to have significantly elevated anti-phospholipid antibodies, which has been associated with a higher risk of developing chronic Q fever infections.[20,25] Patient's serology was positive for Lyme IgM; however, the patient did not experience typical findings (rash, tick bite) of Lyme disease. CT imaging (Fig. 1) showed an infarction of the spleen, likely reflecting cardio emboli from endocarditis.

Indicative of thrombosis in the spleen possibly from vasculitis caused by his *Coxiella* infection. There is some evidence of splenic infarct of patients with Q fever infection[26] He then had further workup, which showed evidence of endocarditis, and to date remains on treatment for this. Treatment for chronic Q fever is with 100 mg of doxycycline twice daily and 200 mg hydroxychloroquine three times a day. The duration can be variable depending upon the clinical course but is a minimum of 18 months.[1]

4. Conclusion

Q fever is a rare disease and diagnosis can be challenging due to non-specific presentation of fever, myalgia, fatigue, and elevated liver enzyme with no clear etiology. The diagnosis is delayed due to the time required to detect appropriate Q fever immunoglobulin titer (4-fold increase) and the organism being difficult to culture. The lesions of endocarditics with chronic Q fever tend to be very small and are often missed by transthoracic or even transesophageal echocardiogram (source?). This case demonstrates the need for a high index of suspicion for Q fever infection and continued follow-up in these patients to evaluate for conversion to chronic Q fever infection. High mortality is associated with patients with chronic Q fever infection that is untreated; therefore, continued monitoring is of utmost importance in these patients. Q fever is insidious in its clinical presentation. Through this case presentation we hope we have highlighted the importance of maintaining a high clinical suspicion for *C. burnetii* infection when caring for a patient with nonspecific signs of infection (i.e., fever) and hepatitis without a clear etiology.

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Conflict of interest

There are no conflicts of interest to report.

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