CASE REPORT

Q fever hepatitis and endocarditis in the context of haemochromatosis

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SUMMARY

Hereditary haemochromatosis is associated with increased susceptibility to some infections. We report here a case of Q fever in a patient with coexistent haemochromatosis. The literature is reviewed in regard to the effect of haemochromatosis on susceptibility to infectious disease in general and Q fever in particular. Although there is documented increased risk in these patients for some infectious conditions, a specific association with Q fever has not been previously reported. The present report raises the possibility of such a clinically relevant connection.

BACKGROUND

Q fever is caused by *Coxiella burnetii*, a spore-forming Gram-negative coccobacillus (historically grouped with *Rickettsia*). It is a worldwide zoonotic disease with acute and chronic stages. Its main route of transmission is inhalational, with the respiratory system being the main organ system affected, but gastrointestinal, hepatic and cardiac systems may also be affected. The most common animal reservoirs for this zoonosis are cattle, sheep and goats. These animals shed the organisms in urine, faeces, milk and especially in birth products.¹ Following exposure, the incubation period is 9–40 days. More than half of the patients are asymptomatic, while most of the rest present with influenza-like symptoms, or as a chest infection. Adults are more commonly symptomatic than children. When symptomatic, 61.9% of cases of acute Q fever are manifested as hepatitis.² Chronic cases are rare and most often manifest as a culture-negative endocarditis.³

CASE PRESENTATION

A 57-year-old white man, new to our clinic, presented with fever of 2 month's duration. He was employed as an equipment technician and has no history of chronic medical illnesses. The patient reported exposure to a sick rabbit while he was hunting; the rabbit acted abnormally and its liver looked abnormal to him on field-dressing it. Nine days later, he began to experience palpitations (more severe at night) associated with fever and chills with a $T_{\max}=39.3^{\circ}\text{C}$ (102.8°F), cough and dyspnoea, chest tightness with diaphoresis, arthralgias, myalgias and headaches. Three weeks after the onset of fever, he developed right upper quadrant pain. He experienced decreased appetite accompanied by a 15-pound weight loss over 4 weeks. Subsequently, a transient, pruritic rash developed on his thighs and lasted for a week. Prior to

presenting to our care, he was treated with moxifloxacin (400 mg daily for 7 days), azithromycin (500 mg on day 1 followed by 250 mg days 2 through 5) and acetaminophen (325 mg every 4 hours as needed) with no improvement.

He had conjunctival injection, tenderness in right upper quadrant, liver palpable 4 cm below the costal margin but no splenomegaly. There was no cardiac murmur; no rash or skin lesions. The remainder of his physical examination was unremarkable.

INVESTIGATIONS

Initial laboratory evaluation showed leucocytosis and moderately elevated liver enzymes with normal bilirubin. Amylase and lipase were moderately elevated. He had positive antinuclear antibodies and antismooth muscle antibodies. His ferritin was significantly elevated, as was his sedimentation rate and C reactive protein. Q fever serology indirect fluorescent antibody (IFA) was negative (table 1).

Abdominal ultrasound scan showed thickening of the gall bladder wall and a small amount of pericholecystic fluid. Transthoracic echocardiogram showed abnormal aortic valve with the right coronary cusp thickened and immobile, but transoesophageal echocardiogram was negative for vegetations. Hepatobiliary iminodiacetic acid scan was negative for cholecystitis. CT-guided liver biopsy was carried out and showed patchy granulomatous inflammation with focal areas of liver necrosis, and structures suspicious for fungal organisms (figure 1A, B). Antifungal medication and prednisone were initiated: itraconazole 200 mg two times a day and prednisone 40 mg daily.

At the 1 week postdischarge follow-up, the patient remained febrile and transaminase levels continued to rise; itraconazole was changed to fluconazole 200 mg daily due to concerns about potential hepatotoxicity of the former agent complicating the picture. Just over a week later, the fever persisted; the antimicrobial regimen was changed to amphotericin B 250 mg daily and empiric doxycycline 100 mg two times a day. A repeat liver biopsy was ordered and subsequently performed as an outpatient.

The patient developed acute kidney injury with a creatinine of 3.2 mg/dL and was re-admitted 25 days after discharge from the initial hospitalisation. Owing to kidney injury, amphotericin B was stopped; in light of the second liver biopsy which showed 'no fungal organisms' and a now afebrile patient, no substitute antifungal agent was started. Echocardiogram and Q fever IFA were repeated

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Table 1 Initial laboratory findings

Complete blood count	
WCC	14.6×10 ³ /μL
Haemoglobin	13.2 g/dL
Platelets	313×10 ³ /μL
Liver function tests	
AST	228 U/L
ALT	227 U/L
ALP	157 U/L
Bilirubin	0.8 mg/dL
Pancreas function tests	
Amylase	295 U/L
Lipase	256 U/L
Rheumatological testing	
ANA	Positive
Anti-smooth muscle antibodies	Positive
Ferritin	3724 ng/mL
ESR	54 mm/hour
CRP	100 mg/dL
Serology	
Q fever phase I and II IgM	Negative

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANA, anti-nuclear antibody; IgM, immunoglobulin M; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; WCC, white cell count.

6 weeks after the initial laboratory testing. The IFA was now positive with both phase I and II IgG titres of 1:4096, and the echocardiogram showed an aortic valve mass. Cardiology was consulted, and the diagnosis of endocarditis was confirmed.

Owing to a higher ferritin level than typically seen as an acute-phase reactant, haemochromatosis testing was ordered and the patient tested positive for C282Y/C282Y mutation. Sections of the second liver biopsy were stained with Prussian blue and demonstrated iron deposits (figure 1C).

DIFFERENTIAL DIAGNOSIS

The final diagnoses were Q fever granulomatous hepatitis and endocarditis, with coexistent hereditary haemochromatosis.

TREATMENT

The patient's Q fever was successfully treated with doxycycline 100 mg two times a day and hydroxychloroquine, 200 mg two times a day; the prednisone was gradually tapered. For his haemochromatosis, phlebotomy was initiated.

OUTCOME AND FOLLOW-UP

He initially experienced clinical recovery. Unfortunately, despite recommendations by the infectious diseases consultant for life-long antibiotic treatment for the Q fever endocarditis, the patient discontinued it due to photosensitivity and developed recurrent active disease.

DISCUSSION

In spite of a drastic expansion in the diversity of laboratory tests and other diagnostic modalities that are readily available, fever of unknown origin (FUO) still presents a challenge to diagnosticians. We present a case of Q fever hepatitis and endocarditis that was diagnosed along with coexistent haemochromatosis during a work up of FUO. To the best of our knowledge, this is the first reported case of Q fever in a patient with haemochromatosis.

The coexistence of this infection with the inherited condition is intriguing. Hereditary haemochromatosis is genetically

Figure 1 (A) H&E stain of initial biopsy demonstrating ill-defined granulomatous inflammation, (B) silver stain of initial biopsy demonstrating intracellular organism (arrows) and (C) Prussian blue stain of subsequent biopsy demonstrating intracellular iron deposits and no fungal organisms.

determined group of disorders characterised by abnormal accumulation of iron in different tissues.⁴ The most common among them is type I caused by variations in *Hfe*, the gene which encodes a class I major histocompatibility complex-like cell surface protein expressed on hepatocytes, macrophages and intestinal crypt cells.⁵ Although it has been established that individuals with hemochromatosis are more prone to infections with pathogens such as *Yersinia enterocolitica* and *Vibrio vulnificus*,^{6–7} a relationship between this condition and susceptibility to Q has not been reported.

Monocytes from hemochromatosis patients are less responsive to lipopolysaccharide-induced tumour necrosis factor- α (TNF) production.⁸ TNF is known to play an important role in the defence against intracellular bacteria such as *C. burnetii*. It promotes internalisation and intracellular killing of *C. burnetii* in monocytes.^{9–10} *C. burnetii*-infected TNF-knockout mice progressed to early bacteraemia and severe heart lesions.¹¹

Decreased TNF production due to his haemochromatosis may have contributed to our patient's development of hepatitis, severe endocarditis and valvulopathy. Though this connection may seem logical, it is not necessarily the case: there appears to be no increased susceptibility to Q fever in patients who are on TNF inhibitors for rheumatoid arthritis.¹²

Other cytokines may also play a role. *Hfe*-deficient mice (an animal model of hereditary haemochromatosis) exhibit diminished iron-dependent translational control of cytokine biosynthesis.¹³ Haemochromatosis may lead to suboptimal recruitment of immune cells to pulmonary system in the face of infections,¹⁴ which might allow for more successful development of bacteraemia from inhaled *C. burnetii*.

Although uncommon, Q fever remains one of the potential causes of FUO and can be fatal if not diagnosed in a timely fashion. We have reported a case of Q fever in the context of hereditary haemochromatosis. Whether patients with haemochromatosis are more prone to Q fever and its complications is yet to be established. However, we believe that this case report raises the possibility of a potentially clinically relevant connection.

Learning points

- ▶ Although uncommon, Q fever remains one of the potential causes of fever of unknown origin and can be fatal if not diagnosed in a timely fashion.
- ▶ Individuals with haemochromatosis are more prone to by *Yersinia enterocolitica* and *Vibrio vulnificus*.
- ▶ No relationship between this condition and susceptibility to Q fever has previously been reported; this case report raises the possibility of a potentially clinically relevant connection.

Contributors The authors affirm substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data; drafting the work or revising it critically for important intellectual content; final approval of the version published; agreement to be accountable for all aspects of the work in

ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. HE was directly involved with the clinical care of the patient reported in this case. HE and MKH were involved in the analysis, interpretation, planning, conduct and writing of the manuscript and are responsible for the overall content as guarantors.

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