Q Fever Manifested as Acalculous Cholecystitis

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**KEY WORDS:** Coxiella burnetii, Q fever, cholecystitis, xanthogranulomatous cholecystitis

***C***oxiella burnetii-induced Q fever, a worldwide occurring zoonosis, is an endemic disease in Israel. The annual incidence, based on documented serological validation in the national reference laboratory, the Ness Ziona Biologic Institute, was 148 cases per year in 2013 and 2014 (http://www.health.gov.il/UnitsOffice/HD/PH/epidemiology/Pages/epidemiology_report.aspx), but conceivably there are many additional undiagnosed cases. Acute Q fever usually presents as a self-limited febrile illness, pneumonia or hepatitis. However, acute Q fever has additional protean clinical manifestations [1], and therefore requires a high index of suspicion in endemic regions.

We present a patient with acute Coxiella burnetii infection, manifested by fever, hepatitis and acalculous cholecystitis. This report and a few previously described patients [2-5] underscore the need for awareness regarding Q fever as a possible cause in cases of cholecystitis without underlying cholelithiasis.

**PATIENT DESCRIPTION**

A 55 year old man was hospitalized for the evaluation of protracted fever and abnormal liver function tests. Intermittent fever developed 10 days prior to hospitalization, reaching 39.5°C, associated with diaphoresis, loss of appetite and mild headache at rising temperature. Otherwise, a systematic review was unremarkable. Prior to hospitalization the patient was treated with roxithromycin for 3 days without apparent improvement.

There were no indications for potential exposure to Brucella, Borrelia, malaria or Rickettsia. The patient reported a trip with his family to the northern Galilee 2 weeks prior to his illness. Family members concomitantly developed transient febrile illness, the daughter presenting respiratory symptoms and his wife developing diarrhea. All their symptoms resolved without treatment within a week or so.

Physical examination on admission was unremarkable, other than minimal epigastric discomfort and mild splenomegaly, with the spleen percussed at the anterior axillary line. Laboratory investigation disclosed a mixed pattern of mildly abnormal liver function tests, with alkaline phosphatase 207 U/L (normal range 40–130 U/L), gamma-glutamyl transpeptidase 189 U/L (8–61 U/L), alanine aminotransferase 114 U/L (0–40 U/L), aspartate aminotransferase 67 U/L (0–35 U/L), lactate dehydrogenase 738 U/L (240–480 U/L). Complete blood counts were normal, but C-reactive protein (CRP) was elevated (18 mg/dl, normal range 0–0.5). Chest X-rays and urinalysis were unremarkable. Abdominal ultrasound showed mild splenomegaly and fatty liver but was otherwise unremarkable. Abdominal ultrasound appeared normal.

Blood cultures were obtained, as were serologies for hepatitis A, B and C virus (HAV, HBV, HCV), Epstein-Barr virus, cytomegalovirus, Brucella, Rickettsia, and Q fever. The blood smear was negative for Borrelia. Intermittent high fever continued for another 4 days, associated with worsening liver function tests. Blood cultures and serologies were all negative, with the exception of Q fever antibodies which were negative for phase I but borderline positive for phase II antibodies in our lab.

Bone marrow samples obtained for cultures and biopsy were unremarkable, other than a single ill-defined non-caseating granuloma. At this point doxycycline treatment was initiated for 10 days; however, daily intermittent fever persisted, and right upper quadrant abdominal pain gradually developed, associated with a positive Murphy sign. Computed tomography (CT) showed retracted gallbladder with concentric enhancing mucosal line creating a halo appearance. No cholecystitis or pericholecystic inflammation was seen and abnormalities were confined to the gallbladder wall [Figure 1A and B]. This finding was confirmed by repeated abdominal ultrasound [Figure 1C], which was completely different from the normal gallbladder ultrasonic appearance 6 days earlier. Cholecystectomy was considered but abandoned due to spontaneous rapid clinical convalescence, with normalization of liver blood tests, CRP and gallbladder appearance on repeat ultrasound examination. Serologic confirmation of Q fever was performed in the Israeli Reference Laboratory of the Ness Ziona Biologic Institute, with detection of a phase II IgG antibody titer by indirect immunofluorescence assay (IFA) of > 1:6400.

**COMMENT**

Coxiella burnetii infection may manifest as acute or chronic febrile illness, the latter usually in the form of endocarditis [1]. This unusual case report illustrates a rather rare condition of Q fever-related acalculous cholecystitis. Seven such patients with an additional two literature cases are described in the largest series from southern France [2], where Q fever is highly endemic. In this series, fever and right upper quadrant pain and tenderness developed concomitantly,
and imaging on admission disclosed cholecystitis with distended gall bladder wall. Cholelithiasis was present in only one of the nine patients described. The diagnosis of acute Q fever was established by rising titers of phase I and phase II antibodies, using IFA for immunoglobulin (Ig) G, IgM and IgA. Six of these patients underwent cholecystectomy within 2–3 days of admission. Interestingly, pathologic evaluation disclosed acute and chronic inflammation with foamy macrophages, and concomitant liver biopsies showed non-caseating granulomas. Cultures from the removed bladders were not reported and immunohistochemical examination for Coxiella burnetii was negative [2]. This might reflect low sensitivity of this test, since PCR for Coxiella burnetii was positive in a gallbladder removed from a butcher with Q fever and acalculous cholecystitis [3].

The radiologic features of cholecystitis in our patient were quite peculiar, both in terms of pattern and pace of evolvement. Besides the absence of cholelithiasis or dilation of the gallbladder, cystic duct or common bile duct, there was a diffuse and symmetric wall thickening with submucosal enhancement and a peripheral hypodense halo, resembling xanthogranulomatous cholecystitis. This imaging pattern, identical to previous case reports [4,5], might reflect the accumulation of foamy macrophages shown on pathologic evaluation in the above mentioned case series [2]. In addition to these peculiar morphologic characteristics, the time for their development may also be suggestive for Q fever. In our patient it took about 14 days from the commencement of symptoms (fever, epigastric discomfort) to the evolution of abnormal gallbladder morphology, whereas at 10 days into the illness the ultrasonic appearance of the gallbladder was unremarkable. This concurs with a previous case report [5], where initial normal sonography transformed into the peculiar xanthogranulomatous-like pattern. It is possible that initial epigastric discomfort in both cases was related to hepatitis, with subsequent transformation of symptoms and signs with the addition of gallbladder inflammation. The time lapse from symptoms to the radiologic imaging in the other few reported cases has not been clearly specified. Our patient and the one described by Reina-Serrano et al. [5] are the only reports of Q fever cholecystitis with repeated radiologic evaluation, showing transformation from normally appearing gallbladder to a diseased pattern. Thus, it is conceivable that indeed the progression of radiologic abnormalities in cholecystitis related to Coxiella burnetii may be relatively slow, as compared to abrupt changes occurring in trivial acute cholecystitis.

In a case series of three American soldiers serving in Iraq, infected with Q fever, Hartzell et al. [4] propose that the presence of pneumonia or hepatitis in addition to acalculous cholecystitis should suggest a Coxiella infection, as would a clinical response to doxycycline within 48 hours. This latter-suggested criterion is not supported by our patient’s clinical course, where the clinical and radiologic features of cholecystitis developed while the patient was being treated with a 10 day course of doxycycline.

Regarding the clinical course and medical decision analysis, Q fever was high on the list of differential diagnoses on admission, based on the initial symptoms, the history of recent travel in a rural area, the abnormal liver function tests and concomitant febrile illness among family members. Yet, the lack of initial clinical response to doxycycline and the development of clinical signs of cholecystitis, associated with evolving peculiar abnormal radiologic appearance of the gallbladder, led us to the differential diagnosis of xanthogranulomatous-like cholecystitis and to consider cholecystectomy. Fortunately, the subsequent amelioration of symptoms and the confirmatory serologic results provided the correct diagnosis of Q fever-associated cholecystitis.

Importantly, pronounced rising titers of phase I antibodies raised concern regarding chronic Q fever, which mandated protracted combined antibiotic regimen [1]. As of publication, this treat-
Excess TGFβ mediates muscle weakness associated with bone metastases in mice

Cancer-associated muscle weakness is a poorly understood phenomenon, and there is no effective treatment. Waning et al. found that seven different mouse models of human osteolytic bone metastases—representing breast, lung and prostate cancers, as well as multiple myeloma—exhibited impaired muscle function, implicating a role for the tumor-bone microenvironment in cancer-associated muscle weakness. The authors found that transforming growth factor-beta (TGFβ), released from the bone surface as a result of metastasis-induced bone destruction, upregulated NADPH oxidase 4 (Nox4), resulting in elevated oxidation of skeletal muscle proteins, including the ryanodine receptor and calcium (Ca²⁺) release channel (RyR1). The oxidized RyR1 channels leaked Ca²⁺, resulting in lower intracellular signaling, which is required for proper muscle contraction. They found that inhibiting RyR1 leakage, TGFβ signaling, TGFβ release from bone or Nox4 activity improved muscle function in mice with MDA-MB-231 bone metastases. Humans with breast or lung cancer-associated bone metastases also had oxidized skeletal muscle RyR1 that is not seen in normal muscle. Similarly, skeletal muscle weakness, increased Nox4 binding to RyR1 and oxidation of RyR1 were present in a mouse model of Camurati-Engelmann disease, a non-malignant metabolic bone disorder associated with increased TGFβ activity. Thus, pathological TGFβ release from bone contributes to muscle weakness by increasing Ca²⁺-induced muscle force production.

Nature Med 2015; 21; 1262
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Everolimus-eluting bioresorbable scaffolds for coronary artery disease

In patients with coronary artery disease who receive metallic drug-eluting coronary stents, adverse events such as late target lesion failure may be related in part to the persistent presence of the metallic stent frame in the coronary vessel wall. In an attempt to improve long-term outcomes Ellis et al. developed bioresorbable vascular scaffolds. In a large multicenter randomized trial, 2008 patients with stable or unstable angina were randomly assigned in a 2:1 ratio to receive an everolimus-eluting bioresorbable vascular (Absorb) scaffold (1322 patients) or an everolimus-eluting cobalt-chromium (Xience) stent (686 patients). The primary endpoint, which was tested for both non-inferiority (margin 4.5 percentage points for the risk difference) and superiority, was target lesion failure (cardiac death, target vessel myocardial infarction, or ischemia-driven target lesion revascularization) at 1 year. Target lesion failure at 1 year occurred in 7.8% of patients in the Absorb group and in 6.1% of patients in the Xience group (difference 1.7 percentage points, 95% confidence interval 0.5–3.9, P = 0.007 for non-inferiority and P = 0.16 for superiority). There was no significant difference between the Absorb group and the Xience group in rates of cardiac death (0.6% and 0.1% respectively, P = 0.29), target vessel myocardial infarction (6.0% and 4.6% respectively, P = 0.18), or ischemia-driven target lesion revascularization (3.3% and 2.5% respectively, P = 0.50). Device thrombosis within 1 year occurred in 1.5% of patients in the Absorb group and in 0.7% of patients in the Xience group (P = 0.13).

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References