Q Fever Manifested as Acalculous Cholecystitis

Moshe Simons MD[1], Samuel N. Heyman MD[1], Michael Bursztyn MD[1], Oded Shalev MD[1], Nurith Hiller MD[2] and Sarah Israel MD[1]

Departments of [1]Medicine and [2]Radiology, Hebrew University Hadassah Medical Center, Mt. Scopus, Jerusalem, Israel

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Coxiella 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. 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 cholelithiasis 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,

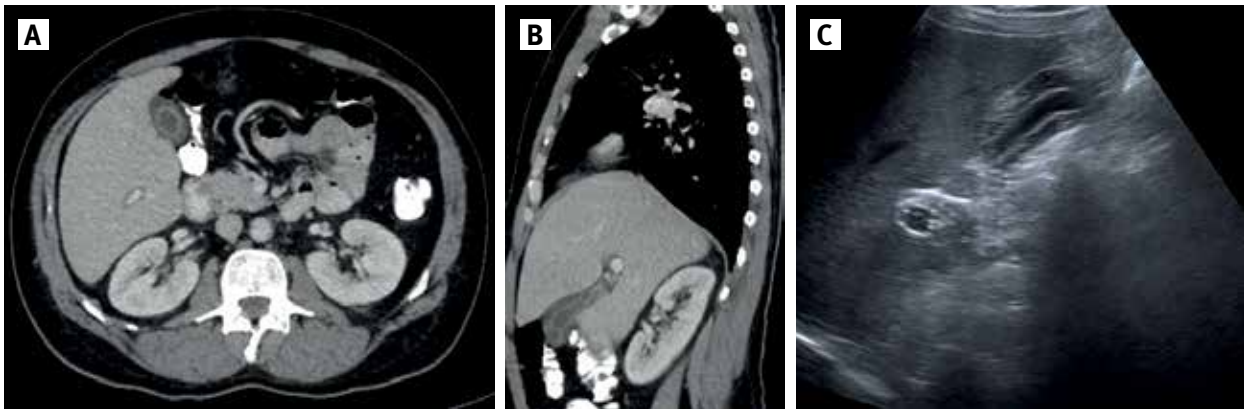

Figure 1. Radiographic findings of Q fever associated acalculous cholecystitis. Computed tomography **[A]** and **[B]** demonstrates diffuse symmetric thickened and hypodense gallbladder wall with normal enhancing mucosal line, creating a halo appearance. Similar findings were shown on sonography **[C],** while initial imaging 10 days earlier were unremarkable

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 choledochus, 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 chocystitis 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 docycyline 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-

ment was not initiated, as the patient remains in good health over 26 months of follow-up, without laboratory abnormalities, with normal echocardiographic findings, including repeated trans-esophageal evaluations, and with unremarkable total body FDG-PET/CT.

In summary, our patient can be added to the few small series and case reports [2-5] indicating that Q fever may be manifested as acute cholecystitis. The initial constitutional signs and symptoms and the late gradual development of local symptoms and radiologic findings differ from the abrupt clinical presentation of typical cholecystitis, particularly with the absence of underlying cholelithiasis or other causes of acalculous cholecystitis, such as diabetes, major trauma or surgery, burns or AIDS. Finally, our case report suggests that Q fever-related cholecystitis cannot be excluded by the lack of response to a short course of doxycycline, as suggested by Hartzell et al. [4].

Correspondence
Dr. S.N. Heyman
Dept. of Medicine, Hadassah University Hospital, P.O. Box 24035, Mt. Scopus, Jerusalem 91240, Israel
Fax: (972-2) 584-4526
email: Heyman@cc.huji.ac.il

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