

Acute hepatitis with or without jaundice: a predominant presentation of acute Q fever in southern Taiwan

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Acute Q fever was previously regarded as an uncommon infectious disease in Taiwan but has been increasingly recognized recently. Acute febrile illness, hepatitis, and pneumonia are the 3 most common manifestations of this condition, whereas jaundice is rarely reported among patients with acute Q fever. We report 2 cases of acute Q fever with jaundice and multi-organ involvement. The first patient presented with fever, severe headache, and acute abdomen necessitating laparotomy and was complicated with acute cholestatic hepatitis, acute non-oliguric renal failure and disseminated intravascular coagulation. The second patient had acute cholestatic hepatitis and thrombocytopenia, and the latter was likely related to the infection of bone marrow by *Coxiella burnetii*, as evidenced by the presence of *C. burnetii* DNA detected by nested polymerase chain reaction. The incidence and clinical significance of hyperbilirubinemia was also determined by review of medical records of 35 cases of acute Q fever cases diagnosed serologically at National Cheng Kung University Hospital from 1994 to 2001. All had biochemical hepatitis and 23% had hyperbilirubinemia (serum bilirubin ≥ 2 mg/dL). The febrile course before admission and the period between the initiation of effective medication to defervescence were longer in patients with hyperbilirubinemia than in patients without hyperbilirubinemia, although this difference was not significant. Our results suggest that the predominant presentation of acute Q fever in southern Taiwan is acute febrile illness with hepatitis and that jaundice is not uncommon. Due to the clinical polymorphism of acute Q fever, the threshold of surveys for *C. burnetii* infections should be low for febrile patients with elevated transaminases or hyperbilirubinemia of unknown cause.

Key words: *Coxiella burnetii*, hepatitis, hyperbilirubinemia, Q fever, Taiwan

Q fever occurs worldwide, with the exception of New Zealand, either sporadically or in clusters. It is caused by an intracellular microorganism, *Coxiella burnetii*, a member of the Rickettsiaceae. Because *C. burnetii* has an endospore-like stage, it can survive in hostile environments and can be spread by aerosols, an effective mode of transmission for initiation of an outbreak [1]. It is a zoonosis and many domestic or wild animals are natural reservoirs of its etiologic agent. Moreover, *C. burnetii* can be maintained in a cycle involving ticks and vertebrates and be transmitted to livestock and humans either through tick bites or contact with tick excreta [2].

In animals, the majority of infections are asymptomatic. However, in humans, it causes 2 disease patterns — acute and chronic. The latter form is of greater concern, can lead to substantial fatality if the

cardiac valve is involved, and can sometimes invade bone, joints, liver [3], nervous system [4] or placenta [5]. Acute Q fever is more common than chronic infection, and such cases often present with acute self-limited febrile illness, hepatitis, pneumonia, or in combination [6]. Central nervous system involvement is less common [7,8]. There are increasing numbers of reports describing unusual manifestations of cases with acute Q fever.

The major clinical features of acute Q fever vary from country to country. For example, pneumonia is the main presentation in Spain and Switzerland [6], while acute biochemical hepatitis is common in France, Ontario, California, and Australia [9]. Elevated transaminases are common in cases of acute Q fever hepatitis, but hyperbilirubinemia is rarely reported. We report 2 cases of acute Q fever with the unusual manifestation of severe jaundice mimicking acute cholangitis or acute viral hepatitis. In addition, the incidence and clinical significance of hyperbilirubinemia in cases with acute Q fever was determined by a

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retrospective review of the clinical records of all serologically-confirmed cases at our hospital from 1994 to 2001.

Materials and Methods

A total of 35 cases of acute Q fever treated from 1994 to 2001 at National Cheng Kung University Hospital (NCKUH) identified by review of records were included in this retrospective analysis. The diagnosis was made based on the presence of a febrile illness and a compatible serologic profile, which required at least a 4-fold increase in phase II immunoglobulin G (IgG) titers between acute and convalescent sera, or the presence of a significant titer of phase II IgM ($\geq 1:50$). The technique of antibody detection was as previously described [10]. Data were collected from medical records including demographic characteristics, exposure history, laboratory data, clinical course, and antimicrobial therapy. Two cases of acute Q fever with extreme hyperbilirubinemia mimicking acute cholestatic hepatitis are reported in detail.

Fever was defined as an axillary body temperature $\geq 38^\circ\text{C}$. Acute hepatitis was defined as the elevation of serum transaminases ≥ 1.5 times of upper limit of normal values [6], i.e., aspartate transaminase (AST) ≥ 60 IU/L or alanine transaminase (ALT) ≥ 78 IU/L. Hyperbilirubinemia was defined as serum total bilirubin equal to or higher than 2 mg/dL. Defervescence (axillary body temperature of less than 37.5°C) for at least 24 hours and absence of constitutional symptoms was regarded as a clinical response to antimicrobial therapy.

Nested PCR

DNA extract prepared from formalin-fixed paraffin-embedded tissue specimen from bone marrow of case 2 was used for direct detection of *C. burnetii* DNA by nested polymerase chain reaction (PCR) assay. The nested PCR was performed with 2 primer pairs as described previously [11]. The PCR target was the *com-1* gene, which encodes the 27-kDa outer membrane protein of *C. burnetii* [12]. The specimen was deparaffinized and digested with proteinase K-containing buffer as described previously [13]. The genomic DNA was extracted by the standard phenol/chloroform technique [13]. The amplification product was purified with a PCR Clean UP kit (Roche Molecular Biochemicals, Mannheim, Germany) and was sequenced on an ABI PRISM 310 sequencer analyzer (Applied Biosystems, California, USA) with the amplification primers.

Statistics

Chi-squared test or 2-tailed Fisher's exact test was used for categorical variables and the Mann-Whitney *U* test for continuous variables. A *p* value less than 0.05 was considered statistically significant and all tests were 2-tailed.

Results

Case 1

A 44-year-old previously healthy male developed spiking fever, chills, and headache for 10 days. Later, tea-colored urine, abdominal pain, and fullness developed. Initial serum biochemistry profile revealed: blood urea nitrogen (BUN) 27 mg/dL, creatinine (Cre) 1.3 mg/dL, AST 63 IU/L, ALT 73 IU/L, total bilirubin (Bil-T) 8.3 mg/dL, and direct bilirubin (Bil-D) 5.7 mg/dL. Because of right upper quadrant pain, jaundice and high fever, acute cholecystitis with empyema formation was suspected and exploratory laparotomy was done. Clear yellow ascites were found within the abdominal cavity. The gallbladder wall was swollen and the liver congested. However, no evidence of biliary tract obstruction was noted and a T-tube was inserted in the gallbladder.

Five days after surgery, fever persisted, jaundice became more prominent (Bil-T/Bil-D, 14.9/11.1 mg/dL), and severe azotemia (BUN/Cre, 112/7.9 mg/dL) with hyperkalemia (7.4 mmol/L) was noted. The latter may have been related to the administration of a non-steroidal anti-inflammatory agent for pyrexia and intravenous gentamicin (60 mg twice daily) during hospitalization. Due to clinical deterioration, he was transferred to NCKUH.

He had no pets at home and had never traveled abroad. Tracing his history, he had consumed processed goat milk for several years. On his way to work, he daily passed through a road next to a sheep farm. On examination, he was disoriented and irritable. Body temperature was 37.3°C , pulse rate 111/min, respiratory rate 28/min and blood pressure 126/82 mm Hg. Sclera was markedly icteric. Diffuse abdominal tenderness but no rebounding tenderness was noted. Pitting edema was present in bilateral tibial regions.

Laboratory tests showed: white blood cells $10,200/\text{mm}^3$; myelocytes 3%; metamyelocytes 2%; band 34%; segmented 44%; hemoglobin 10 g/dL; and platelets $268,000/\text{mm}^3$. Prothrombin time (PT) was 16.2 seconds (control, 12.4) and activated partial thrombin time 54.8 seconds (control, 25.2). Serum level of fibrinogen was 484 mg/dL (normal, 216-318),

antithrombin-III 59% (normal, 78-151), and fibrin degradation product >40 mg/mL (normal, 0-10), compatible with disseminated intravascular coagulation. Blood biochemistry showed azotemia (BUN/Cre 104/7.6 mg/dL), abnormal levels of hepatic enzymes (AST 60 IU/L; ALT 40 IU/L; alkaline phosphatase 137 IU/L; gamma-glutamyl transpeptidase 104 IU/L), jaundice (BiI-T/BiI-D 13.3/13.1 mg/dL), and hyperkalemia (6.6 mmol/L). C-reactive protein was 114 mg/L. Abdominal computed tomography revealed hepatosplenomegaly with fatty liver, enlargement of both kidneys, and a drainage tube in the right subhepatic area.

For acute azotemia and hyperkalemia, he received emergent hemodialysis. The T-tube in the gallbladder was removed. Bacterial cultures were negative. Antibody surveys for human immunodeficiency virus type 1 (HIV-1), *Leptospira*, *Orientia tsutsugamushi*, *Rickettsia typhi*, and hepatitis A, B, and C virus infections were negative. Serum Venereal Disease Research Laboratory (VDRL) test at the 33rd day was non-reactive. Because of the positive serological result for *C. burnetii*, doxycycline was continued for 3 weeks. During the third week, the diuretic phase of acute renal failure commenced and serum total bilirubin declined to the normal range, being 1.1 mg/dL on the 17th day. After discharge, his renal function recovered completely.

Case 2

A 67-year-old retired farmer with a 30-year history of non-insulin-dependent diabetes mellitus had tea colored urine and poor appetite for 2 weeks. In the few days prior to admission, he complained of fever with chills and burning sensation on micturition. No abdominal

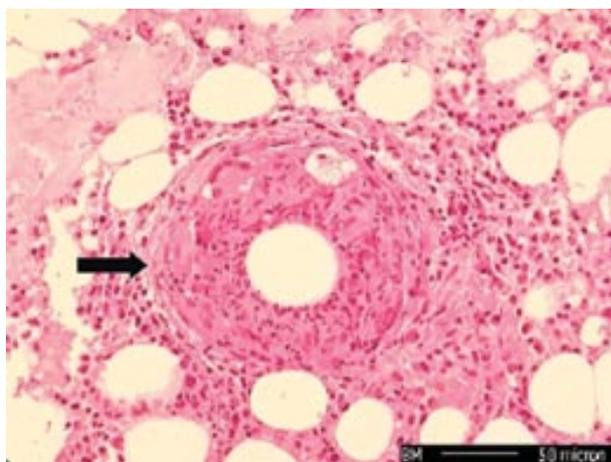


Fig. 1. Bone marrow biopsy in case 2 shows a doughnut granuloma (arrow).

pain or skin rash was noted. He did not have pets at home and had not travelled abroad.

On arrival, fever and jaundice were recognized. Laboratory examinations revealed hyperbilirubinemia (T-Bil/D-Bil 18.7/17.8 mg/dL), thrombocytopenia (platelets 62,000/mm³) and elevated serum C-reactive protein (346.8 mg/L). Under the impression of cholelithiasis with acute cholangitis, parenteral ciprofloxacin was given. Abdominal computerized tomography revealed only gallbladder stones. Endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic nasobiliary drainage (ENBD) was done and also revealed gallbladder stones. There was no radiological evidence of biliary tract obstruction. The ENBD tube was removed 2 days later. Serum total bilirubin level declined a little, but remained high. Low-grade fever persisted.

Antibody surveys for HIV-1, leptospirosis, *O. tsutsugamushi*, *R. typhi*, cytomegalovirus, Epstein-Barr virus infection, dengue virus, and hepatitis A, B, and C virus infections were negative. Bone marrow biopsy was done to survey the cause of fever and thrombocytopenia, and doughnut granuloma with fat vacuoles and multinucleated giant cells were found (Fig. 1). PCR was done on the bone marrow specimen (Fig. 2) and DNA sequence of the amplicon was 100%

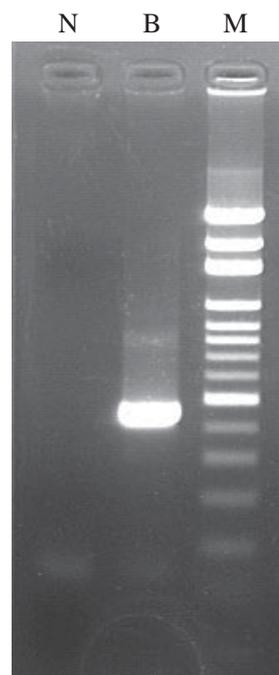


Fig. 2. The gel from nested polymerase chain reaction shows a 438-bp amplicon, with a nucleotide sequence identical to the *com-1* gene of *Coxiella burnetii*. N, negative control; B, bone marrow specimen; M, 100-bp ladder.

Table 1. Comparison of clinical characteristics between cases of acute Q fever with and without hyperbilirubinemia (bilirubin ≥ 2 mg/dL), in National Cheng Kung University Hospital, Tainan

Characteristic	Hyperbilirubinemia	Non-hyperbilirubinemia	<i>p</i>
No. of cases	8	27	
Male (%)	8 (100%)	26 (96.3%)	1.00
Age (years)	52.63 \pm 10.07	47.07 \pm 15.22	0.2
Prolongation of activated partial thromboplastin time/no. of patients (%)	2/5 (40%)	1/9 (11.11%)	0.5
Aspartate aminotransferase (IU/L)	128.63 \pm 57.65	155.3 \pm 163	0.9
Alanine aminotransferase (IU/L)	173.5 \pm 86.81	210.2 \pm 177.7	0.9
Alkaline phosphatase (IU/L)	304.3 \pm 196.7	170.77 \pm 84.79	0.06
Gamma-glutamyl transpeptidase (IU/L)	288.6 \pm 174	206.7 \pm 110.7	0.3
Initial white blood cells (/mm ³)	11,028 \pm 3122	8230 \pm 3143	0.07
Initial hemoglobin (g/L)	12.51 \pm 1.7	14.23 \pm 1.5	0.02 ^a
Initial platelets (/mm ³)	152,750 \pm 65,591	172,889 \pm 7768	0.6
Initial C-reactive protein (mg/dL)	134.4 \pm 107.2	82.9 \pm 53.5	0.3
Fever before admission (days)	11.38 \pm 6.86	9.41 \pm 6.07	0.5
Defervescence after effective therapy (days)	11.63 \pm 14.26	5 \pm 5.33	0.1

^aCalculated by Mann-Whitney *U* test.

identical to the *com-1* gene of *C. burnetii*, indicating the presence of *C. burnetii* DNA. Defervescence and resolution of all symptoms were noted 9 days after the initialization of oral doxycycline.

Cases of acute Q fever in NCKUH

Of 35 patients with acute Q fever identified, all had biochemical hepatitis and 8 (23%) presented with hyperbilirubinemia (Table 1). Total serum bilirubin of the latter patients ranged from 2 to 18.7 mg/dL. Serum ALT levels ranged from 68 to 234 U/L and serum AST from 71 to 254 U/L. The mean age of the 8 patients with hyperbilirubinemia (Table 2) was 51.5 years, and all of them were male. Defervescence and clinical improvement ensued within 2 to 15 days after the initiation of effective antibiotics. Febrile courses before admission tended to be longer in the hyperbilirubinemia group (11.4 \pm 6.9 days) than in the non-hyperbilirubinemia group (9.4 \pm 6.0 days). Time

to defervescence after administration of effective drugs was also longer in the hyperbilirubinemia group (13.1 \pm 14.7 days vs 7.0 \pm 5.5 days). However, neither of these differences were significant. All of the patients were cured without sequelae.

Discussion

Acute Q fever hepatitis has been reported in 11 to 65% of patients with acute Q fever [6,14,15] but jaundice occurs in less than 5% of patients [1]. When liver function tests are considered, 70 to 85% of patients have abnormal values [16]. A previous study which defined hyperbilirubinemia as a total bilirubin >0.93 mg/dL found that 14% of patients with *C. burnetii* pneumonia had this condition [17]. In a study from Spain, the levels of hepatic transaminases and direct bilirubin were significantly higher in Q fever patients without pneumonia when compared with those with

Table 2. Epidemiological and clinical features of 8 cases of acute Q fever with hyperbilirubinemia

Case	Age (years)/gender	Occupation	Pet history	Bilirubin (mg/dL) [maximum/initial]
1	44/M	Farmer	Sheep, consumed sheep milk	14.9/8.3
2	67/M	Farmer	Passed a road with sheep raised alongside it	18.7/18.7
3	36/M	Worker	Chicken, duck	2.5/2.3
4	51/M	Cook	No	2.6/2.6
5	63/M	Policeman	No	3.4/3.4
6	58/M	Farmer	Chicken, squirrel	11/9.5
7	40/M	Textile worker	Cat, kitten	2/1.9
8	53/M	Embroidery worker	Chicken, duck in neighborhood	2.1/2.1

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase

pneumonia [16]. Therefore, biochemical hepatitis is a common finding among patients with acute Q fever, as was found in all patients in this series. Hyperbilirubinemia (total bilirubin >2 mg/dL), a rarely reported condition, was nevertheless noted in 23% of cases in this series.

The mechanism of Q fever hepatitis is not clear. Direct *C. burnetii* infection of hepatocytes or Kupffer's cells is the first consideration. However, immunofluorescent technique failed to demonstrate *Coxiella* antigen in liver granulomas of 2 patients with Q fever [18]. Up to now, there is no adequate evidence supporting such a hypothesis. A hypersensitivity mechanism has been implicated as the possible mechanism and was often associated with the production of various autoantibodies, such as anticardiolipin antibody [19]. It is not clear whether those with hyperbilirubinemia will have a stronger inflammatory response, which leads to a delayed recovery, as we found that these patients had a longer febrile duration after the initiation of effective antimicrobial therapy. Crespo et al [19] suggested that moderate doses of steroids can be useful in patients with acute Q fever granulomatous hepatitis without clinical response to presumed effective antibiotics. None of the 8 cases of Q fever hepatitis in this series required adjuvant steroid therapy and all were cured. The therapeutic role of steroid in Q fever hepatitis remains unresolved.

The 2 unusual cases of acute Q fever described in detail in this report presented with fever, cholestatic hepatitis, and marked hyperbilirubinemia. Since there was no history of exposure to hepatotoxic agents or recent history of blood transfusion in these patients, drug-related hepatitis was not favored and acute infection by hepatitis A, B or C virus could thus be excluded by serologic studies. Severe leptospirosis may present as jaundice, renal dysfunction, or hemorrhagic diathesis.

Leptospirosis was excluded by serologic tests and exposure history. Biliary obstruction was definitely ruled out by the radiological imaging studies. Therefore, the hepatic dysfunction, mainly in the form of cholestatic hepatitis, was related to the acute *C. burnetii* infection in these patients.

Characteristically, a granuloma with a dense fibrin ring surrounded by a central vacuole, the so-called "doughnut granuloma" or lipogranulomatous changes, can be seen in the liver [20] or bone marrow [21,22], as was found in the bone marrow of case 2. The discovery of lipogranulomatous changes in the bone marrow biopsy alerted us to the diagnosis of Q fever. However, doughnut granuloma is not pathognomonic of Q fever and has been seen in certain infectious and non-infectious diseases, such as tuberculosis, cytomegalovirus hepatitis, toxoplasmosis, leishmaniasis, Hodgkin's disease, Crohn's disease, sarcoidosis or drug-induced granulomatous hepatitis [5,15]. The PCR detection of *com-1* gene of *C. burnetii* in the bone marrow specimen provides direct evidence of involvement by *C. burnetii*. Moreover, a previous study found that among patients with post-Q fever fatigue syndrome, a chronic sequelae to acute Q fever, 65% (13 of 20) had low levels of *C. burnetii* DNA in bone marrow aspirates, although the significance of this finding remains obscure [23]. This result indicates that PCR can be used for rapid diagnosis of Q fever in a febrile patient with doughnut granuloma in bone marrow biopsy or liver tissue. To our knowledge, this is the first case report with acute Q fever and the detection of *C. burnetii* DNA in bone marrow.

This study had limitations. First, the retrospective design may have led to incomplete history and clinical information of the patients. Second, in endemic areas of hepatitis virus infection, such as Taiwan, hepatitis as the predominant presentation of acute Q fever may be related to the prevalence of chronic infections of hepatitis

Max. AST/ALT (IU/L)	Initial white blood cell count (L/m ³)	Defervescence after effective therapy (days)	Effective therapy
68/71	10,200	15	Doxycycline for 21 days
72/144	7500	10	Doxycycline for 14 days
139/196	5700	4	Clarithromycin for 20 days
84/72	6100	Unknown	No therapy
234/254	13,500	10	Doxycycline for 14 days
117/96	6000	5	Minocycline for 16 days
121/118	4100	10	Doxycycline for 8 days
181/262	5500	2	Doxycycline for 15 days

B or C virus in the population. Bias of sample selection must be considered. Third, serological tests for Q fever were performed on the patients on the basis of clinical suspicion, especially on those with fever and liver function abnormality. Therefore, the outstanding hepatic form in our cases may have been related to clinical selection bias.

Only 2 cases of Q fever hepatitis have been previously reported from Taiwan [15,24]. Results of this study suggest, however, that acute Q fever should be added to the list of differential diagnoses of patients with fever, elevated serum transaminase levels, and negative abdominal sonography study, irrespective of the presence or absence of abdominal pain or jaundice. In addition, this condition should be considered in patients with a granulomatous disease involving liver or bone marrow.

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