

Acute Q Fever Presenting as Fever of Unknown Origin with Rapidly Progressive Hepatic Failure in a Patient with Alcoholism

Po-Han Lin,¹ Yi-Chun Lo,¹ Fu-Tien Chiang,^{1,2} Jiun-Ling Wang,¹ Yung-Ming Jeng,³
Chi-Tai Fang,^{1*} Shan-Chwen Chang¹

We report a case of fulminant acute Q fever presenting as fever of unknown origin with rapidly progressive hepatic failure in a patient with alcoholism. A 51-year-old electrician, who was a habitual drinker, presented with a 2-week history of intermittent high fever, acute hepatomegaly and rapidly progressive jaundice after being accidentally exposed to dust from bird nests when he was repairing electrical equipment and circuitry at an abandoned factory in Taipei County. Ascites and prolonged prothrombin time were noted at admission. Transjugular liver biopsy and bone marrow biopsy found multiple small fibrinoid-ringing granulomas in liver parenchyma and bone marrow. Doxycycline therapy was empirically started. The fever gradually subsided over a 2-week period, along with the recovery of liver function. The diagnosis of acute Q fever was confirmed by high titers of antibodies against *Coxiella burnetii* (phase I IgM 1:160 and IgG 1:2560, phase II IgM > 1:320 and IgG 1:5120) and a four-fold elevation of phase II IgG titer in the paired serum. The experience of this case shows that the possibility of Q fever should not be overlooked in patients who have an unexplained febrile illness and severe liver function impairment following exposure to a contaminated environment in Taiwan. [*J Formos Med Assoc* 2008;107(11):896–901]

Key Words: doxycycline, hepatitis, liver failure, Q fever

Q fever is a zoonotic disease caused by the organism *Coxiella burnetii*, which has a worldwide distribution.^{1–12} *C. burnetii* is notorious for its ability to survive for an extended period outside of the reservoir and for its extreme infectiousness.¹⁰ Humans are typically infected through inhaled infectious aerosols or drinking contaminated milk.^{1,10–12} The clinical presentations include flu-like syndrome, prolonged fever, pneumonia, hepatitis, pericarditis, myocarditis, endocarditis,

and meningoencephalitis.¹⁰ The existence of Q fever in Taiwan was first documented in 1993.¹³ The majority of cases were reported from southern Taiwan.^{6,14–16} The most common presentation is acute febrile illness of unknown origin, with or without abnormal liver function.^{6,14,15} Jaundice is rare, but two cases with severe jaundice mimicking acute cholangitis or acute viral hepatitis have been described.⁶ We now report a case of fulminant acute Q fever presenting as

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Departments of ¹Internal Medicine, ²Laboratory Medicine, and ³Pathology, National Taiwan University Hospital, Taipei, Taiwan.

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***Correspondence to:** Dr Chi-Tai Fang, Division of Infectious Diseases, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei 100, Taiwan.

E-mail: fangct@ntu.edu.tw



fever of unknown origin with rapidly progressive hepatic failure, which was successfully treated with timely doxycycline therapy.

Case Report

A 51-year-old electrician was referred to our hospital on May 14, 2005 with a 2-week history of intermittent high fever, acute hepatomegaly and rapidly progressive jaundice. He was a habitual drinker for at least 15 years, and had consumed about four bottles of *Kaoliang Liquor* per day in recent years. There were no known medical diseases, except that anti-HCV was known to be positive 7 years ago. On April 28, 2005, he was accidentally exposed to a large amount of dust from bird nests when he repaired electrical equipment and circuitry at an abandoned factory in Taipei County. Three days later, high fever and tea-colored urine developed. He took some antipyretics but the fever did not resolve. On May 10, he was admitted to a community hospital where physical examination revealed jaundice and a non-tender liver enlarged to 2 cm below the costal margin. Blood tests revealed a white cell count of $9.06 \times 10^3/\text{mm}^3$, C-reactive protein (CRP) of 26.39 mg/dL, serum aspartate aminotransferase (AST) of 264 IU/L, alanine aminotransferase (ALT) of 106 IU/L, total/direct bilirubin of 5.6/4.5 mg/dL, alkaline phosphatase (ALP) of 490 IU/L, and γ -glutamyltransferase (GGT) of 1054 IU/L. Abdominal ultrasound showed hepatosplenomegaly, mild ascites, and bilateral pleural effusion, without an obvious focal lesion or biliary tract dilatation. Ceftriaxone (1 g every 12 hours) was given empirically, but spiking fever persisted. In the following days, the jaundice rapidly progressed (total/direct bilirubin, 9.4/9.3 mg/dL), and the liver enlarged to 6 cm below the costal margin. Blood culture was negative. Disseminated tuberculosis was suspected. However, antituberculous therapy was considered too risky in the presence of rapidly progressive hepatic failure. He was referred to our hospital.

On admission, his consciousness was clear, with body temperature of 39°C, pulse rate of

100/min, respiration rate of 22/min, and blood pressure of 114/70 mmHg. The sclera was icteric. The neck was supple. There was neither lymphadenopathy nor oral thrush. Breath sounds were decreased, with bilateral basal crackles. Heart rhythm was regular without audible murmurs. The abdomen was soft, without tenderness or rebounding pain. The liver was enlarged to 6 cm below the right costal margin. There was an increase in left upper quadrant dullness. There were no other significant physical findings. Complete blood count revealed a white blood cell count of $12.4 \times 10^3/\text{mm}^3$ with neutrophils 73%, hemoglobin of 12.4 g/dL, and platelet count of $202 \times 10^3/\text{mm}^3$. Serum biochemical study showed total/direct bilirubin of 9.4/9.38 mg/dL, albumin of 2.53 g/dL, AST of 88 IU/L, ALT of 53 IU/L, ALP of 958 IU/L, GGT of 762 IU/L, and CRP of 17.28 mg/dL. Prothrombin time was prolonged (16.1 seconds; international normalized ratio [INR] was 1.3). Renal function tests were normal, with creatinine of 0.8 mg/dL and blood urea nitrogen of 10.7 mg/dL. There was no pyuria. Chest X-ray showed blunting of bilateral costophrenic angles, but no pneumonia (Figure 1). Both abdominal sonography and abdominal computed tomography

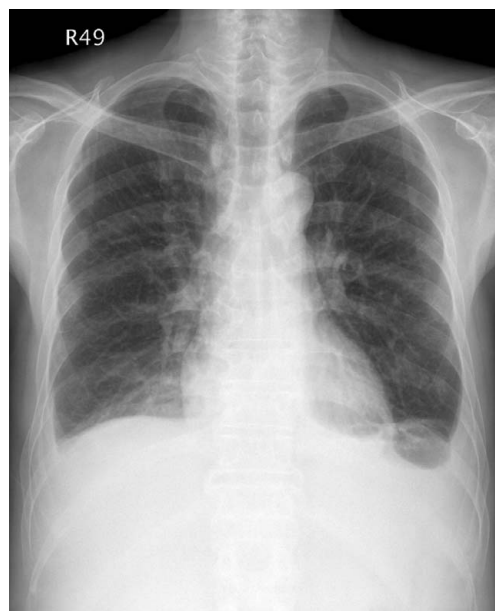


Figure 1. Chest radiography on admission shows blunting of bilateral costophrenic angles. There was no evidence of pneumonia.

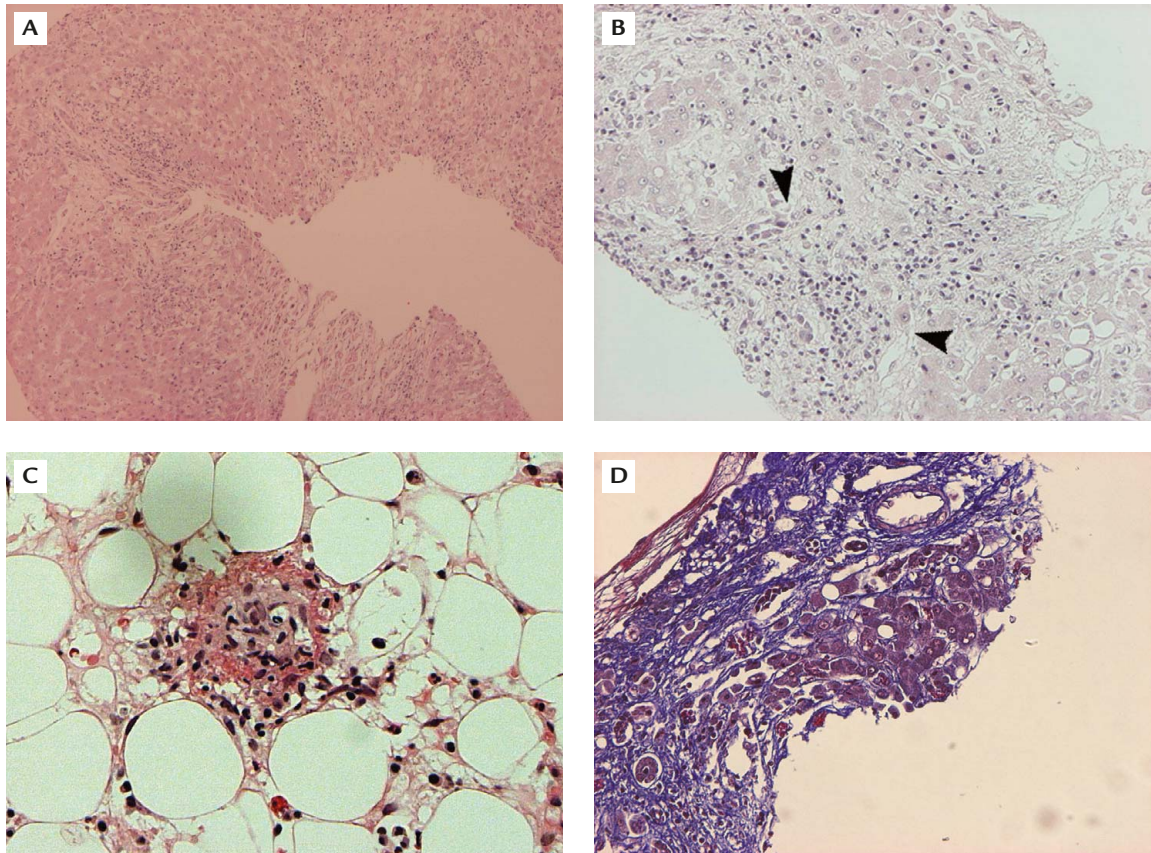


Figure 2. Histopathology of liver and bone marrow. Hematoxylin and eosin staining shows: (A, B) multiple granuloma disseminated in the liver parenchyma, as indicated by arrowheads; (C) fibrinoid ring granuloma in bone marrow. (D) Masson's trichrome staining shows fibrous bands (blue) around regenerative liver parenchyma (red, lower right), indicating progression to cirrhotic stage. (Original magnification, 40×, 100×, 200×, and 100×, respectively).

demonstrated hepatosplenomegaly, ascites, and bilateral pleural effusion. Cefotaxime (1 g every 6 hours) and doxycycline (100 mg twice daily) were started empirically on May 14, 2005. Leptospirosis, Q fever, disseminated tuberculosis, and non-Hodgkin's lymphoma were considered as the differential diagnoses. Nevertheless, needle live biopsy could not be performed due to the presence of both ascites and a prolonged prothrombin time.

Transjugular liver biopsy and bone marrow biopsy were performed on May 19, 2005 after prolonged prothrombin time was corrected by fresh frozen plasma infusion. Multiple small fibrinoid-ring granulomas were found in liver parenchyma and bone marrow (Figures 2A, B and C), without acid-fast bacilli or periodic acid-Schiff-positive fungi. Mallory bodies and focal macrovesicular steatosis were also seen in liver parenchyma, compatible with alcoholic liver

disease. Masson's trichrome stain showed fibrous bands around regenerative liver parenchyma, indicating progression to cirrhotic stage (Figure 2D). Serologic tests for *Leptospira*, HAV, HBV, and HEV were all non-reactive. Anti-HCV was positive but blood HCV-RNA was undetectable. Results of antinuclear antibody, anti-DNA (EIA), anti-ENA and ANCA were all negative or within reference range. HLA-B27 was positive. All blood cultures, bone marrow cultures, Widal test, Weil-Felix test, cryptococcal antigen, *Toxoplasma* IgM, and anti-HIV turned out to be negative. Doxycycline therapy was continued. Fever and jaundice gradually subsided over a 2-week period, along with the normalization of CRP levels (Figure 3). High titers of IgM and IgG against *C. burnetii* in serum sampled at admission were reported by the reference laboratory of the Centers for Disease Control (Taipei, Taiwan) (Table), with a four-fold elevation

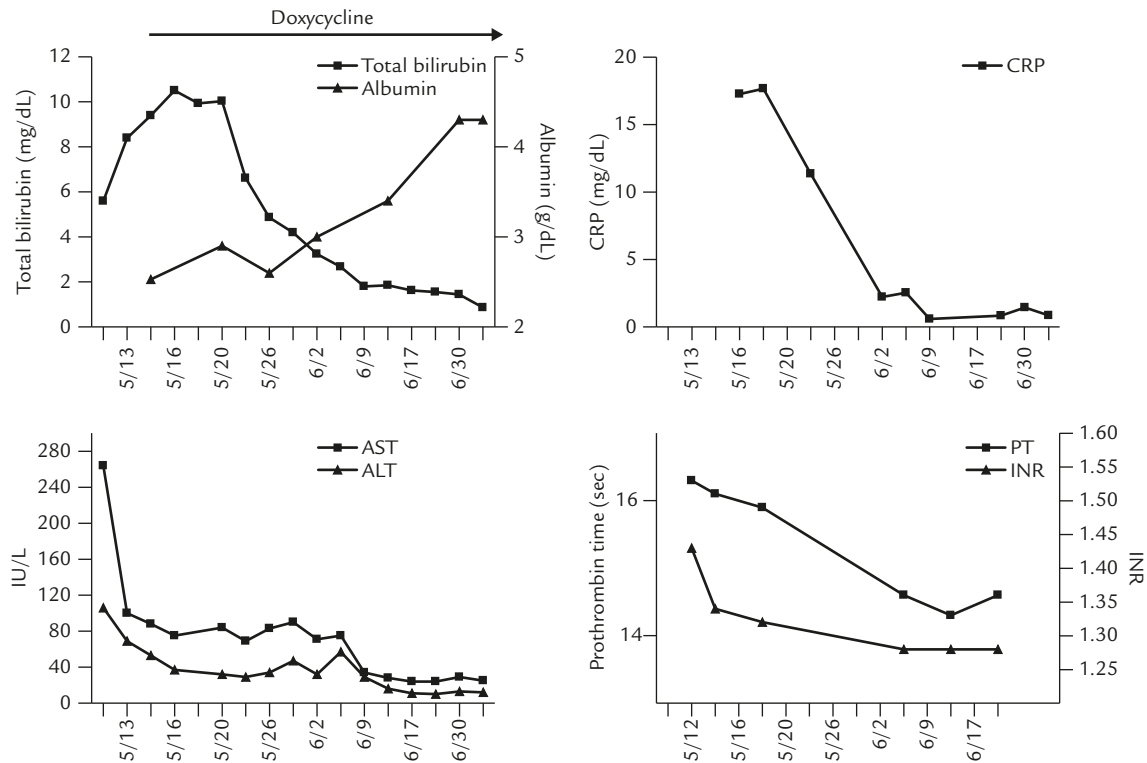


Figure 3. Normalization of liver function after the start of doxycycline therapy on May 14, 2005. CRP=C-reactive protein; AST=aspartate aminotransferase; ALT=alanine aminotransferase; PT=prothrombin time; INR=international normalized ratio.

Table. Results of Q fever serology by indirect immunofluorescence technique

	Phase I antibody titers		Phase II antibody titers	
	IgM	IgG	IgM	IgG
2005/05/17	1:160+	1:2560+	> 1:320+	1:5120+
2005/05/31	1:160+	1:2560+	> 1:320+	> 1:5120+
2005/07/15	1:640+	1:2560+	1:1280+	1:20,480+
2005/12/20	1:40+	1:1280+	1:80+	1:2560+
2007/06/09	Negative	> 1:320+	1:80+	> 1:320+

of phase II IgG titer in the paired serum. Echocardiography found no evidence of infective endocarditis. The eventual diagnosis was acute Q fever with granulomatous hepatitis.

Because of the unusual severity of the disease and a high initial titer of phase I IgG in this patient, hydroxychloroquine (200 mg twice daily) was added to the regimen. AST and ALT returned to normal range on June 9, 2005. Albumin returned to normal range on June 30, 2005. Bilirubin returned to normal range on July 15, 2005 (Figure 3). Prothrombin time remained slightly prolonged

(14.6 seconds; INR, 1.28) at the last test performed on June 20, 2005. After a 6-week treatment, follow-up phase I IgG titer remained at 1:2560+ (sampled on July 15, 2005) (Table). The combination therapy was thus continued for more than 18 months. He remains well and leads an active life.

Discussion

Q fever can present with extremely variable symptoms and signs.¹⁻¹² The proportion of people

presenting with pneumonia and/or hepatitis varies greatly from series to series and depends on the geographic region.¹¹ Compared with patients who present with hepatitis, those who present with pneumonia are older and more likely to be immunocompromised.³ But differences in reported clinical presentations could also be partially explained by different case definitions and selection biases in cases referred to specialists who publish series.¹² Hepatitis is a common presentation in France,³ southern Spain,⁴ Israel,⁵ Taiwan⁶ and southern California.⁷ Rapidly progressive hepatic failure as seen in the present case, however, is unusual.^{6,14–16} The unusual severity of diseases in this patient may be related to underlying alcoholism and alcoholic liver disease, as well as a large amount of organisms inhaled during the exposure accident.

The diagnosis of Q fever is based on serology using indirect immunofluorescence technique in most clinical scenarios.¹ A four-fold increase in phase II IgG is diagnostic for acute Q fever.¹⁰ Significant titers may take 3–4 weeks to appear, so treatment should be started as soon as a clinician suspects the disease to be present.¹² The sensitivity of serum polymerase chain reaction as an early diagnostic tool remains unsatisfactory.¹⁷ Histologic findings of hepatic granuloma may be nonspecific or may have a distinctive doughnut appearance.¹ In the present case, the probabilities of an alternative diagnosis, including disseminated tuberculosis and non-Hodgkin's lymphoma which require prompt specific therapy, mandated a liver biopsy. Despite the presence of ascites and a prolonged prothrombin time, the procedure was safely performed through a transjugular route and provided information that was highly valuable for clinical management before the diagnosis was eventually confirmed by serology.

Doxycycline, 100 mg twice daily for 14 days is recommended for acute illness.^{10,12} For chronic Q fever, the treatment should be continued until phase I IgG titer is less than 1:200.¹⁰ Chloroquine increases the efficacy of doxycycline,¹⁸ and the combination of doxycycline and hydroxychloroquine has been shown to shorten the treatment

duration for Q fever endocarditis.¹⁹ Because of the unusual severity of disease and a high initial titer of phase I IgG in this patient, we added hydroxychloroquine to the regimen and extended the treatment duration to minimize the risk of development of chronic Q fever.

The experience of the present case shows that the possibility of Q fever should not be overlooked in patients who have an unexplained febrile illness and severe liver function impairment following exposure to a contaminated environment in Taiwan. Early diagnosis and timely appropriate therapy can be life-saving.

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