Fatal Systemic Infection with Multifocal Liver and Lung Nodules Caused by *Brucella abortus*

Keo Woon Park, Dong-Min Kim,* Chi Young Park, Hyun Lee Kim, Sook Jin Jang, Young Sil Choi, Mi-Yeoun Park, Hyeon-Je Song, and Seung-Hyun Lee

Division of Infectious Diseases, Departments of Internal Medicine and Research Center for Resistant Cells, Chosun University College of Medicine, Gwangju, Korea; Department of Laboratory Medicine, Chosun University College of Medicine, Gwangju, Korea; Division of Zoonoses, Center for Immunology and Pathology, Korea Center for Disease Control and Prevention, Seoul, Korea; Department of Clinical Pathology, Gwangju Health College, Gwangju, Korea; Departments of Pediatrics, Seonam University College of Medicine, Namwon, Korea

Abstract. We experienced a fatal case caused by *Brucella abortus* with multifocal necrosis confirmed by culture and polymerase chain reaction. Our case highlights that the clinician should be aware of the potential for fatality when a patient with brucellosis shows dissemination of abscess or nodules with no calcification in the liver, lung, pleura, and spine.

INTRODUCTION

A zoonotic infection, brucellosis commonly occurs in livestock such as the cow, the goat, and swine. It is also transmitted to humans, thus termed human brucellosis. According to epidemiologic studies, human brucellosis commonly develops in the Mediterranean area, the Middle East, India, Mexico, some areas of Africa, and Middle and South America. Human brucellosis is a systemic infectious disease with a broad range of clinical manifestations. Local complications have been reported in 20–40% of patients with brucellosis, whereas the majority of the patients manifest as a febrile syndrome with no notable focus. To date, few studies have reported cases of brucellosis in which multifocal abscesses were present in the liver and disseminated to the lung, pleura, and spine.

We experienced a fatal case of human brucellosis in which multifocal abscesses or nodules were present in the liver, lung, and pleura. Here, we report the case of a man with chief complaints of lower back pain and fever, in whom a diagnosis of human brucellosis was established based on culture and polymerase chain reaction (PCR).

CASE REPORT

A 51-year-old man presented with lower back pain that developed during agricultural work in the field 2 weeks before admission. Although he received medication at a local clinic, he developed fever accompanied by perspiration. His lower back pain and fever persisted. He was therefore referred to our clinic. He was a farmer with a 30-pack-year smoking history. He was rearing two cows at his house, one of which died of disease 1 year before his visit. The dead cow was not slaughtered in the slaughterhouse. He did not report it to the public health center, and he ate dead meat from the cow, which died of disease 1 year before his visit. The dead cow was not slaughtered in the slaughterhouse. He did not report it to the public health center, and he ate dead meat from the cow, which died of disease 1 year before his visit. The dead cow was not slaughtered in the slaughterhouse. He did not report it to the public health center, and he ate dead meat from the cow, which died of disease 1 year before his visit.

During his medical history, he reported that he had received anti-tuberculosis medication for pulmonary tuberculosis 30 years earlier. He was being treated with glimepiride for diabetes for the past 3 years. At the time of visit, his vital signs were as follows: blood pressure, 130/80 mm Hg; heart rate, 104/min; respiratory rate, 18/min; body temperature, 38.5°C. On physical examination, three finger-breath hepatomegaly and two finger-breath splenomegaly were palpated at the right sternal border and at the left sternal border, respectively. His laboratory tests revealed the following: white blood count (WBC), 2,290/mm³ (neutrophil 69.9%); hemoglobin (Hb), 11.4 g/dL; platelets, 84,000/mm³; total protein, 6.72 g/dL; albumin, 3.52 g/dL; AST/ALT, 162/169 IU/L; total bilirubin, 1.15 mg/dL; BUN/creatinine, 16.1/0.85 mg/dL; glucose, 126 mg/dL; PT/aPTT, 12.6 seconds/29.1 seconds; Na⁺, 140 mEq/L; K⁺, 4.1 mEq/L; CT, 106 mEq/L; ESR, 11 mm/hr; CRP, 5.12 mg/dL; LDH, 868 U/L. Serologic tests were negative for antinuclear antibody, VDRL, HIV, HBV, and HCV, assessing the potential for pre-existing liver disease or immune compromise in this patient. On chest computed tomography (CT) scans, multiple nodules with central low attenuation were present in the parenchyma of both lungs. Pleural nodules and pleural effusion were also detected (Figure 1). On abdominopelvic CT scans, hepatosplenomegaly and small enhancement of multiple nodules were present in the liver. Lymphadenopathy was seen in the retrocrural area of the thoracic region. Furthermore, osteolytic lesions were present in the lower thoracic spine. On Day 2, a percutaneous lung biopsy was performed in the right upper lung nodule, the left back, and pleural mass using an 18-gauge side cutting needle. Histopathologically, focal coagulative necrosis and fibrosis were noted, but no findings were suggestive of malignancy. On Day 4, a biopsy was performed for multiple small nodules in the liver under ultrasonographic guidance. A histopathologic examination revealed coagulation necrosis. Bone marrow biopsy was performed to evaluate pancytopenia. This revealed reactive marrow (M:E ratio, 1.97:1; cellularity, 40%) but showed no other notable findings. Blood culture was done using an automated blood culture system (BACTEC 9050; BD Co., Sparks, MD). A subculture was done using Trypticase soy agar (TSA; containing 5% sheep blood, 37°C, 38–72 hours, 5–10% CO₂). In our case, *Brucella* was identified based on the standard method. 4 IgM and IgG antibody titers against *B. abortus* using a standard tube agglutination test (STA; 241049; BD Co.) were < 1:20. ELISA (PanBio, Australia; PanBio unit: > 11, positive; < 9, negative) tests against *B. abortus* were positive in a titer of IgM 38 and IgG 3. On detection of the PCR product of *Brucella*-species-common
genes, BCSP31 (223 bp), OMP2 (195 bp), 16srRNA (905 bp), and AMOS multi-PCR assays detected type 1 *Brucella*, which was identical as *B. abortus* ATCC 2308. This confirmed that the causative pathogenic strain was *B. abortus* biotype 1 in our case (Figure 2).

Since admission, he had a persistent fever of > 38°C and lower back pain. From Day 4 onward, he was given doxycycline and streptomycin for the treatment of brucellosis. At follow-up, his laboratory findings were aggravation of pancytopenia and persistent elevation of serum AST/ALT and total bilirubin. On Day 9, he developed hypoglycemia (blood glucose, 11 mg/dL) while he was exhibiting drowsy consciousness and melena. Physical examination revealed the following: blood pressure, 70/40 mm of Hg; heart rate, 120 times/min; respiratory rate, 30/min; temperature, 37.8°C. Blood chemistry revealed the following: WBC, 3,630/mm³; Hb, 5.4 g/dL; platelet, 55,000/mm³; PT/aPTT, 20.3 seconds/55.3 seconds; AST/ALT, 1,420/549 IU/L; total bilirubin, 8.29 mg/dL; albumin, 1.87 g/dL. After a 20% glucose replacement, his consciousness became clear. After fluid resuscitation and blood transfusion, his vital signs became stabilized. On esophagogastroduodenoscopy, a massive amount of old and fresh blood was present in the dependent area of the stomach. However, no bleeding focus was noted. He was intravenously

**Figure 1.** A, Thorax CT. Multiple lung, pleural nodules, and bilateral pleural effusion are noted. B, Abdomen CT. Innumerable small nodules with enhancement are noted in the liver. Hepatosplenomegaly and conglomerated, enlarged lymph nodes in the retrocrural area in the thoracic region are seen.

**Figure 2.** Detection of PCR products of *Brucella* genes from the patient; A, Detection of the *Brucella* 31-kDa genes (BCSP31) PCR products (223 bp) from the patient. Lane M, molecular size marker (100-bp DNA, ladder); Lane 1, DNA of *B. abortus* ATCC 7705 for the positive control; Lane 2, distilled water for the negative control; Lane 3, clinical isolate. B, Detection of the *Brucella* 36-kDa genes (OMP2) PCR products (195 bp) from the patient. Lane M, molecular size marker (100-bp DNA, ladder); Lane 1, DNA of *B. abortus* ATCC 7705 for the positive control; Lane 2, distilled water for the negative control; Lane 3, clinical isolate. C, Detection of the *Brucella* 16S rRNA genes PCR products (905 bp) from the patient. Lane M, molecular size marker (100-bp DNA, ladder); Lane 1, DNA of *B. abortus* ATCC 7705 for the positive control; Lane 2, distilled water for the negative control; Lane 3, clinical isolate. D, AMOS multiplex PCR. Lane M, molecular size marker (100-bp DNA, ladder); Lane 1, DNA of *B. melitensis* ATCC 739; Lane 2, DNA of *B. melitensis* ATCC 802; Lane 3, DNA of *B. abortus* ATCC 23450; Lane 4, DNA of *B. abortus* ATCC 7705; Lane 5, DNA of *B. abortus* ATCC 23453; Lane 6, DNA of *B. abortus* ATCC 2308; Lane 7, DNA of *B. suis* ATCC 23446; Lane 8, DNA of *B. canis*; Lane 9, DNA of *B. abortus* S19; Lane 10, DNA of *Y. enterocolitica*; Lane 11, DNA of clinical isolate.
Given a proton pump inhibitor, and he was admitted to the intensive care unit. On Day 12, however, blood chemistry revealed the following: total bilirubin, 21.8 mg/dL; PT/aPTT, 61.6 seconds/no coagulation; AST/ALT, 421/271 IU/L. He presented with shock and respiratory failure. He was treated with a mechanical ventilator but died on Day 16.

**DISCUSSION**

Approximately 500,000 cases of brucellosis are annually reported worldwide. In Korea, however, no cases of brucellosis have been reported since it was first identified in a Japanese patient in 1939. In 2002, one case of human brucellosis was reported to occur after direct contact with an infected cow, which was the first case that was serologically confirmed. Since then, it has been reported that the numbers of patients with brucellosis were 16 in 2003, 47 in 2004, and 158 in 2005. In Korea, the epidemiology of human brucellosis was closely related to the incidence and area of bovine brucellosis. *B. abortus* biotype 1 commonly infects dairy cattle. *B. abortus* biotype 1 is the major causative species in Korean patients with brucellosis. In our case, *B. abortus* biotype 1 was identified. Korean indigenous cattle are reared to produce meat and not for milk. Therefore, brucellosis in Korea might be transmitted through abraded skin that occurred during the course of handling infected animals or their carcasses rather than through the ingestion of unpasteurized dairy products. In Korean patients, fatigue was the most common symptom, even though fever, chills, and sweating were also common symptoms.

Four species of the facultative intracellular bacterium *Brucella* cause human disease. These include *B. melitensis* (goats and sheep) *Brucella abortus* (cattle), *Brucella suis* (swine), and *Brucella canis* (dogs). In patients with brucellosis, the mononuclear phagocytes derived from the reticuloendothelial system (liver, spleen, or bone marrow) are mainly involved in removing *Brucella*. Therefore, in patients with brucellosis, hepatic invasion is commonly seen. Clinically, patients with brucellosis are characterized by hepatomegaly and the non-specific elevation of serum aminotransferase. Histopathologically, these patients exhibit non-specific or granulomatous hepatitis. These clinical and biochemical abnormalities return to normal without significant sequela after the appropriate treatment.

Hepatosplenic abscess is a rare entity but is a serious, focal complication of chronic brucellosis hepatitis. On CT scans, calcification with a snowflake appearance may be noted in patients with hepatosplenic abscess. This is the characteristic finding of patients with chronic hepatosplenic suppurrative brucellosis and is suggestive of the chronic nature. This also implies the re-activation of silent infection. Suppurative complications may occur in all *Brucella* infections, but it has also been reported that abscesses are formed after a long dormant period in patients with brucellosis caused by *B. suis*. The animal model of brucellosis in guinea pigs was used. *B. suis* causes suppurrative processes such as the hepatic and extraperitoneal abscess more prevalently than other *Brucella* species. In contrast, *B. abortus* has a lower virulence and causes a non-caseating granuloma. It has been reported that *B. melitensis* commonly causes other types of suppurrative processes including chronic hepatosplenic abscesses.

In our case, on chest CT scans, the multiple, ill-defined tiny nodules with no calcification were distributed in the liver and in both lung fields. This finding is not consistent with the chronic hepatosplenic suppurrative brucellosis. Furthermore, in our case, bilateral pleural effusion and pleural nodules were present. Even in areas where brucellosis is epidemic, there are rare cases of brucellosis in which the focal form of brucellosis invaded the respiratory tract. We therefore performed a percutaneous lung biopsy and liver biopsy. On aspiration biopsy, the gross finding was necrotized tissue rather than pus. Histopathologically, an extended lymphocytic infiltration admixed with epithelioid-like cells, focal coagulative necrosis, and fibrosis were noted. These findings are suggestive of non-caseating granuloma. In addition, on thoracolumbar spine MRI scans, an anterior and lateral bulging paraspinal mass was identified from the T9 to the T12 level, and the T11 body showed a heterogenous enhancement. This suggests the concurrent presence of spondylitis caused by *Brucella*. In our case, *Brucella* invaded the liver, lung, and bone; the blood and bone marrow culture were positive for *Brucella*; and the PCR test detected the *Brucella*-specific genes in blood, liver, and bone marrow specimens. These findings confirm the systemic dissemination of *B. abortus* in our case. In cases in which endocarditis was concurrently present, a poor prognosis is commonly seen; the mortality rate increases up to 80%. To rule out the possibility of infective endocarditis being the cause of dissemination, we examined whether cardiac invasion was present. However, there were no clear evidences for it. From Day 4 onward, we administered doxycycline and streptomycin to our patient. Nevertheless, his clinical profile was persistent high fever, prompt deterioration of hepatic function, reduced concentration of albumin and glucose, and elevation of PT/aPTT. This progressed to hepatic failure and was accompanied by gastrointestinal bleeding. His symptoms continued to be aggravated. He was additionally given quinolone for a triple antibiotic combination. Nevertheless, he developed hepatic failure leading to multiple organ failure and died. In our case, there is the possibility of drug-induced liver failure, which is a rare event. His medication history, however, listed only glimepiride. Serum AST/ALT were already elevated at admission and persisted. Other causes of hepatitis were evaluated, but serologic tests were all negative. On liver biopsy, histopathologic feature did not suggest drug-induced hepatitis, such as microvesicular fatty changes caused by tetracycline or centrilobular necrosis caused by acetaminophen or rifampin. In addition, the patient was given doxycycline and streptomycin to treat brucellosis after liver biopsy. It is suggested that fulminant brucellosis is more possible than drug-induced liver failure in this case.

In 1936, Gottlieb and others reported that a fatal course was identified on postmortem heart blood culture in patients with acute brucellosis caused by *B. abortus*. According to these authors, it was associated with the presence of multiple hepatic abscess and abdominal abscess on autopsy findings. In that case, however, a positive blood culture could not be obtained while the patient was living. No radiologic modalities such as abdominal CT or thorax CT confirmed the presence of dissemination. In our case, *B. abortus* was identified from blood and bone marrow. Our case progressed to hepatic failure and was finally fatal. Brucellosis with *B. abortus* could be more fatal in rare cases associated with dissemination of abscess. However, this report also suggests the necessity of con-
ducting systemic studies on the potential for a more virulent strain.

In conclusion, we experienced a fatal case of brucellosis caused by B. abortus. In our case, multifocal abscesses or nodules were present in the liver, in which no calcification was concurrently present. Our case highlights that the clinician should be aware of the potential for fatality when a patient with brucellosis shows dissemination of abscess or nodules with no calcification in the liver, lung, pleura, and spine.

Received March 14, 2007. Accepted for publication August 21, 2007.

Financial support: This study was supported by grants from the Ministry of Science and Technology, Korea and the Korea Science and Engineering Foundation through the Research Center for Resistant Cells (R13-2003-009).

Disclosure: The authors do not have any commercial interest or other association that might pose a conflict of interest.

Authors’ addresses: Koo Woon Park, Dong-Min Kim, Chi Young Park, and Hyun Lee Kim, Department of Internal Medicine, Chosun University College of Medicine, 588 Seosuk-dong, Dong-Gu, Gwangju 501-717, Republic of Korea, Telephone: 82-62-220-3108, Fax: 82-62-234-9653, E-mail: drongkim@chosun.ac.kr. Sook Jin Jang, Department of Laboratory Medicine, Chosun University College of Medicine, 588 Seoseok-dong, Dong-gu, Gwang-Ju 501-717, Republic of Korea, Telephone: 82-62-220-3259, 011-614-8853, Fax: 82-62-232-2063, E-mail: sjjang@chosun.ac.kr. Young Sil Choi, Mi-Yeoun Park, Division of Zoonoses, Center for Immunology and Pathology, National Institute of Health, Korea Center for Disease Control and Prevention, 45 Nokbun-Dong, Eumyung-Gu, Seoul 122-701, Korea. Hyeon-Je Song, Department of Clinical Pathology, Gwangju Health College, Gwangju 506-701, Republic of Korea. Seung-Hyun Lee, Department of Pediatrics, Seonam University College of Medicine, Nam-won, Jellaebuko 590-711, Republic of Korea.

Reprint requests: Dong-Min Kim, Division of Infectious Diseases, Department of Internal Medicine, Chosun University College of Medicine, 588 Seosuk-dong, Dong-gu, Gwangju, 501-717, Republic of Korea. E-mail: drongkim@chosun.ac.kr.

REFERENCES

complications associated with Brucella melitensis infection: a study of 530 cases. Medicine (Baltimore) 75: 195–211.
13. Williams RK, Crossley K, 1982. Acute and chronic hepatic in-