INTRODUCTION

Brucellosis is the most common zoonotic infection worldwide, caused by intracellular gram-negative coccobacilli of genus *Brucella.* It is a multisystem disease that presents with a broad spectrum of clinical manifestations such as fever, malaise, night sweats, arthralgia, headache, dizziness, anorexia, cough, abdominal pain, and weight loss. In about 30% of cases, the complication of brucellosis can occur with the involvement of one or more focal sites, including osteoarticular, genitourinary, neurological, cardiovascular, pulmonary, dermatological, ocular, and intraabdominal sites.

We report a case of a 26-year-old male patient with cholecystitis associated with brucellosis who was successfully treated with laparoscopic cholecystectomy followed by six weeks of doxycycline and rifampicin.

CASE PRESENTATION

A 26-year-old male patient with no significant past medical history presented to the emergency room with complaints of right upper quadrant abdominal pain, nausea, vomiting, and malaise for 21 days. He was a resident of northeast Nebraska who moved to California three months ago to work on wind farms in the Mojave Desert. While working in California, he started to have an intermittent low-grade fever, nausea, vomiting, malaise, and abdominal pain. He took over-the-counter cold medication (combination of acetaminophen, guaifenesin, phenylephrine, and dextromethorphan) and ibuprofen for his symptoms. However, ten days before presentation to our center, he was admitted to the local hospital at Tehachapi Valley, California, with worsening symptoms. He was found to have rhabdomyolysis with an elevated creatine kinase level of 1451 U/L, which was presumed to be secondary to extreme exertion with dehydration and was treated with intravenous hydration. The rest of his laboratory workups were unremarkable except for mild elevation of liver enzymes, which are summarized (Table 1). His ultrasound and CT scan of the abdomen revealed the fatty infiltration of the liver with hepatosplenomegaly. His urine and blood cultures were negative, and he was discharged after six days to follow-up with a primary care physician. Subsequently, he returned to his home in northeast Nebraska.
Nebraska. However, his symptoms gradually worsened, and he presented to our emergency room three days after his discharge from hospitalization in California. He denied consumption of unpasteurized animal products and had no contact history with cattle, ships, goats, pigs, deer, and other wild animals. He reported no recent sick contact or history of similar symptoms in his family members.

At the emergency room, his initial vitals were blood pressure of 124/55 mm Hg, pulse rate of 64 beats per minute, temperature of 98.3 F, and respiratory rate of 16 breaths per minute with 99% oxygen saturation in room air. There was tenderness in the right upper quadrant on the physical examination with a positive Murphy’s sign. The rest of the physical examinations were unremarkable.

TABLE 1 Initial laboratory studies at faith regional health services and local hospital at California

| Variables              | Laboratory studies on presentation to faith regional health services (day 10) | Laboratory studies on presentation to local hospital at California (day 1) | Reference range       |
|------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------------------|
| White blood cell count | $7.5 \times 10^3/\mu l$                                                        | $4.2 \times 10^3/\mu l$                                                    | 4.0–10.0 $\times 10^3/\mu l$ |
| Neutrophil count       | $4.6 \times 10^3/\mu l$                                                        | $2.6 \times 10^3/\mu l$                                                    | 1.6–8.0 $\times 10^3/\mu l$ |
| Lymphocyte count       | $2.2 \times 10^3/\mu l$                                                        | $1.2 \times 10^3/\mu l$                                                    | 0.8–4.5 $\times 10^3/\mu l$ |
| Monocyte count         | $0.6 \times 10^3/\mu l$                                                        | $0.3 \times 10^3/\mu l$                                                    | 0–1.2 $\times 10^3/\mu l$ |
| Eosinophil count       | $0.1 \times 10^3/\mu l$                                                        | $0.1 \times 10^3/\mu l$                                                    | 0–0.7 $\times 10^3/\mu l$ |
| Basophil count         | $0.0 \times 10^3/\mu l$                                                        | $0.0 \times 10^3/\mu l$                                                    | 0–0.2 $\times 10^3/\mu l$ |
| Hemoglobin             | 14.8 g/dl                                                                       | 14.2 g/dl                                                                  | 13.5–17.0 g/dl         |
| Platelets              | $217 \times 10^3/\mu l$                                                        | $210 \times 10^3/\mu l$                                                    | 150–450 $\times 10^3/\mu l$ |
| Sodium                 | 136 mEq/L                                                                       | 140 mEq/L                                                                  | 134–146 mEq/L          |
| Potassium              | 4.0 mEq/L                                                                       | 3.5 mEq/L                                                                  | 3.5–5.3 mEq/L          |
| Chloride               | 103 mEq/L                                                                       | 107 mEq/L                                                                  | 98–110 mEq/L           |
| Bicarbonate            | 25 mM/L                                                                         | 24 mM/L                                                                    | 21–30 mM/L             |
| Blood urea nitrogen    | 9 mg/dl                                                                         | 8 mg/dl                                                                    | 7.0–25 mg/dl           |
| Creatinine             | 0.73 mg/dl                                                                      | 0.73 mg/dl                                                                 | 0.7–1.30 mg/dl         |
| Glucose                | 103 mg/dl                                                                       | 102 mg/dl                                                                  | 65–95 mg/dl            |
| Alanine transaminase   | 145 U/L                                                                         | 218 U/L                                                                    | 2.0–60 U/L             |
| Aspartate transaminase | 65 U/L                                                                          | 216 U/L                                                                    | 2.0–50 U/L             |
| Alkaline phosphatase   | 85 U/L                                                                          | 101 U/L                                                                    | 20–125 U/L             |
| Total Bilirubin        | 0.7 U/L                                                                         | 0.9 U/L                                                                    | 0.1–1.5 mg/dl          |
| Creatine kinase        | 40 U/L                                                                          | 1451 U/L                                                                   | 40–250 U/L             |

FIGURE 1 Ultrasound of the abdomen showing small gallstones with echogenic sludge with gallbladder wall thickening
The laboratory workups were unremarkable except for mild elevation of liver enzymes which are summarized in (Table 1). The abdomen ultrasound revealed small, calcified stones with echogenic sludge with gallbladder wall thickening and positive Murphy's sign suggestive of acute cholecystitis (Figure 1). He was started on ceftriaxone and intravenous hydration and subsequently underwent laparoscopic cholecystectomy the next day.

After the laparoscopic cholecystectomy, he had postoperative blood loss anemia (hemoglobin decreased from 14.8 to 12.4 mg/dl) with mild tachycardia (heart rate in 110–115 beats per minute) and low blood pressure (90–98/50–55 mm Hg). This improved with intravenous hydration and one unit packed red blood cell transfusion. His blood cultures drawn ten days ago in California were reported growing gram-negative coccobacilli suspicious of Brucella, which was subsequently confirmed as Brucella species by detection of Brucella DNA with polymerase chain reaction (PCR). Repeat blood cultures were obtained that grew gram-negative coccobacilli suspicious of Brucella in about five days and later was identified as Brucella melitensis (Figure 2). Additional workup with transthoracic echocardiogram was unremarkable with no vegetation. His chest was unremarkable. However, a CT scan of the abdomen revealed hepatosplenomegaly with post-surgical changes of recent laparoscopic cholecystectomy with a small amount of free air in the peritoneal cavity and a small amount of free fluid in the pelvis (Figure 3).

He was treated with a loading dose of intravenous doxycycline 200 mg, followed by 100 mg twice a day, and intravenous gentamicin 5 mg/kg daily during hospitalization for four days. Subsequently, he was transitioned to oral doxycycline 100 mg twice a day and rifampin 900 mg daily for a total of six weeks. The elevated liver enzymes normalized at time of discharge (Figure 4). He had outpatient follow-up visits with an infectious disease physician in one week, three weeks, six weeks, and three months of discharge. His repeat blood cultures remained negative, and his symptoms resolved with no evidence of relapse in three months post-discharge follow-up visit.

3 | DISCUSSION

Brucellosis is a zoonotic disease transmitted to humans from infected animals by ingestion of unpasteurized food products or direct contact with infected tissues or fluids.\(^1\) It is the most common zoonosis worldwide and endemic in Central Asia, China, the Indian subcontinent, sub-Saharan Africa, the Middle East, Mediterranean basin, Mexico, and Central and South America.\(^6\) Approximately 100–200 cases are reported annually in the United States, with an incidence of 0.02–0.09/100,000 per year.\(^5,7\) The consumption of unpasteurized dairy products imported from endemic countries (especially neighboring Mexico) is the most common source of infection in the United States.\(^3,6\) Four species of Brucella which include Brucella melitensis (isolated from goats and sheep), Brucella abortus (isolated from cattle), Brucella suis (isolated from swine), and Brucella canis (isolated from dogs) cause human disease.\(^1\) Most human cases of brucellosis are from Brucella melitensis.\(^1\)

The incubation period of brucellosis is usually 2–4 weeks and typically presents with nonspecific symptoms such as intermittent fever, malaise, night sweats, and arthralgia.\(^1,2\) In about 30% of cases, it disseminates via bloodstream or lymphatics and affects organ systems causing focal brucellosis.\(^4,5\) Osteoarticular disease, which includes peripheral arthritis, sacroiliitis, and spondylitis, is the most common form of focal brucellosis.\(^9\) Intraabdominal involvement, which may include hepatic or splenic abscess, cholecystitis, pancreatitis, ileitis, colitis, and peritonitis, is a rare manifestation of focal brucellosis.\(^3,5\) To the best of our knowledge, there are 30 case reports of cholecystitis associated with brucellosis reported to the date, and only 6 case reports involving seven patients reported between January 2010 to December 2021.\(^10–15\) The pathogenesis of cholecystitis associated with brucellosis is unclear; Brucella may reach the gallbladder via lymphatic spread or bloodstream as a part of bacteremia, and chronic latent infection may lead to gallstone formation.\(^16\)

Brucellosis is usually suspected in a patient with symptoms of intermittent fever, malaise, night sweats, and arthralgia with a history of consuming unpasteurized dairy products or contact with infected animal tissue or fluid in an endemic area.\(^1\) The definitive diagnosis of brucellosis is made by culture of the organism from blood, blood fluids (urine, cerebrospinal fluid, synovial fluid, pleural fluid), or tissue (bone marrow or liver biopsy).\(^17\) A fourfold rise

**FIGURE 2** Blood culture growing gram-negative coccobacilli
in *Brucella* antibody from acute and convalescent plasma specimens taken two weeks apart can also be used for the definitive diagnosis of brucellosis.\(^\text{17}\) Most blood cultures are positive between 7 and 21 days.\(^\text{18}\) The presumptive diagnosis can be made by detecting *Brucella* DNA by polymerase chain reaction (PCR) assay or *Brucella* total antibody titer more than 1:160 by standard tube agglutination test in serum specimen.\(^\text{19}\) The sensitivity of blood cultures is 15%–70% for the diagnosis of brucellosis.\(^\text{20}\) The sensitivity and specificity of the standard tube agglutination test were noted to be 95% and 100%, respectively, in one study.\(^\text{21}\) However, the serological test has many disadvantages, including false negative in the early course of infection or setting of immunosuppression and cross-reactivity with other bacteria such as *Escherichia coli*, *Salmonella Urbana*, *Vibrio Cholerae*, *Francisella tularensis*, and *Yersinia enterocolitica*.\(^\text{1,21–23}\)

The treatment of brucellosis consists of antibiotics with activity in the acidic intracellular environment such as tetracyclines, aminoglycosides, and rifampicin.\(^\text{24}\) Fluoroquinolones and trimethoprim-sulfamethoxazole are alternative second-line agents.\(^\text{24}\) The use of combination therapy (gentamicin/streptomycin or rifampicin with doxycycline) for a prolonged duration (usually six weeks) is recommended due to the high rate of relapse with monotherapy.\(^\text{25}\) Following treatment, the relapse rate is 5%–15% and usually occurs within the first six months of treatment completion.\(^\text{26}\) The preferred regimen is doxycycline combined with aminoglycosides; however, doxycycline-rifampin is more favored due to the convenience of the oral route and better tolerated than aminoglycosides (may lead to nephrotoxicity or ototoxicity).\(^\text{26}\) The optimal duration of treatment for the intraabdominal manifestation of brucellosis is not well established.\(^\text{11}\) The combination therapy of gentamicin/streptomycin or rifampin with doxycycline for six weeks is the most common regimen; however, it has been used from 3 weeks to 3 months in previously reported cases.\(^\text{11}\)

In our case, the patient had symptoms of intermittent fever, night sweats, malaise, nausea, and abdominal pain for 2–3 weeks. However, he has no history of consumption of unpasteurized animal products or exposure to infected animal tissues or fluids and has not been to an endemic area. The other probable causes of intermittent prolonged fever were diligently excluded with history, laboratory, and clinical data. Viral studies including cytomegalovirus, Epstein–Barr virus, hepatitis B, hepatitis C, and human immunodeficiency virus were negative. Fungal studies, including *coccidioides*, endemic in California's Central Valley, were negative. His echocardiogram ruled out endocarditis, and his rheumatological workup was unremarkable. His initial blood cultures were negative. However, it grew gram-negative coccobacilli suspicious of *Brucella* species on the seventh day. A probable diagnosis was made by detecting *Brucella* DNA by PCR assay. Subsequently, the confirmatory diagnosis with species identification was made with blood cultures. His initial abdomen ultrasound revealed hepatosplenomegaly but no gallbladder calculi with negative murphy sign; however, repeat ultrasound was positive for acute cholecystitis with small gallbladder calculi in about ten days that points toward focal intrabdominal complications of brucellosis. He responded well with surgical laparoscopic cholecystectomy and six weeks course of rifampin and doxycycline with no relapse in the three-month post-discharge follow-up.

## 4 | Conclusion

The clinical presentation of brucellosis is usually nonspecific, and without a history of exposure to the significant risk factors in the non-endemic areas, the diagnosis of brucellosis can be challenging and delayed. Brucellosis...
may progress to rare focal forms such as cholecystitis, as in our case, which may lead to increased morbidity, healthcare cost, and even mortality. This case highlights the need to keep brucellosis as a differential diagnosis in a patient presenting with intermittent fever, malaise, night sweats, nausea, and abdominal pain even in the non-endemic area.

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CONFLICTS OF INTEREST
The authors declare that we have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTION
Ojbindra KC, Punya Hari Dahal, and Manisha Koirala contributed to clinical data collection and prepared the case report. Afua D Ntem-Mensah was actively involved in the clinical care of the patient and revised the manuscript.

CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

DATA AVAILABILITY STATEMENT
No datasets were generated or analyzed for the study.

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