MRI and PET-CT Failed to Differentiate Between Hepatic Malignancy and Brucellosa

Peter W. Schreiber,1,2a Adrian Schmid,1,3 Stefania Fagagnini,1 Arne Kröger,1,4 Bart Vrugt,1 Cäcilia S. Reiner,1 Katia Boggian,3 Marc Schiesser,1 Beat Müllhaupt,3 and Huldrych F. Günthard1,2

1Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; 2Institute of Medical Virology, University of Zurich, and Huldrych F. Günthard

Brucellosa is a common, worldwide zoonosis. Clinical presentation is protean and often goes unrecognized. Hepatic brucellosa is a rare local complication of chronic brucellosa. We report a case in which magnetic resonance imaging and positron emission tomography imaging prompted suspicion of a hepatic malignancy. Diagnosis was ultimately made by serology and polymerase chain reaction of resected liver tissue.

Keywords. Brucella; brucellosa; hepatic abscess; hepatic brucellosa; PET-CT.

CASE DESCRIPTION

A 56-year-old man without relevant medical history reported an episode of malaise, weakness, night sweats, and unintended weight loss followed by right upper quadrant abdominal pain worsened by inspiration. Laboratory testing (Table 1) revealed mild anemia, an elevated C-reactive protein of 55 mg/L, slightly elevated alkaline phosphatase, and negative tumor markers. Abdominal ultrasound and computed tomography (CT) identified an ill-defined mass of 9x5.5x6cm in the periphery of liver segments V/VI/VIII with one subcapsular, peripheral coarse calcification and inhomogeneous contrast enhancement in CT. As a fibrolamellar hepatocellular carcinoma was suspected, a positron emission tomography (PET–CT) was added for staging (Figure 1), which revealed high focal fluorodeoxyglucose (FDG) uptake of the hepatic mass without other lesions. A liver biopsy showed no malignancy, but periportal and portal fibrosis.

Further workup included magnetic resonance imaging (MRI) with hepatobiliary contrast agent (Gd-EOB-DTPA), which confirmed an ill-defined mass in liver segments V/VI/VIII. Adjacent to the calcification, an ill-defined area with T2 fat-sat hyperintense signal and arterial hyperenhancement was present. In the center of this area, portal-venous and hepatobiliary contrast enhancement was decreased, representing the area of chronic inflammation. A fluid collection resembling a hepatic abscess was not seen. A second biopsy confirmed chronic portal and lobular inflammation with non-necrotizing microgranulomas, respectively (Figure 2). Histology triggered serologic testing for Bartonella spp., Brucella spp., and Coxella burnettii. Agglutination test for brucellosa was reactive, and enzyme-linked immunosorbent assay (ELISA) confirmed elevated titers of Brucella IgG and IgA. However, Brucella spp.–specific polymerase chain reaction (PCR) of paraffin-embedded liver tissue tested negative. Serology for Coxella burnettii and B. henselae tested negative. Serological, radiological, and histological findings together with the risk factor, consumption of unpasteurized dairy products, resulted in the diagnosis of hepatic brucellosa. Treatment with doxycycline 100 mg bis in die (BID) and rifampin 300 mg ter in die (TID) was initiated. After initial improvement, abdominal pain and persistent elevation of inflammatory markers recurred. Abdominal MRI 5 months after treatment initiation revealed a new septated, subcapsular hepatic fluid collection suspicious of an abscess, prompting diagnostic and therapeutic puncture. Histopathology showed persistence of chronic granulomatous hepatitis. Brucella spp.–specific PCR and culture were negative. At this time, trimethoprim/sulfamethoxazole 160/800 mg BID was added to the antibiotic therapy. Due to subsequent clinical and laboratory improvement (C-reactive protein 10 mg/L, erythrocyte sedimentation rate 16 mm/h), antibiotics were stopped after 13 months of treatment. After 12 weeks, a clinically, laboratory-, and imaging-verified relapse occurred. Doxycycline and rifampin were resumed, and the decision for surgical removal was taken. Perioperatively, gentamicin was added to reduce bacterial load and discontinued 1 week after partial hemihepatectomy. The postoperative course was uncomplicated, with rapid clinical and laboratory improvement. Brucella spp.–specific PCR of the resected liver tissue was positive; culture remained negative. A follow up CT 3 months postoperation confirmed complete resection, and antibiotic therapy was stopped.
Brucellosis is a frequent zoonosis caused by gram-negative facultative intracellular coccobacilli *Brucella* spp. Humans constitute secondary hosts. Transmission results either from ingestion of unpasteurized dairy products or direct contact with infected animals. After an incubation period of 2 to 4 weeks, an unspecific syndrome of fever, weight loss, malaise, myalgia, and arthralgia presents [1]. Subclinical presentations are possible. No or insufficient treatment can lead to chronic brucellosis [1], of which hepatic brucelloma is an infrequent complication, with a reported incidence of 1.7% [2]. Symptoms of hepatic brucelloma are unspecific, including fever, chills, sweating, weakness, and upper abdominal pain. Laboratory tests frequently show signs of inflammation and occasionally elevations of gamma-glutamyl transpeptidase and alkaline phosphatase [2]. Serological tests, mostly agglutination assays, can be used for diagnosis. Cultural approaches are characterized by a low sensitivity (29.4%) [3], whereas PCR of biopsy samples is reported to be highly sensitive (97.1%) [3]. Here, *Brucella* spp. PCR of percutaneous liver biopsies was negative, likely reflecting reduced sensitivity with the use of paraffin-embedded tissue and prior antibiotic therapy. *Brucella* spp. PCR was only positive in operatively obtained samples.

Hepatic brucelloma presents as a hypodense lesion with perifocal calcium deposits and contrast enhancement on CT scans [4]. In the only published case describing PET-CT findings, high focal FDG uptake was reported [1]. Liver biopsies frequently display granulomatous, portal, and peripheral inflammation [5, 6].

Treatment recommendations for hepatic brucelloma are scarce. In a recent review, combination therapy with doxycycline and rifampin was most often used, with a wide variability of treatment duration [1]. Occasionally, puncture or surgical resection was necessary for cure [7]. A decay in antibody titers during treatment is described, but no cutoff corresponding to treatment success has been established [8].

### Table 1. Laboratory Results

| Parameter                        | Measurement [Reference Range]                         |
|----------------------------------|-------------------------------------------------------|
| Hemoglobin                       | 125 g/L [134–170 g/L]                                 |
| White blood count                | 9.07 G/L [3.0–9.6 G/L]                                |
| Platelets                        | 270 G/L [143–400 G/L]                                 |
| AST                              | 21 U/L [<50 U/L]                                      |
| ALT                              | 21 U/L [<50 U/L]                                      |
| gGT                              | 58 U/L [<80 U/L]                                      |
| AP                               | 146 U/L [40–129 U/L]                                  |
| Bilirubine                       | 5 μmol/L [<21 μmol/L]                                 |
| CRP                              | 55 mg/L [<5 mg/L]                                     |
| AFP                              | 3.1 μg/L [<13.1 μg/L]                                 |
| CA 19-9                          | 79 kU/L [<37 kU/L]                                    |
| CEA                              | <1.0 μg/L [<5.0 μg/L]                                 |
| *Brucella* agglutination assay   | Positive (negative) [11/15]                           |
| *Brucella* IgM                   | <5 U/L [<15 U/L] [11/15]                              |
| *Brucella* IgG                   | 2078 U/L [<20 U/L]                                    |
| *Brucella* IgA                   | 1276 U/L [<20 U/L]                                    |
| *Brucella* spp.–specific PCR (liver biopsy) | Negative (negative) [11/15]                           |

Laboratory results at time of presentation (11/15), if other not specified.

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CRP, C-reactive protein; gGT, gamma-glutamyl transpeptidase; PCR, polymerase chain reaction.

*Virion/serion SERION enzyme-linked immunosorbent assay (ELISA) classic *Brucella* IgM.

*Virion/serion SERION ELISA classic *Brucella* IgG.

*Virion/serion SERION ELISA classic *Brucella* IgA.

**DISCUSSION**

Brucellosis is a frequent zoonosis caused by gram-negative facultative intracellular coccobacilli *Brucella* spp. Humans constitute secondary hosts. Transmission results either from ingestion of unpasteurized dairy products or direct contact with infected animals. After an incubation period of 2 to 4 weeks, an unspecific syndrome of fever, weight loss, malaise, myalgia, and arthralgia presents [1]. Subclinical presentations are possible. No or insufficient treatment can lead to chronic brucellosis [1], of which hepatic brucelloma is an infrequent complication, with a reported incidence of 1.7% [2]. Symptoms of hepatic brucelloma are unspecific, including fever, chills, sweating, weakness, and upper abdominal pain. Laboratory tests frequently show signs of inflammation and occasionally elevations of gamma-glutamyl transpeptidase and alkaline phosphatase [2]. Serological tests, mostly agglutination assays, can be used for diagnosis. Cultural approaches are characterized by a low sensitivity (29.4%) [3], whereas PCR of biopsy samples is reported to be highly sensitive (97.1%) [3]. Here, *Brucella* spp. PCR of percutaneous liver biopsies was negative, likely reflecting reduced sensitivity with the use of paraffin-embedded tissue and prior antibiotic therapy. *Brucella* spp. PCR was only positive in operatively obtained samples.

Hepatic brucelloma presents as a hypodense lesion with perifocal calcium deposits and contrast enhancement on CT scans [4]. In the only published case describing PET-CT findings, high focal FDG uptake was reported [1]. Liver biopsies frequently display granulomatous, portal, and peripheral inflammation [5, 6].

Treatment recommendations for hepatic brucelloma are scarce. In a recent review, combination therapy with doxycycline and rifampin was most often used, with a wide variability of treatment duration [1]. Occasionally, puncture or surgical resection was necessary for cure [7]. A decay in antibody titers during treatment is described, but no cutoff corresponding to treatment success has been established [8].

![Image of CT scans](image-url)
CONCLUSIONS

Even advanced, noninvasive imaging methods cannot distinguish between hepatic malignancy and brucelloma. The optimal treatment for hepatic brucelloma is unknown, but prolonged antibiotic treatment combined with surgery can be necessary.

Acknowledgments

We thank the patient for his willingness to have his case published.

Financial support. This study was supported by the Clinical Research Priority Program: Viral Infectious Diseases of the University of Zurich (to H.F.G. and P.W.S.).

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Barutta L, Ferrigno D, Melchio R, et al. Hepatic brucelloma. Lancet Infect Dis 2013;13:987–93.
2. Ariza J, Pigrau C, Cañas C, et al. Current understanding and management of chronic hepatosplenic suppurative brucellosis. Clin Infect Dis 2001;32:1024–33.
3. Morata P, Quizpo-Ortuño ML, Reguera JM, et al. Diagnostic yield of a PCR assay in focal complications of brucellosis. J Clin Microbiol 2001;39:7843–6.
4. Sisteron O, Souci J, Chevallier P, et al. Hepatic abscess caused by Brucella US, CT and MRI findings: case report and review of the literature. Clin Imaging 2002;26:414–7.
5. Albayrak A, Albayrak F. Hepatic granulomas associated with brucellosis: hepatic granulomas and brucellosis. Hepat Mon 2011;11:1–2.
6. Cervantes F, Bruguera M, Carbonell I, et al. Liver disease in brucellosis. A clinical and pathological study of 40 cases. Postgrad Med J 1982;58:346–50.
7. Vallejo JG, Stevens AM, Dutton RV, Kaplan SL. Hepatosplenic abscesses due to Brucella melitensis: report of a case involving a child and review of the literature. Clin Infect Dis 1996;22:485–9.
8. Ariza J, Pellicer T, Pallarés R, et al. Specific antibody profile in human brucellosis. Clin Infect Dis 1992;14:131–40.