

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

Peter W. Schreiber,^{1,2,a} Adrian Schmid,^{1,a} Stefania Fagagnini,³ Arne Kröger,^{3,4} Bart Vrugt,⁵ Căcilia S. Reiner,⁶ Katia Boggian,⁷ Marc Schiesser,⁸ Beat Müllhaupt,³ and Huldrych F. Günthard^{1,2}

¹Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland and ²Institute of Medical Virology, University of Zurich, Zurich, Switzerland; ³Department of Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland; ⁴See-Spital Horgen, Internal Medicine, Gastroenterology, Horgen, Switzerland; ⁵Institute of Pathology and Molecular Pathology, University Hospital Zurich, Zurich, Switzerland; ⁶Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Zurich, Switzerland; ⁷Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital St. Gallen, St. Gallen, Switzerland; and ⁸Department of General, Visceral, Endocrine and Transplantation Surgery, Cantonal Hospital St. Gallen, St. Gallen, Switzerland

Brucellosis is a common, worldwide zoonosis. Clinical presentation is protean and often goes unrecognized. Hepatic brucelloma is a rare local complication of chronic brucellosis. 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*; brucellosis; hepatic abscess; hepatic brucelloma; 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 *Coxiella burnetii*. Agglutination test for brucellosis 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 *Coxiella burnetii* 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 brucelloma. 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 reoccurred. 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.

Received 8 December 2017; editorial decision 18 February 2018; accepted 7 March 2018.

^aEqual contribution

Correspondence: P. W. Schreiber, MD, University Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology, Rämistrasse 100, 8091 Zurich, Switzerland (peter.werner.schreiber@usz.ch).

Open Forum Infectious Diseases®

© The Author(s) 2018. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
DOI: 10.1093/ofid/ofy052

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 [<60 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	7.9 kU/L [<37 kU/L]
CEA	<1.0 µg/L [<5.0 µg/L]
<i>Brucella</i> agglutination assay	Positive [negative] (11/15) Positive [negative] (01/16) Positive [negative] (02/16)
<i>Brucella</i> IgM ^a	<5 U/L [<15 U/L] (11/15) <5 U/L [<15 U/L] (01/16) 5.54 U/L [<15 U/L] (02/16)
<i>Brucella</i> IgG ^b	207.8 U/L [<20 U/L] (11/15) 163.0 U/L [<20 U/L] (01/16) 127.6 U/L [<20 U/L] (02/16)
<i>Brucella</i> IgA ^c	>100 U/L [<10 U/L] (11/15) 89.7 U/L [<10 U/L] (01/16) >100 U/L [<10 U/L] (02/16)
<i>Brucella</i> spp.–specific PCR (liver biopsy)	Negative [negative] (11/15) Negative [negative] (07/16) Positive [negative] (05/17)

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.

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

^bVirion/serion SERION ELISA classic *Brucella* IgG.

^cVirion/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].

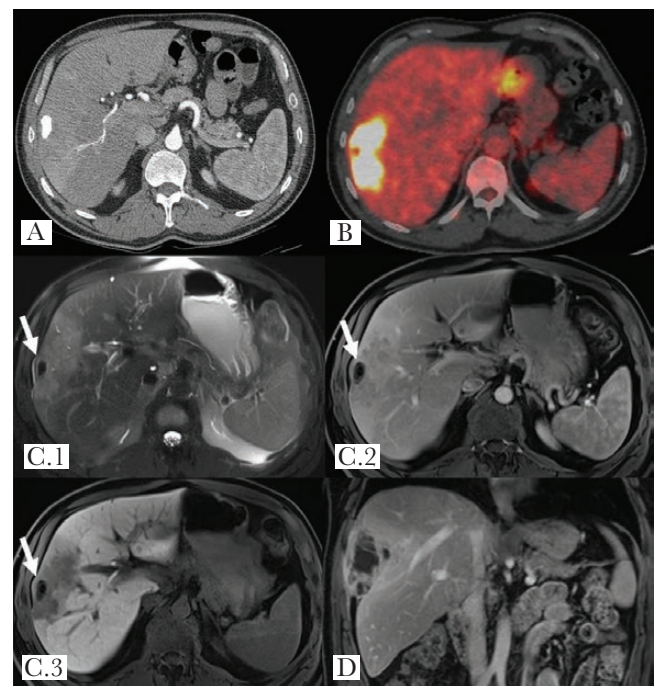


Figure 1. Computed tomography (CT), positron emission tomography (PET)-CT, and magnetic resonance imaging (MRI) of the liver mass. A, Contrast-enhanced CT at initial diagnosis (08/15) with a coarse calcification and adjacent hyperenhancement of the liver parenchyma in segments V/VI/VIII. B, FDG-PET-CT (09/15) shows corresponding FDG uptake of the hepatic lesion (SUV_{max}, standardized uptake value, 16.8). C, Contrast-enhanced MRI (10/15) with a T2-weighted fat-saturated image (C.1), contrast-enhanced images in the portal-venous (C.2), and hepatobiliary phase (C.3) showing the hypointense calcification (arrow). The adjacent area is hyperintense on T2 with increased contrast enhancement in the portal-venous phase and markedly decreased contrast enhancement in the hepatobiliary phase. D, Follow-up MRI (04/16) with contrast-enhanced image showing a subcapsular, septated hepatic abscess.

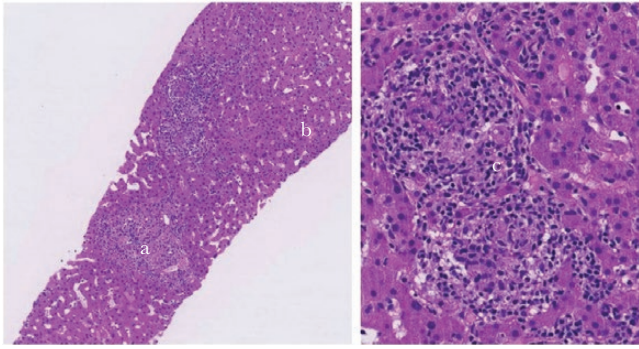


Figure 2. Liver biopsy (11/15) showing portal and peripheral inflammation and a microgranuloma. ^aPortal inflammation. ^bPeripheral inflammation. ^cMagnification of a microgranuloma.

CONCLUSIONS

Even advanced, noninvasive imaging methods cannot distinguish between hepatic malignancy and brucellosis. The optimal treatment for hepatic brucellosis 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 brucellosis. *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, Queipo-Ortuño MI, Reguera JM, et al. Diagnostic yield of a PCR assay in focal complications of brucellosis. *J Clin Microbiol* **2001**; 39:3743–6.
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 E, Bruguera M, Carbonell J, 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.