Patterns of Hepatosplenic *Brucella* Abscesses on Cross-Sectional Imaging: A Review of Clinical and Imaging Features

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Abstract. While diffuse involvement of liver and spleen is frequently seen in brucellosis, suppurative abscesses caused by *Brucella* are less common but well described. With the increased availability of cross-sectional imaging techniques, reports have become more frequent. Four patients with hepatosplenic abscesses caused by *Brucella* spp. are described and included in a review of 115 previously published cases. Clinical characteristics and patterns on ultrasound (US) and computed tomography imaging were analyzed. Furthermore, the proportion of patients with brucellosis affected by suppurative hepatosplenic lesions was estimated. Hepatosplenic abscesses were seen in 1.2% of patients with brucellosis and were mostly caused by *Brucella melitensis*. Imaging analysis revealed two main distinct patterns. Solitary abscesses involving liver more frequently than spleen, and showing characteristic central calcifications, characterize the first pattern. Multiple smaller abscesses, frequent spleen involvement, and absence of calcifications characterize the second pattern. Blood and aspirate cultures were frequently negative, however, the positivity rate increased over the past years. Indirect Coombs test was positive in 96%. Half of the patients were cured by antibiotic treatment; case fatality in this series was 1.9%. Hepatosplenic abscesses due to *Brucella* infections have characteristic imaging findings. Clinicians should be aware of these and the proactive use of cross-sectional imaging, particularly US, should be encouraged in endemic regions.

INTRODUCTION

Brucellosis is the most common zoonosis worldwide with more than 500,000 cases annually and a wide geographic distribution.[1] *Brucella* is endemic in the Mediterranean area and the Middle East as well as in Central Asian countries and to a lesser extent in South America. Brucellosis commonly presents as a systemic infection with fever and symptoms such as anorexia and night sweats. Focal lesions may occur in almost any organ, by far the most common localization being osteoarticular sites.[2]

Diffuse involvement of liver and spleen is frequently seen in human cases[3]; this may be attributed to intracellular survival and replication of bacteria in the mononuclear-phagocytic system of these organs. Hepatosplenomegaly and mild elevation of liver enzyme levels are observed as signs of this diffuse inflammation.

Suppurative abscess formation in liver and spleen is far less common but nevertheless well described in literature. Following the first reported case, diagnosed postmortem in 1904,[4] only few further cases have been described in subsequent decades. This was partly due to the difficulty in making the diagnosis without imaging techniques such as those available today. Clinical signs and symptoms are nonspecific; plain radiographs of the abdomen may show calcifications in the hepatic area, but these are difficult to interpret and also nonspecific.[5] With the advent of cross-sectional imaging techniques such as ultrasound (US) and computed tomography (CT), case reports have become more frequent during the past three decades.

In this article, we describe four cases of *Brucella* liver abscesses diagnosed by US. We also review published cases of hepatic and splenic abscesses in which imaging with US and/or CT were used in the diagnostic workup.

METHODS

For all patients with hepatosplenic abscesses due to *Brucella* spp., diagnosed in the Department of Infectious and Tropical diseases, Istituto Di Ricovero e Cura a Carattere Scientifico San Matteo, Pavia, Italy, in the past 15 years, information on US and CT imaging as well as clinical data was collected.

A literature review using the key words "*Brucella*," "liver," "spleen," and "abscess" as well as their extensions, was performed in Medline. Publications containing information on diagnostic findings on CT or US were selected and references of the articles were reviewed. Publications in English, Spanish, French, Italian, Portuguese, and German were included. Data were analyzed using χ^2, Fisher exact and Mann–Whitney U tests, as appropriate.

RESULTS

Four cases were identified in our department.

Case 1. A 34-year old, previously healthy male butcher from Tuscany, Italy, was transferred to our hospital with a history of fever up to 39°C, joint, and abdominal pain. Laboratory tests revealed hemoglobin of 11.5 g/dL, white blood cells (WBC) of 11,500/μL with 75.9% neutrophils, and an erythrocyte sedimentation rate of 113 mm/hour. Liver function tests showed an increased alkaline phosphatase (ALP) (335 U/L) and gamma-glutamyl transferase (GGT) (151 U/L). Blood cultures were negative. Abdominal US revealed a lesion in liver segment VII of 6 cm in diameter and without significant doppler flow in or around the lesion. A calcification was seen in the central part of the lesion (Figure 1). Abdominal CT confirmed the presence of a hypo-dense lesion and the central calcification. An US-guided aspiration was performed, which yielded 25 mL of purulent material. The material was

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FIGURE 1. Ultrasonography of the liver (patient 1) showing a solitary brucellar abscess with typical echogenic calcification in the central area.

FIGURE 2. (**A**) Ultrasonography of the liver (patient 2) showing hepatic mass with complex contours, a well demarcated border and a pattern of mixed echogenecity with hypo- and hyper-echoic areas. A central calcification of approximately 1 cm diameter is visible as often seen in brucellar abscesses (**B**) Computer tomography scan of the same abscess showing a large lobulated hypodense lesion in liver segments VII–VIII with a central calcification.

sent for microbiological analysis; culture results were negative after 20 days of incubation. Serological Wright test was negative, Coombs serology for incomplete *Brucella* antibodies was positive with a titer of 1:400. Therapy was started with doxycycline, rifampicin, and penfloxacin. The anti-*Brucella* titers rose to 1:640 in the Wright test and to 1:3,200 in Coombs' serology after initiation of therapy. After clinical improvement, the patient was discharged from hospital and antibiotic treatment was continued for a period of 3 months.

Case 2. A 35-year-old male patient from Campania, Italy, was seen for suspected cystic echinococcosis (CE). Laboratory tests showed elevated WBC and GGT, and ALP. An abdominal US confirmed a mass in liver segments VII–VIII, with complex contours, a clear-cut border and a pattern of mixed echogenecity with hypo- and hyper-echoic areas and a central calcification of 1 cm diameter (Figure 2A). A CT scan of the abdomen confirmed the lesion (Figure 2B). Aspiration biopsy produced granulomatous material; microbiological cultures remained sterile. Wright serology was positive with a titer of 1:640, Coombs-incomplete *Brucella* antibodies were positive with a titer of 1:1,600. The patient improved clinically during treatment (doxycycline/rifampicin). On an US performed 3 years after the initial diagnosis, the liver still showed a lesion, which was smaller than at diagnosis and homogenous; the central calcification had resolved.

Case 3. A 33-year-old female patient from Lombardy, Italy, presented with an external US report compatible with a liver abscess in the left hepatic lobe with a central calcification, as well as a fluid collection in the abdominal wall with a diameter of approximately 6 cm. The CT scan confirmed an abscess in the left abdominal wall with an intraperitoneal component connected with the hepatic lesions in segment III and a cutaneous incision was performed in the surgical department, yielding large amounts of pus-like material. The patient was then referred to our clinic for suspected CE, but the central calcification immediately raised the suspicion of *Brucella* abscess and serological tests were performed (Wright nega-

tive; Coombs-incomplete antibodies 1:1,600). After treatment (doxycycline/rifampicin), the patient improved; the hepatic lesion had disappeared on a follow-up US after 1 year.

Case 4. A 44-year-old female Italian patient with known sickle-cell anemia was seen for fever of unknown origin. Abdominal sonography showed a round lesion in liver segment VI (2.5 × 3 cm) with a large central calcification (1.5 cm). Following the experience of the previous cases, *Brucella* abscess was immediately suspected. Wright serology was negative, incomplete *Brucella* antibodies were highly positive (1:800) strengthening the diagnosis. Treatment with doxycycline/rifampicin was successful. On sonographic follow-up after 1 year, the hepatic abscess had disappeared, only the calcification remained visible.

Results from literature review of previously reported cases. Literature review identified 80 reports (Supplemental Table 1 and references 1–80) published since 1979 describing diagnostic findings on US and/or CT imaging in patients with focal hepatic or splenic brucellosis. Including our own four cases, data on 119 cases of hepatosplenic *Brucella* abscesses

Demographic and clinical information on 119 patients with hepatosplenic abscesses due to *Brucella* spp. (proportion in % and 95% confidence interval)

Demographic	Age, median years (range)	43 (3–78)
	Sex, male/female (ratio)	65/49 (1,3:1)
Clinical presentation	Abdominal pain and fever	57% (48–67%)
	Fever only	37% (28–46%)
	Abdominal pain only	6% (1–10%)
Imaging findings	Single lesion	68% (59–76%)
	Multiple lesions	32% (23–40%)
	Liver lesions	70% (61–78%)
	Spleen lesions	28% (20–36%)
	Liver and spleen lesions	2% (0–10%)
	Liver abscess, right lobe	71% (59–82%)
	Liver abscess, left lobe	19% (9–29%)
	Liver abscess, both lobes	10% (2–17%)
	Liver abscess with calcification	77% (68–86%)
	Spleen abscess with calcification	26% (11–42%)
Microbiology results	Positive blood culture	22% (14–31%)
	Positive pus culture	17% (8–27%)
	Direct serology > 1:160	40% (30–50%)
	Coombs serology > 1:320	96% (91–100%)
Treatment used	Antibiotic only	47% (38–57%)
	Antibiotic and surgery	48% (39–58%)
	Antibiotic and percutaneous	5% (1–9%)
Outcome	Improved	98% (95–100%)
	Died	2% (0–5%)

were analyzed. Demographic information and the findings of diagnostic investigations are summarized in Table 1.

Demographic and clinical information. A total of 57% of the patients were male, 43% female. The median age was 43 years ranging from 3 to 78 years. Only 4 cases were reported in children below the age of 14 years. The majority of cases were from Spain (49%), Turkey (18%), Italy (11%), and France (6%); from other countries only individual cases (less than five) have been reported. The majority of patients (57%) presented with fever and abdominal pain; 37% presented with fever only and 5% reported local symptoms only.

Underlying medical conditions, possibly explaining the development of focal abscesses due to immune suppression or shedding from endocardial infection, were reported rarely: three patients had hematologic disorders (thalassemia,[6] monoclonal gammopathy,[7] sickle-cell anemia [own]); three patients suffered from cardiac diseases (two endocarditis,[8,9] one rheumatic aortic valve replacement[10]); two patients were pregnant at the time of diagnosis[11,12]; two patients suffered from diabetes[13,14]; one patient had hepatitis[15] and one patient allergic rhinitis.[16] Other patients were described as having no underlying disease or no condition was specified.

Imaging findings. CT and US imaging studies revealed solitary abscesses in the majority of cases (68%); multiple lesions were seen in 37 cases (32%). Abscesses predominantly involved the liver (70%); 28% of patients presented with lesions in the spleen and 3 (2%) had abscesses in both. Of the 62 patients for whom information on the localization of the liver lesion was reported, the abscesses were localized in the right liver lobe in 44 (71%), in the left liver lobe in 12 (19%), and in 6 (10%) lesions were seen in both lobes. Liver abscesses were significantly more frequently solitary (77%, 95% CI: 68–86%) than those in the spleen (39%, 95% CI: 24–55%; *P* < 0.001). Liver lesions were larger (mean 6.0 ± 0.3 cm) than lesions in the spleen (mean 2.5 ± 0.3 cm, *P* < 0.01). When multiple lesions were present, these were

significantly smaller than solitary lesions (*P* < 0.01); cases with multiple abscesses sized 1 cm and smaller were frequently seen.

In the large majority (77%) of the liver abscesses, a central calcification was visible. In splenic abscesses, calcifications were also described, but only in a lower proportion (26%; *P* < 0.001). In the liver, solitary abscesses more often showed a central calcification (82%, 95% CI: 73–92%) compared with multiple abscesses (43%, 95% CI: 24–70%; *P* < 0.01). Splenic abscesses contained calcifications less frequently, independent whether solitary (25%, 95% CI: 0–50%) or multiple (24%, 95% CI: 5–42%; *P* = n.s.).

Only four children were reported with abscesses due to *Brucella* spp.; in three of them multiple abscesses were seen. In all children the spleen was involved, in two the liver showed additional lesions. None of the pediatric cases showed calcifications, which was statistically significantly different from adults (*P* < 0.05).

Microbiology results. In patients for whom isolation of the pathogen from blood cultures was attempted, only 21/90 (23%) grew *Brucella* spp. Material from the abscess was obtained by aspiration or as part of abdominal surgery in 65 patients; only in 12 (18%) the bacteria could successfully be cultured. In 25 cases, the causative pathogen was further characterized; *Brucella melitensis* was isolated in 20 (80%), *B. abortus* in 3 (12%), and *B. suis* in 2 (8%). The yield of positive blood cultures has increased in recent years, presumably due to improvements in culture technique and, possibly, due to better communication of clinical suspicion to the laboratory. In cases reported in the past 10 years (2005–2015), 11/25 (44%) blood cultures grew the causative organism. Although this is still a low rate, it is significantly higher than that seen in the patients diagnosed before 2005; 10/65 (15%, *P* < 0.01). Abscess material culture reported between 2005 and 2015 grew organisms in 25% (4/16), whereas in previous years 16% (8/49, *P* = n.s.) were positive.

In the absence of bacteriologic confirmation, high antibody titers can support the presumptive diagnosis of *Brucella* infection. A wide range of serologic tests has been used to indirectly diagnose brucellosis, including direct agglutination tests and ELISA. In the reviewed reports, the most widely used assays were serum agglutination tests, that is, Wright's reaction, performed both in tubes or micro-plates, or indirect Coombs test performed in tubes. Direct serology results were reported for 92 patients and the Wright's reaction titers were higher than 1:160 in 37 patients (40%). Indirect Coombs test was performed in 68 patients and was positive (titer > 1:320 or ≥ 1:400 depending on the serum dilution used) in 65 (96%); many patients showed titers of 1:1,280 (1:1,600, respectively) and above. The use of polymerase chain reaction (PCR) was reported from blood samples in seven patients and from pus or biopsy material in seven patients; in all 14 samples *Brucella* DNA was isolated.[17–20]

Treatment and outcome. In 90 cases, the antibiotic regimen was specified; in the remaining "*Brucella*-specific antibiotic treatment" was reported. In 36 cases (40%), a combination of doxycycline with an aminoglycoside was used, in 27 cases (30%) doxycycline was combined with rifampicin. In 17 patients (19%), a triple combination was used (doxycycline, rifampicin, aminoglycoside in 12; combinations including TMP-SMZ in 5). In some patients, the antibiotics were prescribed for longer than 6 weeks; the combination of

TABLE 2
Proportion of patients with brucellosis showing suppurative hepatosplenic abscesses due to *Brucella* spp.

	N	Liver abscess	% (95% CI)	Spleen abscess	% (95% CI)	All	% (95% CI)
Retrospective*							
Reference[15]	905	14	1.5 (0.8–2.5)	2	0.2 (0.02–0.7)	16	1.7 (1.0–2.8)
Reference[2]	530	1	0.2 (0.01–1.0)	0	0 (0–0.7)	1	0.2 (0.01–1.0)
Sub-Total	1,435	15	1.0 (0.6–1.7)	2	0.1 (0.01–0.5)	17	1.2 (0.7–1.8)
Prospective clinical†							
Reference[17]	709	4	0.6 (0.14–1.5)	3	0.4 (0.09–1.2)	7	1.0 (0.4–2.0)
Prospective screening‡							
Reference[21]	80	2	2.5 (0.3–8.7)	1	1.3 (0.03–6.7)	3	3.8 (0.8–10.6)
Reference[22]	251	0	0 (0–1.4)	4	1.6 (0.4–4.0)	4	1.6 (0.4–4.0)
Sub-Total	331	2	0.6 (0.1–2.1)	5	1.5 (0.5–3.5)	7	2.1 (0.9–4.3)
Total	2,475	21	0.8 (0.5–1.3)	10	0.4 (0.2–0.7)	31	1.2 (0.8–1.8)

CI = confidence interval.
* Review of patient's files after discharge.
† Patients prospectively screened clinically for signs and symptoms of liver/spleen abscess at the time of diagnosis of brucellosis then imaged.
‡ Patients prospectively screened by ultrasound at the time of diagnosis of brucellosis.

doxycycline/rifampicin was given for up to 3–9 months in individual patients.

Successful management by antibiotic treatment was reported for 51 patients (47%). Surgery (splenectomy, hepatic lobectomy) in combination with antibiotic treatment was reported for 52 patients (48%). Antibiotic treatment combined with percutaneous drainage was described in nine patients (8%); four of these patients required surgical intervention later. The indication for surgery was not uniform and depending on the treating physicians; in some cases, surgery was performed as first-line treatment. The efficacy of each strategy can thus not be assessed from the data.

103/105 (98%) patients for whom outcome was reported improved clinically and were eventually cured. This was documented clinically by subsiding fever and/or sonographical shrinking or resolving lesions. Two patients died[13,14] amounting to a case-fatality rate of 1.9% (95% CI: 0–4.6%) in this case-report series.

Estimated prevalence of suppurative lesions. To estimate the proportion of patients with brucellosis who develop abscesses in liver or spleen, five studies reporting on the size of the total patient population, were identified. Two of these studies performed a retrospective review of clinical files of patients diagnosed with brucellosis.[2,15] One study assessed patients with the diagnosis of brucellosis prospectively; clinical criteria were used and imaging studies were only performed when the patient showed clinical abnormalities.[17] Two studies prospectively screened all brucellosis patients by US for liver and spleen lesions.[21,22] The results are summarized in Table 2. From a total of 2,475 patients, 31 cases with hepatosplenic abscesses were identified (1.2% of all patients, 95% CI: 0.8–1.8%). Liver abscesses occurred in 0.8% (95% CI: 0.5–1.3%), spleen abscesses in 0.4% (95% CI: 0.2–0.7%) of patients with brucellosis.

DISCUSSION

Although nonspecific hepatitis and enlargement of liver and spleen occurs frequently in patients with systemic *Brucella* infection,[23] suppurative abscess formation appears to be less common. We found that hepatosplenic abscesses are a characteristic entity with a prevalence of approximately 1% in brucellosis patients and mainly due to *B. melitensis*. In reviews on clinical manifestations of brucellosis, hepatosplenic abscesses are not represented, probably being subsumed under broader clinical categories such as "hepatitis" or "hepatosplenomegaly."[3] Since the advent of US and CT, the number of cases diagnosed has increased and may increase further with US being now increasingly used in low-resource settings where brucellosis is prevalent.

The imaging findings of hepatosplenic *Brucella* abscesses are relatively uniform and should raise suspicion even in cases when brucellosis is not yet diagnosed or suspected. On the basis of the data available, we suggest two general imaging patterns: "solitary abscess with calcification" and "miliary."

"Solitary abscess with calcification" is characterized by a solitary, often large abscess, most frequently affecting the liver, and marked by a central calcification (Figures 1 and 2). It has only been reported in adults and, given the calcifications, which need time to develop, one may surmise a more chronic and smoldering course of the disease. The imaging appears characteristic enough to formulate the diagnosis of brucellosis, especially in an endemic setting. Possible differential diagnoses include hepatocellular carcinoma and metastasis of the liver (both usually without calcification); posttraumatic or postoperative calcified hematomas (in which calcifications are often not central but peripheral), vascular calcifications and hemangiomas (which are usually not calcified). Potential infectious disease differential diagnoses include hydatid cysts (especially type CE 4 and CE 5) caused by *Echinococcus granulosus*.[24] However, calcifications are always peripheral in these lesions.[25] Bacterial abscesses usually have a hypo-echoic appearance and may show hyper-echoic areas due to gas collections, which may mimic calcifications and are thus a potential confounder.

Multiple hypo-echoic, smaller abscesses mark the "miliary" pattern, which predominantly involves the spleen (Figure 3). The lesions may be smaller than 1 cm, show few calcifications and have been observed in adults and children. Given the wider spread of the lesions and the fact that the two patients who died due to their brucellosis showed the "miliary" pattern, one may speculate whether it indicates a less favorable balance between host-immune system and the pathogen.

The "miliary" pattern is less characteristic; the main confounder is disseminated tuberculosis (TB), especially in regions where both diseases are endemic. The pattern of multiple hypo-echoic lesions in the spleen, and less frequently, in the liver, has been described as highly suggestive for disseminated TB and has been included into point-of-care US protocols for extra-pulmonary TB.[26] Miliary TB lesions are most
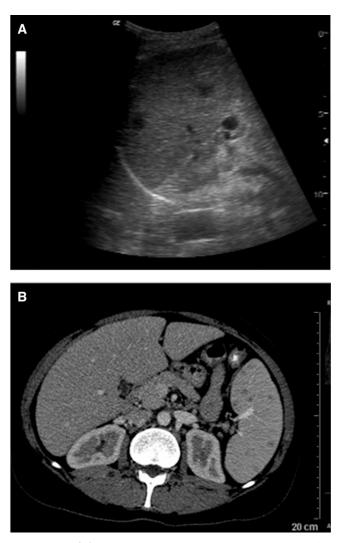
In all patients suspected of brucellosis, isolation of the pathogen by blood culture, as well as of aspirated material should be attempted, although cultures are only positive in a minority of cases. Even if the diagnostic yield seems to have increased in recent years, a negative culture cannot rule out the diagnosis of brucellosis.

Although rarely reported in the reviewed cases, the development of specific PCR techniques has additionally improved the diagnosis of brucellosis.[31] Multiplex PCR has been shown to successfully differentiate between focal complications due to *Brucella* spp. and *Mycobacterium tuberculosis*.[32] Currently serology is the most commonly used test to support a diagnosis of brucellosis in suppurative lesions; especially indirect Coombs test, which is almost invariably positive, often showing high titers.

No standardized treatment approach can be deduced from the literature, but it seems that antibiotic treatment, for example, with doxycycline and rifampicin, is successful in most cases. If medical treatment is unsuccessful, percutaneous drainage or surgical intervention may be indicated and with these options successful outcome is seen in almost all cases.

In summary, although hepatosplenic abscesses are only seen in a relatively small proportion of patients with *Brucella* infections, in areas where the disease is prevalent a significant number of patients suffer from them. Imaging findings can be characterized as "solitary abscess with calcification" or "miliary" pattern and clinicians should be aware of these to suspect brucellosis. The use of cross-sectional imaging, especially relatively inexpensive and noninvasive US, should be encouraged in endemic regions to prompt the diagnosis by visualizing the focal complications of *Brucella* infection.

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FIGURE 3. (**A**) Ultrasonography of the spleen in a patient with suppurative lesions in the spleen showing two hypo- to anechoic small lesions (diameter approximately 1 cm) (courtesy of D. Kotlar, Jeddah, Saudi Arabia) (**B**) Computer tomography scan of a patient with *Brucella* spleen abscesses showing as multiple hypodense lesions in the spleen (courtesy of M. Yilmaz, Istanbul, Turkey).

frequently seen in immune-compromised HIV patients[27] but have also been reported in children without HIV coinfection.[28] Infection with *Bartonella,* for example, HIV-associated bacillary angiomatosis or cat-scratch-disease may cause peliosis[29] which is another differential diagnosis of hypo-echoic focal lesions, but peliosis is rare and associated with a positive serology for *Bartonella*. In Southeast Asian patients, melioidosis, caused by *Burkholderia pseudomallei*, should be considered as it may present with similar imaging features.[30] Disseminated fungal abscesses may also appear similar,[29] however, these characteristically show a "wheel-in-wheel" US appearance and are mainly seen in immune-compromised individuals with hematological disorders. Noninfectious differential diagnoses are sarcoidosis, lymphoma, and focal lesions in chronic lymphatic leukemia.

Overall, the two abovementioned patterns of suppurative *Brucella* lesions should be seen as two ends of a spectrum and a proportion of cases will fall in between and show mixed features.

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