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Splenic abscesses in childhood brucellosis: a case-based review

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Abstract. – OBJECTIVE: Human brucellosis is a zoonosis with an extremely wide spectrum of clinical manifestations. Focal splenic involvement is very uncommon, particularly in the pediatric age group, during the illness' acute phase.

CASE REPORT: A 4-year-old boy, already receiving third-generation cephalosporin treatment, was transferred from a local hospital to the University Pediatric Department for fever, anemia, increased inflammation index, and multiple, hyper-echogenic splenic lesions on abdominal ultrasound. Initial diagnostic laboratory investigations for Brucella infection, including the Widal-Wright test, were found to be negative. However, further diagnostic laboratory analysis using the chemiluminescent immunoassay was positive for Brucella IgM antibodies. Treatment with rifampicin at a dose of 150 mg/Kg/twice daily and co-trimethoprim at a dose of 80 mg/Kg/twice daily was started and continued for 7 weeks. IgM antibodies were undetectable after 2 weeks of treatment, and after 6 weeks of treatment, abdominal ultrasound documented a reduction of the diameter of the major splenic infiltrate from 1 to 0.5 cm. At 3 and 5 months of follow-up, re-evaluation of the abdominal lesions displayed complete resolution of the splenic lesions and a complete clinical recovery.

CONCLUSIONS: The present case and a literature review are presented in this study since a standard diagnostic laboratory evaluation for brucellosis may miss the diagnosis, and in suspected cases, the laboratory analysis should be extended. Splenic abscesses are known to be rare in brucellosis, but the diagnosis should be considered in children with severe focal lesions, as specific antibiotic treatment may result in complete clinical recovery.

Key Words:
Splenic abscess, Acute brucellosis, Childhood brucellosis, Brucellosis treatment.

Introduction

Human brucellosis is described as a zoonosis with an extremely wide spectrum of clinical manifestations which may involve one or multi-organ systems. Given the wide spectrum of symptoms associated with this infection, especially during childhood, the diagnosis is often not a straightforward process. Multiple different species of Brucella are involved in human brucellosis including B. melitensis, B. suis, and B. abortus. Generally, the cause of infection in children is ingestion of products of infected animals such as unpasteurized milk and cheese. Brucellosis is an important zoonotic infection particularly spread throughout the Mediterranean area[1]. In 2015, 27 countries in the European Union reported a total of 437 confirmed cases of human brucellosis, with a prevalence of 0.09/100,000 individuals. The countries with the highest rate of brucellosis were Greece (109 confirmed cases with a prevalence of 1/100,000 individuals), Italy (105 confirmed cases with a prevalence of 0.17/100,000 individuals), and Portugal (46 confirmed cases with a prevalence of 0.44/100,0000 individuals). In a 2015 Italian annual report on animal brucellosis, the Italian region with the highest prevalence of animal brucellosis was found to be Sicily (3.3%)[1]. A statistically significant correlation

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between the prevalence of human brucellosis and animal cases was observed[1]. In human brucellosis, the most common symptoms at presentation are fever, arthralgia, pallor, weakness, sweating, and peripheral arthritis, but other symptoms may also be found depending on the affected organs[2]. Al-Eissa et al[3], in 102 consecutive cases of childhood brucellosis, noted that 91% had fever, 35% had splenomegaly, 28% hepatomegaly, and 16% lymphadenopathy. The hematological manifestations of the affected patients mainly consist of anemia, pancytopenia, leukopenia, and thrombocytopenia[4]. In patients affected by this disorder, hematological complications may occur as in the patients reported by Makis et al[5], who presented with severe thrombocytopenia with significant hemorrhagic manifestations due to autoimmune stimulation, and the case of Brucella-related hemophagocytic lymphohistiocytosis reported by Pekpak and Cetin[6]. The infection can involve several organs including the liver and spleen. Involvement of these organs has been associated with intracellular survival and replication of the bacteria in the mononuclear phagocytic system[7]. Abscesses involving the spleen are an uncommon but severe and dangerous complication. The incidence of splenic abscess in brucellosis has been reported to be in less than 2% of cases[7]. This complication affects mainly adults, and it has been rarely reported in young children[8-10]. This report describes a 4-year-old boy affected by acute brucellosis who presented with mild general clinical manifestations and isolated splenic abscesses. Initially, laboratory testing, including the Widal-Wright test for brucellosis, was negative. Subsequently, chemiluminescent immunoassays were found to be positive for Brucella IgM antibodies. Specific antibiotic treatment resulted in a slow but constant improvement and recovery.

Case Report

A 4-year-old boy was transferred to the Pediatric Department of Catania University from a local hospital due to fever and anemia of 10 days' duration. He had received a treatment with a third-generation cephalosporin, 800 mg/KG/twice a day, for the presence of splenic lesions on abdominal ultrasound (US). Upon admission, he presented with fever, marked cutaneous pallor, bilateral cervical lymphadenopathy, weakness, and episodes of abdominal pain. Laboratory studies showed the following: hemoglobin = 9.9 g/dl; RBC = 3,700,000; mean corpuscular volume = 81 fL; platelets = 114,000/μL; white blood cell count = 8,680/μL (neutrophils, 60%, lymphocytes, 27%, monocytes 7%, eosinophils 6%); erythrocyte sedimentation rate (ESR) = 59 mg/dl; C-Reactive Protein (CRP) = 19; and ferritin = 42 ng/mL. Cultures of blood, urine, and fecal samples were not positive for bacteria, viruses, or parasites including the Widal-Wright test for Brucella. Abdominal US revealed splenic parenchyma with an irregular echogenic structure and multiple hypoechoic lesions with a maximum diameter of almost 1 cm (Figure 1) and avascular hypoechoic lesion (Figure 2). The splenic volume was mildly increased (longitudinal diameter = 9.5 cm) with no other pathological findings. The splenic lesions were non-specific and suggested a differential diagnosis, including leukemia, as well as other lesions of infectious origin. A biomarker evaluation excluded tumor infiltration. Chest and abdominal contrast computed tomography (CT) showed mediastinal and abdominal lymphadenomegaly, a small increased volume of the liver, and several unspecific lesions in the spleen. These were visualized only in the venous phase after contrast injection, and the CT scanning confirmed the increase in splenic

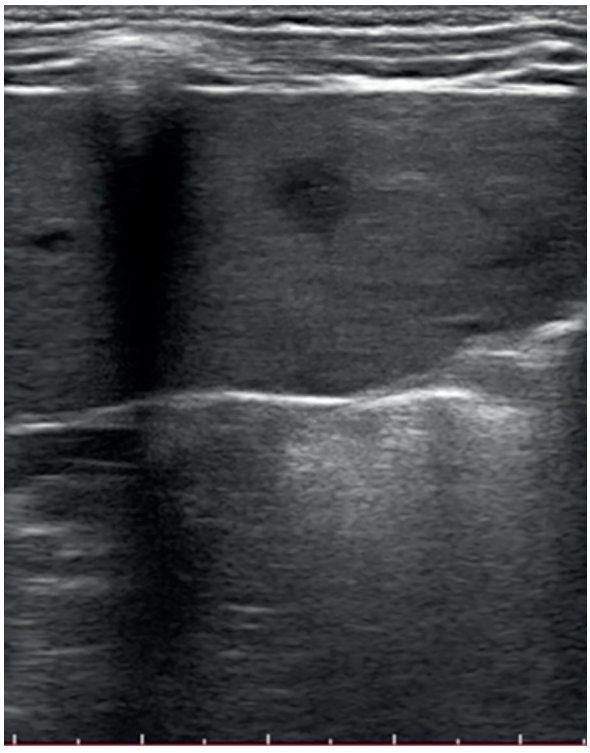

Figure 1. First US exam (high frequency probe): irregular echostructure and hypoechoic lesions, with the maximum diameter of almost 1 cm.

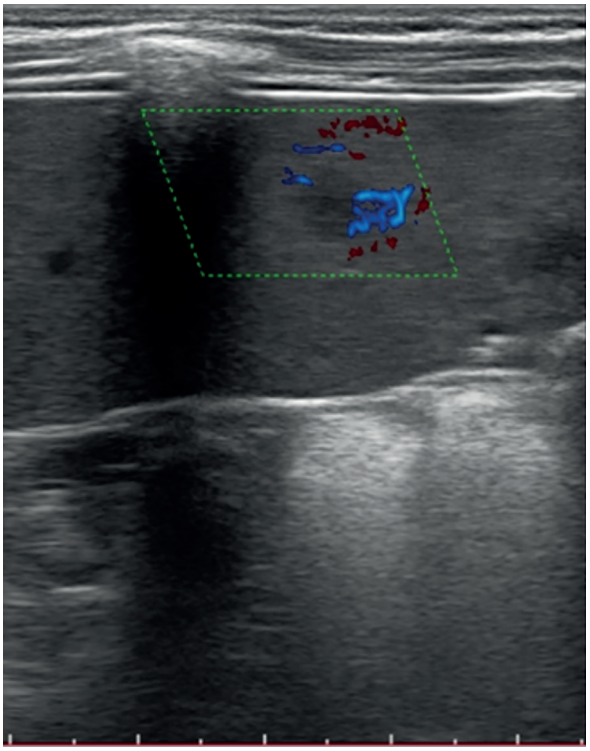

Figure 2. Avascular hypoechoic lesion.

volume and multiple non-specific, hypodense lesions (Figure 3), with an axial diameter of a few millimeters (maximum size = 8×6 mm) (Figure 4). Given a suspicion of Brucella infection, additional laboratory analyses were performed including chemiluminescent immunoassays (CLIA), which were thereafter found to be positive for the presence of Brucella IgM antibodies. Based on this result, therapy with rifampicin at a dose of 150 mg/Kg/twice daily and co-trimethoprim at a dose of 80 mg/Kg/twice daily

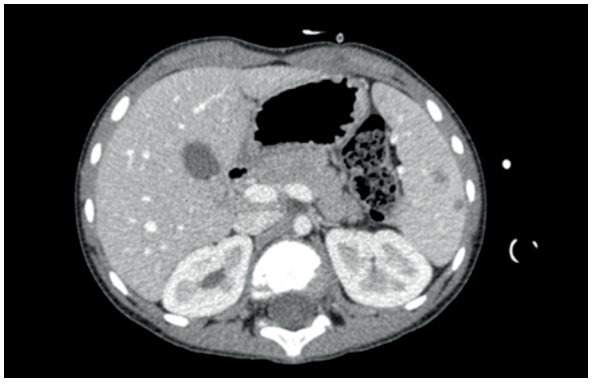

Figure 3. CT scan image in venous phase showing increased volume of the spleen.

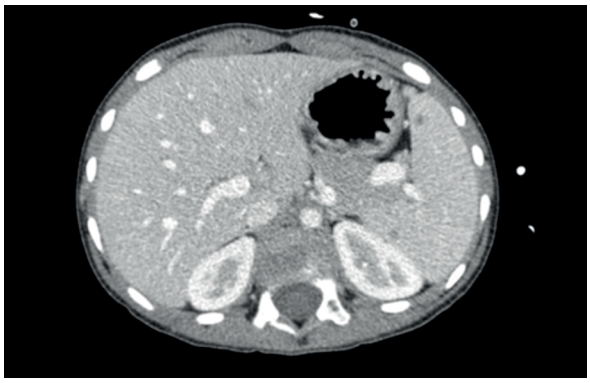

Figure 4. Various non-specific hypodense lesions with the axial diameter in the range of few millimeters (maximum lesions: 8×6 mm).

was started and continued for a total of 7 weeks. During the hospitalization, a low-grade fever was constantly present with a maximum level of 37.8°C daily. The serum IgM titer became negative after 2 weeks of treatment. An abdominal US performed 6 weeks after admission revealed partial resolution of the hypoechoic lesions (Figure 5) with a diameter of 5 mm (Figure 6). The child remained afebrile after 2 weeks and was then discharged from the hospital. Treatment was continued at home. At follow-up, the child was afebrile with no significant symptomatology. An US examination performed 3 months after admission showed complete resolution of the splenic abscesses (spleen with a maximum

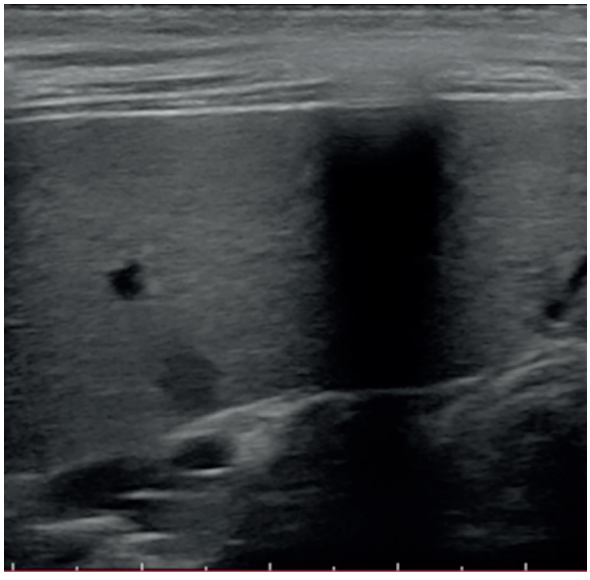

Figure 5. US exam control after 1 month and half showing partial resolution of the hypoechoic lesion.

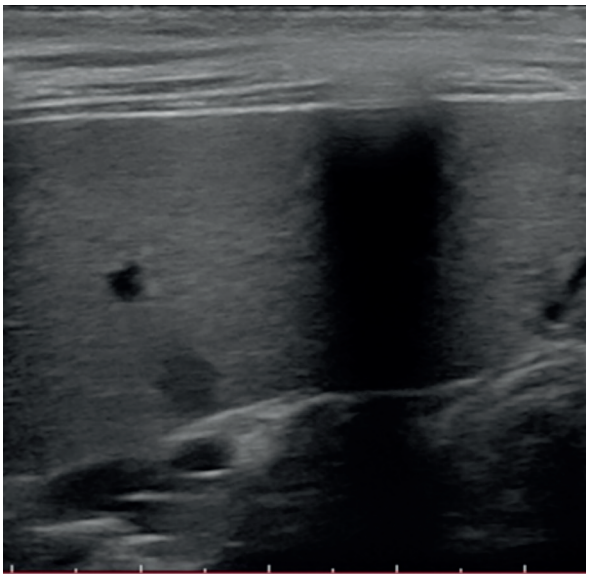

Figure 6. US exam control after 1 month and half showing hypoechoic lesion of almost 5 mm diameter.

diameter 100 mm and normal echogenic structure). A splenic ultrasound performed 5 months after admission showed complete resolution of the previously documented infiltrates (Figure 7) and complete organ healing (Figure 8).

Search Strategy and Methodology

This case report was based on a 4-year-old child treated in the Pediatrics Department. Research for similar cases was conducted using PubMed with the following keywords: "pediatric brucellosis", "splenic abscess in brucellosis", "brucellosis complications", and "brucellosis treatment". There were very few cases of splenic abscess in patients with acute brucellosis, and among these, there were only 4 cases in the pediatric age group. References from these selected articles were reviewed for information on the current topic.

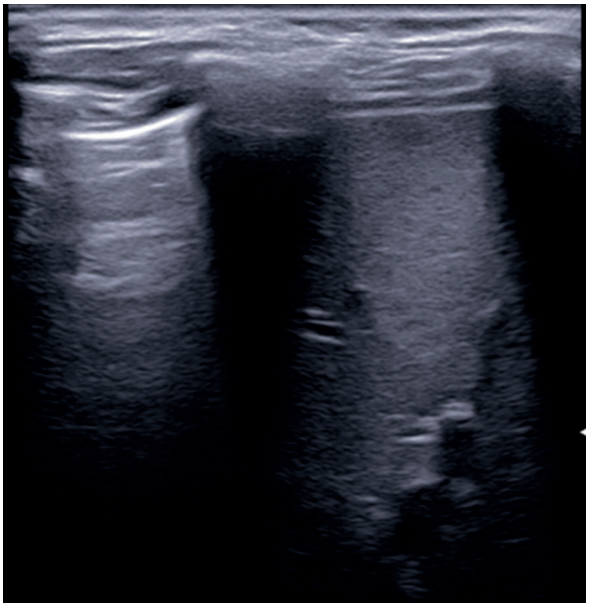

Figure 7. US exam control at five month showing complete resolution of the spleen lesions.

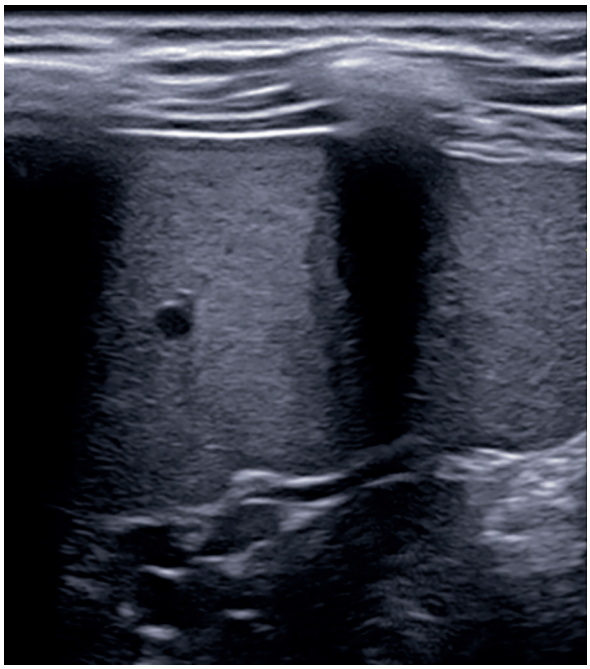

Figure 8. US exam control showing complete organ healing.

Discussion

Brucellosis is a zoonosis which is endemic in Sicily, and its prevalence in animals, particularly sheep and goats, suggests the need to improve official control measures and eradication efforts. Human brucellosis has a significant variety of clinical manifestations that make the diagnosis difficult. The child in this report (Table I) presented with symptoms characterized by fever with low temperature, weakness, pallor, and episodes of mild abdominal pain. Inflammatory indices were positive. Splenic lesions were found on abdomen ultrasound. The initial studies for a causative agent were negative including the Widal-Wright test for brucellosis. The final diagnosis of Brucella infection was ultimately

Table I. Clinical, haematological, instrumental data, treatment and prognosis of our patient.

Clinical signs	Fever, cutaneous pallor, laterocervical lymphoadenia, weariness, abdominal pain
Hematological results at onset	Hb 9.9 g/dl, RBC 3,700,000/mmc, WBC 8.680 (N 60%, L 27%, M 7%, E 6%, ESR 59; CRP 19 mg/dl
Serum laboratory investigation	Widal – Wright test negative
Abdomen ultrasound	Splenic parenchyma: Irregular echostructure, multiple hypoechogenic and avascular lesions
CT scan	Spleen: increased volume and various non-specific hypodense lesions with an axial diameter of a few millimeter (8×6 mm)
Serum laboratory investigation	chemiluminescent immune assay positive with Brucella IG M antibodies
Treatment	Rifampicin 150 mg/kg /twice daily; trimethoprim 80 mg/Kg/twice daily
Clinical course	Progressive reduction of clinical signs and IgM title negative after two weeks
Course of the abscesses at US (ultrasound) abdomen control	At 1 and ½ month partial resolution of the hypoechoic lesions at 3 months complete resolution

determined with the use of a CLIA which was determined positive for Brucella IgM antibodies. Abdominal ultrasound showed signs of splenic abscesses with an irregular echogenic structure and multiple hypoechoic and avascular lesions. These features were subsequently confirmed by abdominal CT scan.

Splenic abscesses in brucellosis are very rare and must be distinguished from those caused by other etiologies. The primary etiologies of splenic abscesses include the following: (a) infection, particularly anaerobic infection, and metastatic infection from perinephric abscesses or infected pancreatitis, (b) splenic infarction and superimposed infection, (c) trauma, and (d) immunocompromised state (receiving chemotherapy, being a transplant recipient, or having leukemia or AIDS)[7]. In this child, the clinical manifestations were mild and non-specific with a low-grade fever and episodes of mild abdominal pain. Current imaging techniques such as US, CT scan, or magnetic resonance imaging may help to reach a correct diagnosis in splenic abscess and also to evaluate the course of complications. Splenic abscesses in brucellosis on US are typically poorly demarcated with a variable profile, usually showing a hypoechoic pattern with some internal echoes. Rarely, they may occur as multiple hyperechoic areas[11]. On CT scans, the lesions appear as low density with attenuation values of 20-40 HU[12]. Splenic abscesses in brucellosis may be present as a serous fluid collection[13] or as a calcified lesion. The presence of calcifications is characteristic of chronic splenic brucellosis, pancreatitis, or perinephric abscesses[12].

Cases of splenic abscess in children affected by acute brucellosis are extremely rare; however, the incidence of this type of complication appears to be approximately 2% of all brucellosis complications[7]. Liver and spleen abscesses are quite serious when undiagnosed or not treated with appropriate antibiotic therapy[14]. Table II shows cases currently described in the literature. To the best of our knowledge, only three cases in young children have been reported[8-10], with the majority of cases having been described in adults[14-27]. Among the cases in children, including this case, B. melitensis was reported in 2 of 4 cases. Among 21 cases in adults, B. melitensis was reported in 12, B. suis in 4, B. abortus in 1, and no specific species in 4. Among the 4 children, remission was obtained in 3, and data was not available in the other child. Among the adults, remission was obtained in 18, 2 patients died due to other causes, and 1 had a relapse.

The first case of a Brucella hepatosplenic abscess in children was reported by Vallejo et al[9] in a 3-year-old Mexican boy. The child presented with a high temperature spiking to 40°C. He was awake and alert with no specific clinical disturbances other than moderate right upper quadrant tenderness. Abdominal US revealed a single hypoechoic lesion in the right lobe of the liver with irregular margins and multiple small lesions within the spleen. These US lesions were con-

Table II. Cases of splenic abscess in acute brucellosis (in bold font pediatric cases).

Case	Age (y)/ sex	Organ involved	Antibody title	Isolate	Therapy	Outcome
Seçmeer et al[8], 1995	11 y	Spleen	Data not available	Data not available	Data not available	Data not available
Vallejo et al[9], 1996	3 y/M	Liver and spleen	1:1280	B. melitensis	Percutaneus drainage + Rif TMP-SMZ × 2 m	Remission
Parande et al[10], 2010	8 y/M	Spleen	1:640 (SAT) 1:20 (2ME)	B. melitensis	Doxycycline 4 mg/Kg/day × 6 w + Streptomycin 15 mg/kg/day × 2 w	Remission
Present Case	4 y/M	Spleen	1.1 (CLIA)	None	Rifampicin 150 mg/2 a day, and co-trimoxazole 80 mg for 2 a day for 7 w	Remission
Spink[14], 1964	51 y/M	Liver/spleen, bone	1:320	B. suis	Surgical drainage + Tet	Recovered
Spink[14], 1964	58 y/M	Spleen	1:320	B. suis	Splenectomy + Tet × 3 m	Recovered
Spink[14], 1964	54 y/M	Liver/spleen, lymphonode	1:80	B. suis	Not specified	Died of hemorrhage from esophageal varices
Spink[14], 1964	53 y/M	Spleen	1:1280	B. suis	Splenectomy + Tet	Recovered
Spink[14], 1964	53 y/M	Spleen	1:1280	None	Splenectomy + antibiotic	Recovered
Ates et al[15], 1992	30 y/F	Liver/spleen	1:1280	B. melitensis	Tet + Strep IM × 4 w	Recovered
Ates et al[15], 1992	50 y/M	Spleen	1:1280	B. melitensis	Tet + Strep IM × 4 w then RIF 4 w	Recovered
Saadeh et al[16], 1996	23 y/M	Spleen/aortic valve	1:2560	B. melitensis	Rif + Dox × 6 m, splenectomy	Recovered
Solera et al[17], 1996	49 y/F	Spleen	1:640	None	Antibiotics (NA), splenectomy	Recovered
Colmenero et al[18], 2002	53 y/M	Spleen	1:80	B. melitensis	2 cycles of Dox × 2 m + Strep IM × 3 w	Relapsed
Colmenero et al[18], 2002	80 y/ not available	Spleen	1:320	B. melitensis	Dox × 2 m + Strep IM × 3 w + splenectomy	Died for other causes
Colmenero et al[18], 2002	72 y/ not available	Spleen	1:40	B. melitensis	Dox × 2 m + Strep IM × 3 w + splenectomy	Recovered
Yayli et al[19], 2002	70 y/F	Spleen	1:320	B. melitensis	Dox + Rif × 6 w and Strep IM × 3 w	Recovered
Yilmaz et al[20], 2003	19 y/M	Spleen, aortic valve	High titer	B. melitensis	Splenectomy + antibiotic (NA)	Recovered
Ruiz Carazo et al[21], 2005	60 y/M	Spleen	NA	NA	Splenectomy+ antibiotic (NA)	Recovered
Del Arco et al[22], 2007	39 y/F	Spleen	1:1280	B. melitensis	Dox × 6 w + Strep IM × 2 w, splenectomy, Rif +Dox 1 m	Recovered
Sayilir et al[23], 2008	61 y/M	Spleen	1:1280	Negative	Rif + Dox and TMP-SMZ	Recovered
Park et al[24], 2009	45 y/M	Spleen, aortic valve	1:160	B. abortus	Gen and Rif + Dox + TMP-SMZ 12 m	Recovered
Eruz et al[25], 2011	52 y/F	Spleen, respiratory system	1:640	B. melitensis	Rif+Dox × 6 w	Recovered
Deveer et al[26], 2013	21 y/M	Spleen	1:1280	B. melitensis	Dox + Cip × 12 w + Strep IM × 3 w	Recovered
Yilmaz et al[27], 2014	45 y/F	Spleen	1:640	B. melitensis	Rif + Dox × 6 w	Recovered

Rif: Rifampicin; TMP-SMZ: trimethoprim-sulfamethoxazole; SAT: Standard Tube Agglutination test; 2ME: 2mercaptoethanol; Dox: Doxycycline; Strep: streptomycin; NA: not available; GEN: gentamicin; CIP: ciprofloxacin; w: weeks; m: months.

firmed by CT scan. The child completed a 56-day course of treatment including 28 days of antibiotic therapy. Follow-up CT scan of the abdomen at the end of intravenous therapy showed complete resolution of the splenic abscesses. Meanwhile, the child reported by Seçmeer et al[8] was an 11-year-old who presented with fever, upper quadrant abdominal pain, tenderness, and splenomegaly. US and CT scan showed the presence of multiple splenic abscesses. Treatment was carried out only with antibiotics, and a complete recovery was obtained. A splenic abscess due to B. melitensis in an 8-year-old was reported by Parande et al[10]. The child complained of intermittent fever and occasional pain in the abdomen and right shoulder with a history of decreased appetite and weight loss of 45 days' duration without response to an unspecified antibiotic regime. The overall condition of the child was good, and the temperature was 101°F. The spleen was palpable 2 cm below the costal margin. Neither hematologic results nor the Widal-Wright test was informative. The rose Bengal plate agglutination test was positive at a dilution of 1:640 by standard tube agglutination testing and at a dilution of 1:20 by tube agglutination testing using 2-mercaptoethanol. Abdominal US revealed multiple 2-4-mm echo-poor focal splenic infiltrates. Blood and splenic aspirate cultures grew Brucella melitensis. The child was treated with oral doxycycline 4 mg/kg/day in two divided doses for 6 weeks in association with injectable streptomycin 15 mg/kg/twice daily once a day for the initial 2 weeks. At follow-up, the child showed progressive improvement of his clinical state with a progressive reduction in size and number of the splenic abscesses.

From a review of the literature[8-10], it appears as there are only 4 pediatric cases similar to the one described in this study. Initial symptoms in the case reported here consisted of fever and anemia. In children, fever and cytopenia are the most common presenting symptoms of brucellosis, with cytopenia being especially common in febrile bacteremic episodes. In a recent review[4] of 511 children with brucellosis, anemia was identified in 13% (N=68) of the cases. Difficulties with detecting Brucella serum positivity can initially delay the correct diagnosis, like what had happened in this present case. False positives and false negatives are frequently reported with the serum agglutination method. After the initial negative laboratory test, the CLIA was positive for Brucella IgM antibodies confirming the diagnosis. At that point, specific therapy with rifampicin, 150 mg/Kg/twice daily, and co-trimethoprim, 80 mg/Kg/twice daily, was administered for 7 weeks. The serum IgM titers became negative after 2 weeks of treatment and thereafter remained negative. The diameter of the main splenic infiltrates decreased from 1 cm to 0.5 cm after 6 weeks of antibiotic treatment. However, complete resolution of the splenic infiltrates, which occurred only after 3 months, was also observed in other cases[10]. The abdominal US in this case was repeated 5 months after presentation, and it showed complete resolution of the described lesions and complete clinical healing. Antibiotic treatment of human brucellosis includes doxycycline for children older than 8 years of age and rifampicin and trimethoprim/sulfamethoxazole combination therapy for children under 8 years of age for the intracellular effect of these antibiotics under acidic conditions[28]. Generally, there is a good response with medical treatments, but in some cases surgical intervention is required. It should be considered in particular when there are severe complications such as endocarditis, cerebral, splenic or other abscesses, or complications which are usually resistant to antibiotic therapy[29]. The main objective of anti-Brucella treatment is to reduce the symptomatic period, the risk of complications, and Brucella disease relapse. Brucella can persist in macrophage cells, and only a prolonged duration of antimicrobial therapy with activity in an intracellular acidic environment can have a beneficial effect[30]. In the child presented in this study, medical treatment only, with the use of antibiotics and without other therapeutic approaches, was deemed successful. This has been reported in other similar cases, in which conservative treatment with antibiotics alone was successful in clearing splenic abscesses in patients with brucellosis[13].

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

The study was conducted ethically in accordance with the World Medical Association's Declaration of Helsinki and was approved by the University School of Medicine Bioethics Committee of Catania (Approval ID No.17-2021 4023).

Informed Consent
The parents provided written informed consent.

Availability of Data and Materials
Not applicable.

Funding
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Authors' Contribution
GP, CG. SDA contributed to diagnosis and treatment; PP, GP, LM, and GLR drafted the manuscript; RL, PF, GB, AB, and SP critically revised the manuscript. All authors read and approved the final manuscript.

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