Hepatosplenic Cat Scratch Disease in Immunocompetent Adults

Report of 3 Cases and Review of the Literature

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Abstract: Cat-scratch disease (CSD) is the most frequent presentation of *Bartonella henselae* infection. It has a worldwide distribution and is associated with a previous history of scratch or bite from a cat or dog. CSD affects children and teenagers more often (80%) than adults, and it usually has a self-limiting clinical course. Atypical clinical course or systemic symptoms are described in 5%–20% of patients. Among them, hepatosplenic (HS) forms (abscess) have been described. The majority of published cases have affected children or immunosuppressed patients. Few cases of HS forms of CSD in immunocompetent adult hosts have been reported, and data about the management of this condition are scarce. Herein, we present 3 new cases of HS forms of CSD in immunocompetent adults and review 33 other cases retrieved from the literature. We propose an approach to clinical diagnosis and treatment with oral azithromycin.

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Abbreviations: ALP = alkaline phosphatase, CIBIR = Centre for Biomedical Research in La Rioja, CMV = cytomegalovirus, CRP = C-reactive protein, CSD = cat-scratch disease, CT = computed tomography, EBV = Epstein-Barr virus, ESR = erythrocyte sedimentation rate, GGT = gamma-glutamyl transpeptidase, HAV = hepatitis A virus, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HS = hepatosplenic, IFA = immunofluorescence assay, Ig = immunoglobulin, MRI = magnetic resonance imaging, PCR = polymerase chain reaction, *rpoB* gene = RNA polymerase beta-subunit-encoding gene, SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic-pyruvic transaminase.

INTRODUCTION

Cat scratch disease (CSD) is the main and most frequent clinical presentation of *Bartonella henselae* infection. CSD typically presents as subacute regional lymphadenopathy after a scratch or bite from a cat. It has also been reported after contact with dogs, although it is not frequent (only 3.2% of the cases).[43] CSD affects most often children and teenagers (80%), and it usually has a self-limiting clinical course. The use of antimicrobials for its therapeutic management is rarely necessary. Atypical clinical course or systemic involvement is described in 5%–20% of patients. Among them, the hepatosplenic (HS) forms have been described in 2.3% of cases (data reported before 2003).[1,21,28] In a previous review of this syndrome published in 1996, half of the patients were immunocompetent children while the adults were immunosuppressed (human immunodeficiency virus [HIV], solid organ transplanted or neoplastic conditions).[25] Lastly, a review of the clinical description and therapeutic management in children has been published.[5]

To the best of our knowledge, there has been no review of CSD in the last 10 years, and no review of clinical HS-CSD cases in immunocompetent adults. In addition, the treatment has not been well defined.[31,34] Herein, we describe 3 new cases of HS-CSD and review 33 previously reported cases with a focus on clinical descriptions, diagnosis, and therapeutic approaches.[4,6,9,10,12–18,23,24,26,27,29,30,33,35,36,38–42,44,45]

PATIENTS AND METHODS

We present 3 cases of HS-CSD in immunocompetent adults from a single hospital in northwestern Spain from September 2008 to January 2010. A literature search was performed (MEDLINE, National Library of Medicine, Bethesda, MD) to identify relevant studies related to this topic reported up to and including December 2013 using the keywords "*Bartonella*," "*Rochalimaea*," "cat scratch disease," "liver," "spleen," "spleen abscess," "hepatitis," "hepatosplenic," "immunocompetent adults." The inclusion criteria were as follows: aged older than 20 years, immunocompetent, and meeting at least 3 of the modified Liston and Koehler criteria[25]: radiographic evidence of liver and/or spleen hypodense or hypoechogenic lesion on computed tomography (CT) scan films, ultrasonographic scan films, or magnetic resonance imaging (MRI); compatible gross pathology of multiple nodules; compatible histologic findings of granulomas or bacillary peliosis, with or without necrosis; positive Warthin-Starry or Steiner silver stains; positive polymerase chain reaction (PCR) for *Bartonella* spp.; successful culture of *B. henselae;* serologic increase in titers of immunoglobulin G (IgG) antibodies against *Bartonella* spp.; electron microscopic findings compatible with *Bartonella* spp.; positive CSD skin test results; and epidemiologic antecedent of cat or dog contact.

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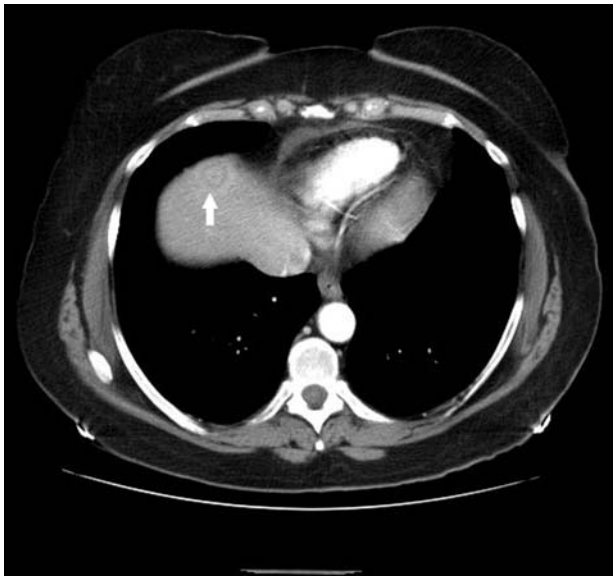

FIGURE 1. Solitary liver hypodense lesion with target aspect (arrow) of Case 1.

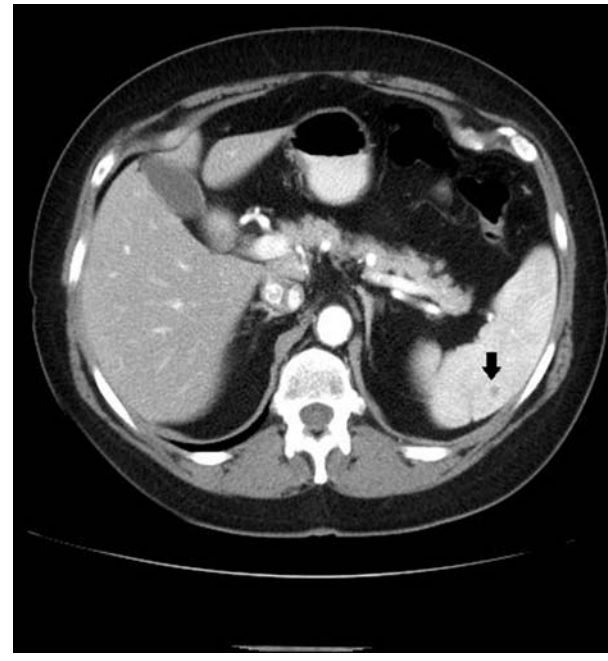

FIGURE 2. Solitary spleen hypodense lesion (arrow) of Case 1.

Demographic data (sex, age, geographic localization), epidemiologic (cat or dog contact or scratch or bite, flea contact), clinical presentation, laboratory findings (including microbiologic assays), radiologic image, surgery and histologic findings were collected. In addition, we recorded the clinical course and treatments used. We defined "clinical resolution" as the disappearance of clinical signs and symptoms with normal physical examination and laboratory findings, and "cure" as clinical resolution along with the disappearance of the radiologic findings.

Patients

Case 1

In September 2008, a 61-year-old woman came to the emergency department of the Hospital del Salnés presenting with cervical swelling. She had no relevant clinical history and was not taking any drugs. She described productive cough and fever of 6 weeks' duration, neck pain and occurrence of left cervical and supraclavicular swelling associated with constitutional symptoms during the last 2 weeks. Her physician prescribed cefditoren which resolved the fever and cough, although the constitutional symptoms continued. In addition, she had observed the growth of cervical and supraclavicular tumors with appearance of others at the right side of her neck. She owned several kittens and often suffered scratches.

On physical examination, she had an axillary temperature of 36.5°C, blood pressure 112/54 mm Hg, and heart rate 85 bpm. She had bilateral cervical and supraclavicular and 1 axillary lymphadenopathies that were elastic, mobile, and painful to palpation. She had a scar on her left thigh. The rest of the examination did not present significant findings. Hemogram and coagulation tests were within normal limits; C-reactive protein (CRP) was 169 mg/L, gamma-glutamyl transpeptidase (GGT) was 46 U/L, and alkaline phosphatase (ALP) was 108 U/L. The other biochemical parameters and urine sediment did not show abnormalities. Chest radiography was normal. A CT scan showed multiple cervical, supraclavicular and right axillary lymphadenopathy and 1 hypodense lesion in each of liver (target aspect) and spleen. Lymphadenopathy was also observed at the level of the gastrohepatic ligament (Figures 1 and 2).

With suspicion of lymphoma, a lymph node biopsy was performed and showed necrotizing granulomas without evidence of malignancy. Periodic acid-Schiff, Ziehl-Neelsen, and Warthin-Starry staining did not reveal any organisms. Bacterial cultures of mycobacterium and fungi were negative. Blood cultures, sputum cultures in Lowenstein medium, and Ziehl-Neelsen staining were negative. Serologic tests against Epstein-Barr virus (EBV), cytomegalovirus (CMV), syphilis, hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), *Brucella* spp., *Toxoplasma gondii*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* were negative. An immunofluorescence assay (IFA) detected the presence of IgG antibodies against *B. henselae* with a titer of 400 or higher. A lymph node specimen was sent to the Special Pathogens Laboratory at the Centre for Biomedical Research in La Rioja (CIBIR) for molecular biologic study. PCR targeting a region of the RNA polymerase beta-subunit-encoding gene (*rpoB*) of *Bartonella* species was carried out as previously described.[32] Sequencing of the amplicon and BLAST analysis revealed 100% identity with the *rpoB* gene of *B. henselae* (GenBank accession no. AF171071). Because of suspected CSD, the patient began empirical treatment with oral azithromycin 500 mg/24 h for 5 days. After 3 weeks, the patient was asymptomatic, and most cervical lymphadenopathies were resolved. CRP and liver enzymes were normal. A CT scan showed resolution of the spleen lesion and the hepatic lesion was reduced in size. After 5 months the patient was completely asymptomatic, and a CT scan showed resolution of the liver lesion. A convalescent serum sample showed IgG antibodies against *B. henselae* with a titer of 800.

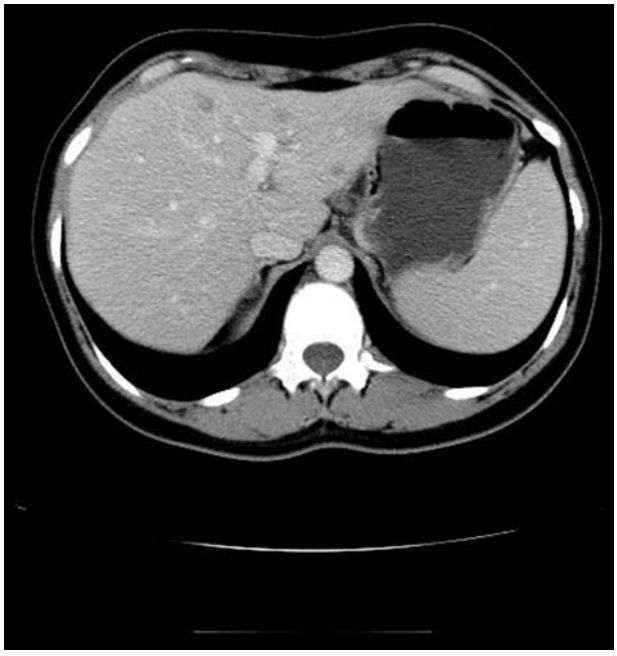

FIGURE 3. Multiple hypodense liver lesions of Case 2.

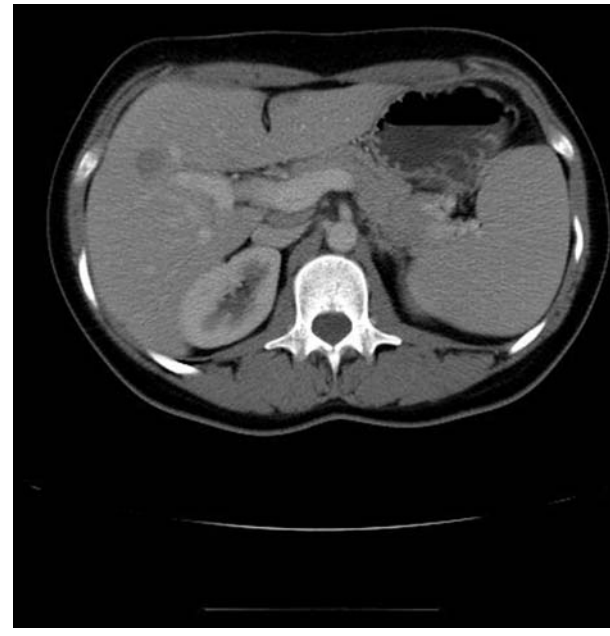

FIGURE 4. Multiple hypodense liver lesions of Case 2.

Case 2

In September 2009, a 41-year-old woman was admitted to the emergency department of the Hospital del Salnés presenting a painful right axillary swelling of 1 week's duration. She had no relevant medical history and was not taking drugs. Three months before she had had contact with a cat during its parturition. She then looked after the resulting kittens. A few weeks prior to admission, a cat scratched her on the right fifth finger. She also gave a history of flea bites during the summer. Upon presentation she had an axillary temperature of 38°C, blood pressure 155/69 mm Hg, and heart rate of 95 bpm. She had also a painful 5 cm right axillary tumor and discomfort on palpation of the right upper abdominal quadrant without hepatomegaly. A small scar on the fifth finger of her right hand was also observed. Hemogram and coagulation tests were within normal limits; CRP was 86.9 mg/L, serum glutamic-oxaloacetic transaminase (SGOT) was 73 IU/L, GGT was 78 IU/L, and ALP was 131 IU/L. The remaining biochemical parameters and the urine test did not show abnormalities. The chest radiography and a mammogram were normal. Ultrasound soft tissue examination of the armpit showed a hypoechoic 4.7 cm polylobulated lesion and another 1.2 cm solid lesion compatible with adenitis. A CT body scan showed right supraclavicular and axillary lymphadenopathies, hepatic hilar, peripancreatic and periportocaval lymphadenopathies, and multiple hypodense hepatic lesions (Figures 3 and 4). A lymph node biopsy was analyzed revealing necrotizing granulomatous lymphadenitis without evidence of malignancy. Periodic acid-Schiff, Ziehl-Neelsen, and Warthin-Starry staining were negative. Cultures of mycobacteria and fungi were negative after 8 and 1 weeks' incubation, respectively. Blood cultures were negative after a week of incubation. The HBV, HCV, HIV, syphilis, *Brucella* spp., *Borrelia burgdorferi* s.l. and *T. gondii* serology tests were negative, whereas the EBV and CMV tests showed past infection. IFA detected the presence of phase II IgG antibodies against *Coxiella burnetii* with a titer of 64, and phase I IgG antibodies were negative. Serologic tests confirmed the presence of IgG antibodies against *B. henselae* (titer of 400). PCR assays of the lymph node biopsy (sent to CIBIR) did not detect the presence of *Bartonella* DNA. Before the biopsy results, and with the suspicion of CSD, the patient began empirical treatment with oral azithromycin 500 mg/24 h for 5 days. The fever disappeared within 72 hours and the axillary swelling improved. A CT scan showed a significant reduction in the size of the liver lesions and the lymphadenopathies. The patient was discharged on the 10th day with CRP of 28 mg/L and liver enzymes normalized. At that point, the titer of IgG antibodies against *B. henselae* was 800. This twofold increase is not significant and may be due to the antimicrobial treatment that the patient received. Eight months later the

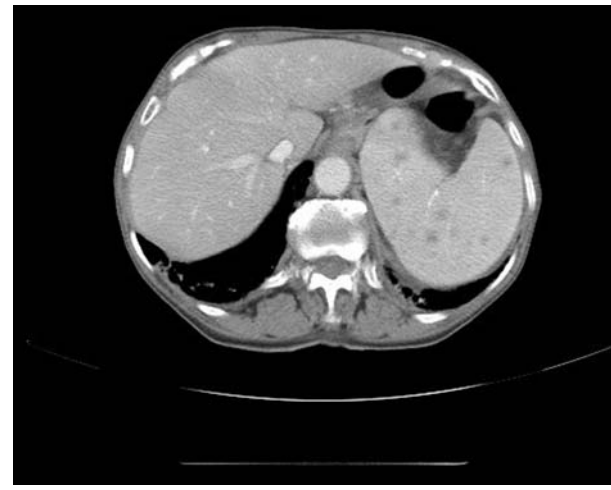

FIGURE 5. Multiple hypodense spleen lesions of Case 3.

TABLE 1. Clinical Data From 36 Immunocompetent Adults With Hepatosplenic Cat Scratch Disease

Case (Ref)	Age (yr)/ Sex	Cat Scratch/ Exposure	Clinical presentation. Duration	Laboratory Data (WBC, CRP, LE)	Imaging Findings (US, CT, MRI, Other, Laparotomy)	Histopathology	Microbiology	Treatment and Evolution
1 (4)	28/M	Yes/Yes	Fever and abdominal pain. 3 d	Leukocytosis CRP: Elevated LE: Normal	Spleen abscess.	ND	Culture positive. PCR ND. Serology positive.	Splenectomy. CIP 2 wk. Clinical resolution: 2 wk. Cure: NA
2 (24)	34/F	Yes/Yes	Fever and abdominal pain. 3 wk	WBC count normal. CRP: NA LE: NA.	Multiple hypoechogenic spleen lesions.	ND	Culture ND. PCR positive. Serology positive.	AZM + DOX 5 d CLR + RIF 8 d Clinical resolution: NA Cure: 2.5 mo
3 (39)	36/F	No/Yes	Fever and abdominal pain. 2 wk	WBC count normal. CRP: NA LE: Elevated	Multiple hypodense liver lesions.	Necrotizing granulomatous hepatitis.Steiner stain negative.IHC positive.	Culture positive. PCR positive. Serology negative.	Partial hepatectomy. AZM 2 w. CLR 9 wk. CIP 6 wk. RIF + DOX 8 wk. Clinical resolution: 12 wk. Cure: NA.
4 (16)	47/M	No/Yes	Fever and adenopathy. 2 wk	WBC count normal CRP: Elevated LE: Elevated	Multiple hypoechogenic spleen lesions. Cervical C7 osteomyelitis.	Necrotizing granulomatous lymphadenitis.Warthin-Starry stain: ND.	Culture ND. PCR positive. Serology positive	DOX +RIF 6 wk. Clinical resolution: 12 wk. Cure: NA.
5 (45)	45/F	No/Yes	Fever and abdominal pain. 3 wk	WBC count normal CRP: Elevated LE: Normal.	Multiple hypodense liver and spleen lesions.	ND.	Culture ND. PCR ND. Serology positive	CIP+GEN i.v 10 d. CIP+DOX 3 wk. Clinical resolution: 2 wk. Cure: 4 mo.
6 (45)	27/M	No/Yes	Fever and constitutional symptoms. 4 wk	WBC count normal CRP: Elevated LE: Normal	Multiple hypodense liver lesions. Celiac lymphadenopathy.	ND	Culture ND PCR ND. Serology positive	CIP+GEN i.v 10 d. CIP+ERY 3 wk. Clinical resolution: 2 wk. Cure: 4 mo.
7 (45)	33/M	No/Yes	Fever and abdominal pain. 3 wk	WBC count normal CRP: Elevated LE: Normal.	Multiple hypodense spleen lesions. Celiac lymphadenopathy.	ND	Culture ND. PCR ND. Serology positive	DOX v.o. 3 wk. Clinical resolution: days? Cure: 3 mo.
8 (45)	71/M	Yes/Yes	Fever and constitutional symptoms. 4 wk	WBC count normal. CRP: Elevated. LE: Normal.	Multiple hypodense liver and spleen lesions.	ND	Culture ND. PCR ND. Serology positive	DOX+RIF 3 wk. Clinical resolution: days? Cure: NA.
9 (33)	57/M	Yes/Yes	Fever and adenopathy. 2 weeks.	WBC count normal. CRP: Elevated LE: Normal.	Multiple hypodense liver lesions. Lymphadenopathy of hepatic hilum.	ND	Culture ND. PCR ND. Serology positive	DOX 1 mo. Clinical resolution: 4 wk. Cure: 2 mo.

10 (30)	40/F	No/Yes	Fever and constitutional symptoms. 1 mo.	WBC count normal. CRP: Elevated LE: Elevated	Multiple hypodense liver and spleen lesions. Osteolytic lesion of sixth rib.	Necrotizing granulomatous hepatitis. Necrotizing granulomas of bone. Warthin-Starry stain: ND.	Culture ND. PCR ND. Serology positive.	CLR 3 mo. Clinical resolution: 20 wk. Cure: 5 mo.
11 (36)	56/F	No/Yes	Fever and abdominal pain. 2 mo.	Leukocytosis CRP: Elevated LE: Normal.	Multiple hypodense liver and spleen lesions. Lymphadenopathy of hepatic hilum.	ND	Culture ND. PCR ND. Serology positive.	AZM 6 wk. Clinical resolution: 6 wk. Cure: 6 mo.
12 (27)	34/F	No/Yes	Fever and constitutional symptoms. NA.	WBC count: NA. CRP: Elevated LE: Elevated	Multiple hypoechogenic liver lesions. Peripancreatic lymphadenopathy.	Necrotizing granulomatous hepatitis. Warthin-Starry stain: ND.	Culture ND. PCR positive. Serology negative.	Antibiotic specific? Clinical resolution: rapid. Cure: NA.
13 (40)	49/M	Yes/Yes	Fever and adenopathy. 2 wk	Leukocytosis CRP: Elevated LE: NA.	Multiple hypodense spleen lesions. Paraaortal lymphadenopathy.	Lymph node with sclerotic aspect. Warthin-Starry stain: ND	Culture ND. PCR ND. Serology positive.	None. Clinical resolution: NA. Cure: 3 mo.
14 (17)	51/F	NA	Fever. NA	WBC count NA. CRP: Elevated. LE: NA.	Multiple hypodense liver and spleen lesions. Lymphadenopathy of hepatic hilum.	Necrotizing granulomatous lymphadenitis. Warthin-Starry stain: ND.	Culture ND. PCR positive. Serology positive	Multiple antibiotic therapy? 24 wk. Clinical resolution: 24 wk. Cure: 9 mo.
15 (26)	48/M	NA	Abdominal pain and constitutional symptoms. NA	WBC count: NA CRP: NA LE: Normal.	Extensive nodular lesion of liver.	Necrotizing granulomatous hepatitis Warthin-Starry stain: ND.	Culture ND. PCR positive. Serology ND	Curative partial hepatectomy. Clinical resolution: NA. Cure: NA
16 (26)	57/F	NA	Abdominal pain and constitutional symptoms. NA	WBC count: NA. CRP: NA. LE: Normal	Ill-defined hepatic lesion with gallbladder involvement.	Necrotizing granulomatous hepatitis. Warthin-Starry stain: ND	Culture ND. PCR positive. Serology ND.	Curative partial hepatectomy Clinical resolution: NA. Cure: NA
17 (13)	75/F	No/Yes	Fever and constitutional symptoms. 2 mo	WBC count normal CRP: Elevated. LE: Normal.	Multiple hypodense spleen lesions. Echocardiography: Aortic valve vegetations.	ND	Culture ND. PCR ND. Serology positive	GEN 2 wk., CRO 1 mo.; DOX 6 mo. Clinical resolution: 2 wk. Cure: 8 mo.
18 (13)	45/M	No/Yes	Fever and abdominal pain. 2 wk	Leukocytosis. CRP: Elevated LE: Elevated.	Multiple hypodense liver and spleen lesions.	ND	Culture ND. PCR ND. Serology positive.	None. Clinical resolution: 1 wk. Cure: 4 mo.

(*Continued*)

19 (18)	43/M	No/Yes	Fever. NA.	NA	Multiple hypodense liver and spleen lesions.	ND	Culture ND. PCR ND. Serology positive.	NA
20 (10)	65/M	No/Yes	Spontaneous rupture of spleen. Hours	Leukocytosis. CRP: NA LE: Normal.	Hemoperitoneum. Laparotomy: 3 macroscopic well-circumscribed masses to spleen surface.	Necrotizing granulomatous splenitis and lymphadenitis of splenic hilum. Unspecific chronic hepatitis. Steiner stain positive. IHC staining positive.	Culture ND. PCR ND. Serology positive	Splenectomy. DOX 20 wk. Clinical resolution: 20 wk. Cure: 5 mo.
21 (35)	30/M	No/Yes	Adenopathies and lower back pain. 1 mo.	WBC count normal CRP: Elevated LE: Normal	Multiple hypodense spleen lesions. Osteolytic lesion of L3 vertebra.	Necrotizing granulomatous lymphadenitis. Warthin-Starry stain: ND.IHC staining positive	Culture ND. PCR positive. Serology positive.	DOX+RXM 1 mo. CIP+CLR 2 mo. Clinical resolution: rapid? Cure: 3 mo.
22 (23)	41/F	No/Yes	Fever and constitutional symptoms. 1 mo	WBC count: NA CRP: Elevated. LE: Elevated	Multiple hypodense liver and spleen lesions.	Necrotizing granulomatous hepatitis. Warthin-Starry stain negative.	Culture ND. PCR ND. Serology positive	AZM 3 wk. Clinical resolution: 2 wk. Cure: 4 mo.
23 (23)	44/M	Yes/Yes	Fever and adenopathy. 1 mo.	WBC count: NA CRP: Elevated LE: Elevated.	Multiple hypodense liver and spleen lesions.	Necrotizing granulomatous hepatitis. Necrotizing granulomatous lymphadenitis. Warthin-Starry stain negative.	Culture ND. PCR negative. Serology positive	FLQ 6 wk. Clinical resolution: 6 wk. Cure: 1.5 mo.
24 (15)	43/F	No/Yes	Fever and constitutional symptoms. 1 mo.	WBC count normal. CRP: Elevated. LE: Normal.	Multiple hypodense spleen lesions.	Necrotizing granulomatous splenitis. Warthin-Starry stain: ND.	Culture ND PCR positive Serology positive.	Splenectomy. Clinical resolution: NA Cure: NA

25 (42)	29/F	Yes/Yes	Adenopathy. 1 mo.	WBC count normal CRP: NA LE: Elevated	Multiple hypoechoic liver and spleen lesions.	Necrotizing granulomatous lymphadenitis. Warthin-Starry stain: ND	Culture ND. PCR ND. Serology positive.	None. Clinical resolution: 16 wk. Cure: NA.
26 (14)	40/M	Yes/Yes	Fever and constitutional symptoms. 3 wk	Leukocytosis. CRP: Elevated LE: Elevated.	Multiple hypoechoic spleen lesions. Multiple abdominal adenopathies.	ND	Culture ND. PCR ND. Serology positive.	RIF + CIP 2 wk. Clinical resolution: 1 wk. Cure: 0.5 mo.
27 (41)	28/M	No/Yes	Fever and abdominal pain. 3 d	WBC count normal CRP: Elevated. LE: Normal	Multiple small focal lesions of liver. L-1 vertebral osteomyelitis.	Polymorphonuclear infiltration. Warthin-Starry stain negative.	Culture ND. PCR positive. Serology positive.	AMK 1 wk. + CIP 3 wk. Clinical resolution: 12 wk. Cure: NA
28 (44)	33/M	Yes/Yes	Fever and adenopathy. 1 mo	WBC count NA. CRP: NA LE: NA	Multiple hypoechoic liver and spleen lesions.	Necrotizing granulomatous hepatitis. Warthin-Starry stain: ND.	Culture ND. PCR negative. Serology positive	CLR + DOX wk.? Clinical resolution: 8 wk. Cure: 2 mo.
29 (29)	25//F	No/Yes	Fever. 2 wk	WBC count normal CRP: Elevated. LE: NA.	Multiple hypoechoic liver and spleen lesions.	Necrotizing granulomatous splenitis. Warthin-Starry stain: ND.	Culture ND. PCR positive. Serology positive	CLR + INH + RIF 2 mo. Splenectomy. MIN+TFLX +CFP/SBT? Clinical resolution: 16 wk. Cure: NA
30 (6)	57/F	NA	Fever and abdominal pain. 3 wk	WBC count: NA. CRP: NA. LE: Elevated.	Multiple hypodense liver and spleen lesions. Lymphadenopathy to hepatoduodenal ligament. Echocardiography: Pericardial effusion.	Necrotizing granulomatous hepatitis. Warthin-Starry stain: ND.	Culture ND. PCR ND. Serology positive	CLR? Clinical resolution: NA. Cure: NA.
31 (9)	32/F	Yes/Yes	Fever and adenopathy. 1 mo	Leukocytosis. CRP: Elevated LE: Elevated.	Multiple hypoechoic liver lesions.	Necrotizing granulomatous hepatitis. Necrotizing suppurative lymphadenitis. Warthin-Starry stain: ND	Culture ND. PCR ND. Serology positive	DOX + FLQ 8wk. Clinical resolution: 10 wk. Cure: 2.5 mo.

(*Continued*)

32 (38)	56/?	No/Yes	Fever and abdominal pain. 2 wk	WBC count: NA CRP: NA LE: Elevated.	Focal hypodense spleen lesion. Laparotomy: 3 nodules to spleen.	Necrotizing splenitis without granulomas. Warthin-Starry stain positive	Culture ND. PCR positive. Serology ND.	Splenectomy. ERY 6 wk. Clinical resolution: NA. Cure: NA.
33 (12)	51/M	No/No	Fever and abdominal pain. 10 d	WBC count normal CRP: NA. LE: Elevated	CT: no findings. Laparotomy: multiples nodules in the liver surface and celiac adenopathy.	Necrotizing granulomatous hepatitis and celiac lymphadenitis. Warthin-Starry stain positive.	Culture ND. PCR ND. Serology ND.	INH + RIF 4 wk. PDN. Clinical resolution: 16 wk. Cure: NA.
34 (PR1)	61/F	Yes/Yes	Fever and adenopathy. 1 mo	WBC count normal CRP: Elevated LE: Elevated	Solitary hypodense liver and spleen lesion. Cervical and gastrohepatic ligament lymphadenopathy.	Necrotizing granulomatous lymphadenitis. Warthin-Starry stain negative.	Culture ND. PCR positive. Serology positive	AZM 5 d. Clinical resolution: 3 wk. Cure: 5 mo.
35 (PR2)	41/F	Yes/Yes	Fever and adenopathy. 1 wk	WBC count normal. CRP: Elevated LE: Elevated.	Multiple hypodense liver lesions. Right axillary and multiple abdominal lymphadenopathy.	Necrotizing granulomatous lymphadenitis. Warthin-Starry stain negative.	Culture ND. PCR negative. Serology positive	DOX+RIF 8 d. AZM 5 d. Clinical resolution: 4 wk. Cure: 8 mo.
36 (PR3)	86/F	No/Yes	Fever and abdominal pain. 2 wk	WBC count normal CRP: Elevated LE: Elevated.	Multiple hypodense spleen lesions. Multiple abdominal lymphadenopathy.	ND	Culture ND. PCR ND. Serology positive	CRO + VAN + GEN 1w AZM 5 d. Clinical resolution: 4 wk. Cure: 4 mo.

Abbreviations: AMK = Amikacin; AZM = Azithromycin; CFP = cefoperazone; CRO = Ceftriaxone; CIP = Ciprofloxacin; CLR = Clarithromycin; CRP = C-reactive protein; DOX = Doxycycline; ERY = Erythromycin; FLQ = Fluoroquinolone; GEN = Gentamicin; IHC = Immunohistochemical stain; INH = Isoniazid; i.v = intravenous; LE = Liver enzymes; MIN = Minocycline; NA = Not available; ND = Not determined; PDN = Prednisone; PR = present report, RIF = Rifampicin; RXM = Roxithromycin; SBT = Sulbactam; TFLX = Tosufloxacin; US = Ultrasound scan; VAN = Vancomycin; v.o. = via oral; WBC = White blood count.

TABLE 2. Symptoms and Signs Exhibited by 36 Patients With Hepatosplenic Cat Scratch Disease

Symptoms and Signs	No. (%)
Fever	31 (86)
Constitutional symptoms	18 (50)
Abdominal pain	16 (44)
Adenopathy	12 (33)
Weight loss	7 (19)
Skin lesion	6 (17)
Splenomegaly	3 (8)
Nausea/vomiting	3 (8)
Ocular lesions	2 (6)
Hepatomegaly	2 (6)
Dyspnea	2 (6)
Low-back pain	2 (6)
Chest pain	1 (3)
Diarrhea	1 (3)
Headache	1 (3)

patient was asymptomatic and CT body scan did not show abnormalities.

Case 3

In January 2010, an 86-year-old woman was admitted at the emergency room at Hospital del Salnés due to fever and epigastric pain of 2 weeks' duration. She had a hip prosthesis, chronic atrial fibrillation, and had also been admitted in 2006 due to pneumonia with secondary sepsis. She did not take drugs. She was on treatment with amoxicillin plus clavulanic acid because 3 days previously she had attended for a urinary tract infection. Blood and urinary cultures from that day were negative.

She lived in a rural area and consumed nonchlorinated water. She owned a dog, several cats, and chickens. She did not recall bites or scratches from insects or pets. She had an axillary temperature of 39.4°C, blood pressure 122/70 mm Hg, and heart rate 94 bpm. She had a nonrhythmic cardiac auscultation without murmurs, and epigastric pain upon palpation. Hemogram and coagulation tests were in the normal range; CRP was 148 mg/L, SGOT was 51 IU/L, and serum glutamic-pyruvic transaminase (SGPT) was 46 IU/L. The remaining biochemical parameters were in the normal range. Chest radiography showed signs of emphysema. A CT abdominal scan revealed multiple adenopathies with HS enlargement and several hypodense lesions in the splenic area in addition to left pleural effusion (Figure 5). A transthoracic echocardiogram did not show signs of endocarditis. Blood and urinary cultures were repeatedly negative. Serologic tests for HAV, HBV, HCV, syphilis, *Brucella* spp., and *C. burnetii* were negative. At first, endocarditis was suspected and ceftriaxone 2 g/12 h, gentamicin 240 mg/24 h, and vancomycin 1 g/12 h were prescribed. Four days later she was afebrile. On the 5th day, suspicion of endocarditis was excluded after transesophageal echocardiogram examination. The treatment was changed to ceftriaxone 2 g/24 h plus metronidazole 500 mg/8 h. Three days later, the result of an IFA-IgG test against *B. henselae* showed a titer of 1600, and ceftriaxone plus metronidazole were substituted with oral azithromycin (500 mg/24 h for 5 days). The patient was discharged from the hospital on the 13th day with liver enzymes in the normal range and CRP of 21 mg/L. A new abdominal CT showed that the number and size of the spleen lesions were less than at admission. IgG antibodies against *B. henselae* were detected at a titer of 3200 in the convalescent phase. Four months later a CT abdominal scan did not show any spleen lesion.

REVIEW OF CLINICAL CASES

We have included a total of 36 clinical cases in this study: 3 presented herein and 33 obtained from the literature. A summary of the cases is presented in Table 1.

Demographic Data

Twenty-nine patients (81%) were reported from Europe, 4 from the United States (11%), 2 from Japan (6%), and 1 from Israel (3%). Half of all cases were reported from France and 75% from the Mediterranean area. Seventeen were men and 18, women. In 1 case the sex was unknown. The mean age of the patients was 45.5 years (median, 43 yr; range, 25–86 yr).

Epidemiologic and Clinical Data

Thirty of the 33 cases recalled cat exposure, while 1 had exposure to dogs. Cat scratches or bites were recalled by 35% of patients. The frequency of clinical signs and symptoms is shown in Table 2. The most common clinical syndromes as well as the time to diagnosis are shown in Table 3.

TABLE 3. Clinical Syndromes and Time to Diagnosis

Clinical Presentation	No. of Patients (%)	Duration Mean (SD)/(Range) wk
Fever + abdominal pain	12 (33)	—
Fever + lymphadenopathy	8 (22)	—
Fever + constitutional symptoms	8 (22)	—
Fever	3 (8)	—
Lymphadenopathy	2 (6)	—
Abdominal pain + constitutional symptoms	2 (6)	—
Spontaneous splenic rupture	1 (3)	—
Duration of clinical symptomatology (*)	31 (86)	3.15 (1.73)/(0.5–8)
Time to diagnosis (*)	26 (72)	7.78 (9.77)/(1–52)

*Expressed in weeks.

TABLE 4. Summary of Available Laboratory Data

Laboratory Data	N	N With Elevated Values (%)	Mean (SD)/(Range)
WBC count, leukocyte/mm^3	30	8 (27)	14,700 (4500)/(11,600–23,600)
CRP, mg/L	25	25 (100)	133 (73)/(13–270)
ESR, mm/1 h	18	17 (94)	58 (25)/(24–103)
ASAT and/or ALAT, IU/L	52	18 (35)	91 (50)/(46–208)
GGT, IU/L	23	10 (43)	117 (55)/(46–195)
ALP, IU/L	24	10 (42)	195 (32)/(108–300)

Abbreviations: N = number of patients, SD = standard deviation, WBC = white blood cells, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, ASAT = aspartate aminotransferase, ALAT = alanine aminotransferase, IU = international units, GGT = gamma-glutamyl transpeptidase, ALP = alkaline phosphatase.

Laboratory Data

White blood cell count was within the normal range for 73% of cases. CRP was elevated in all patients and erythrocyte sedimentation rate (ESR), in 94%. Liver enzymes were raised in 38% of cases. These elevations were less than 5 times the normal range and always with a normal bilirubin value (Table 4).

Radiologic and Surgical Image Data

Nineteen percent of patients were examined by ultrasound scans, 47% by CT scan, and 25% with both techniques. MRI and ultrasounds were used in 2 patients, and MRI and CT in 1 patient (Table 5). Discordances between radiologic techniques were observed in 6 of 9 patients (67%). The ultrasound examinations did not detect the lesions observed in CT scans in 5 cases (56%). In 1 patient (11%) the CT scan did not detect the findings of the ultrasound scan.

Most patients (81%) showed multiple hypodense lesions except for 5 patients (14%) who had single lesions. In 2 cases the radiologic studies did not find any lesions.

A surgical inspection (laparotomy) was made in 10 patients (28%), and 3 partial liver resections, 5 splenectomies, and 2 liver biopsies were performed. In 1 patient a partial rib resection led to the diagnosis. In 2 cases surgical inspection allowed retrospective observation of multiple lesions in the liver or in the spleen, respectively. In another patient in whom the CT scan showed a unique spleen lesion, surgical inspection revealed multiple lesions. In summary, the liver was affected in 24 patients and the spleen in 26 patients. The liver alone was affected in 10 cases (28%), 8 of them had multiple lesions and 2 had a single lesion. The spleen alone was affected in 12 patients (33%), 11 of them had multiple lesions and 1 had a single lesion. Both organs were affected in 14 cases (39%), 13 of them had multiple lesions and 1 case had a single lesion. Abdominal adenopathies were observed in 14 patients (39%), 50% of cases with liver involvement, 42% with spleen involvement, and 29% with both of them.

In 12 patients (33%) echocardiogram studies were performed, and only 1 case had concomitant endocarditis. In 3 patients gammagraphic scan images detected lumbar and rib osteomyelitis. Vertebral osteomyelitis was diagnosed in 3 cases after MRI of spinal cord. In 1 case PET/CT was performed for high suspicion of malignancy.

Pathology Data

A total of 35 biopsy samples were taken from 23 patients (64%). Twelve of the 15 liver biopsies exhibited necrotizing granulomatous hepatitis, and 3 showed unspecific chronic hepatitis. Eleven biopsies were taken from adenopathies (8 peripheral and 3 abdominal). Ten out of 11 showed necrotizing granulomatous lymphadenitis and the eleventh, sclerotic tissue. In 4 biopsies from spleen, 3 necrotizing granulomatous splenitis and 1 necrotizing splenitis without granulomas were found. Three bone biopsies (1 rib and 2 vertebral) exhibited tuberculoid granulomas in the case of the rib, multiple foci of polymorphonuclear infiltrates in 1 of the vertebras, and no findings in the other vertebra. Bone marrow biopsies taken from 2 patients showed nonspecific findings and no granulomas.

Silver stains were made in 9 of 23 patients (in 7, Warthin-Starry and in 2, Steiner) and were positive in 3

TABLE 5. Summary of Radiologic Data

Results	US (n = 18) N (%)	CT (n = 27) N (%)	MRI (n = 3) N (%)
Detection of lesion	15 (83)	24 (89)	3 (100)
Single lesion	3 (20)	3 (13)	1 (33)
Multiple lesions	12 (80)	21 (87)	2 (66)
Liver involvement	7 (47)	15 (63)	2 (66)
Spleen involvement	9 (60)	19 (79)	2 (66)
Abdominal adenopathy	5 (33)	9 (38)	—

Abbreviations: US = ultrasonographic scan, n = number of medical tests, CT = computed tomography, MRI = magnetic resonance imaging, N = number of patients.

cases. In 3 patients, immunohistochemical staining for *B. henselae* showed rod-shaped bacteria. Electron microscopy from 1 biopsy showed many bacilli.

Microbiologic Studies

B. henselae cultures were performed in 2 cases (from a blood sample and from pus of a spleen abscess) and both were positive. In 13/16 patients (81%), PCR assays from biopsies or blood samples detected DNA from *B. henselae* (3/3 patients with spleen biopsy; 4/5 patients with liver biopsy; 2/4 patients with adenopathy biopsies; 1/1 patient with bone biopsy; 1/1 patient with blood sample; 1/1 patient with liver biopsy and blood sample; and 1/1 patient with bone and adenopathy biopsies).

Serologic assays were performed for 32 patients (89%), and 30 of them (94%) showed an IgG titer >128 against *B. henselae* antigen. Cross-reactions or concomitant or past infections with *B. quintana* (n = 3) or *C. burnetii* (n = 2) were observed. However, these bacteria were not considered to be the agents responsible for the clinical pictures in any of the cases.

In 19 of 32 patients only serologic assays were performed, and all of these had an IgG titer >128 against *B. henselae* antigen. Three cases (all positive) were evaluated using only PCR assays. Serologic and PCR assays were performed for 13 patients. Eight of these cases were positive with both techniques, 3 yielded only positive serologic results (titer >128), and 2 were only positive by PCR.

Patient Management

Data were obtained from 35 patients (97%) and are summarized in Table 6. Antibiotics used were as follows: 14 (48%) macrolides (8 in monotherapy and 6 in combination); 11 (38%) tetracyclines (3 in monotherapy and 8 in combination); 9 (31%) fluoroquinolones (2 in monotherapy and 7 in combination); 6 (21%) rifampicin (always in combination with others). Antibiotics such as gentamicin, ceftriaxone, or amikacin were always used in combination with others.

Data about duration of antibiotic treatment were retrieved from 25 patients (86%); monotherapy was administered in 12 cases and antibiotic combinations in 13 (see Table 6).

The treatment of choice for our 3 patients was azithromycin for 5 days. Duration of the treatment was less than 2 weeks, including empirical treatment before diagnosis.

Surgical treatment included 3 partial hepatectomies (presenting single lesions with suspicion of malignancy); 5 splenectomies (2 diagnostic; 1 prophylactic procedure; 1 by spleen abscess; and 1 by spontaneous spleen rupture). Diagnostic partial rib resection was performed in 1 case.

Evolution

All patients were cured without sequelae regardless of treatment. For the cases in the literature, in 71% of cases (data from 21 patients) clinical resolution was achieved in 1–12 weeks (mean, 9.24; SD, 7.27; median, 8; range, 1–24 wk). In 78% of cases (data from 18 patients) cure was achieved in 2–5 months (mean, 3.83; SD, 2.15; median, 4; range, 0.5–9 mo).

In the 3 cases presented herein, the clinical resolution was achieved in less than 4 weeks (mean, 3.67; SD, 0.58; median, 4; range, 3–4 wk). In 2 of them, cure was achieved in less than 5 months (mean, 5.67; SD, 2.08; median, 5; range, 4–8 mo).

DISCUSSION

HS complications among immunocompetent adults with CSD are unusual. To our knowledge, this has not been previously reviewed. Much current knowledge on this unusual form of CSD is derived from cases in children.[5,21] Furthermore, treatment of this syndrome has not been well defined.[31,34] In an effort to answer these questions we have reviewed 36 cases (3 from our experience and 33 from the literature).

Sixty-four percent of the clinical cases had been diagnosed during the last 10 years, probably resulting from incorporation of serologic and molecular techniques into routine clinical laboratories. *B. henselae* infection and CSD are distributed worldwide.[8] However, most cases of HS-CSD have been reported in Europe, especially in the Mediterranean area and more specifically in France. This fact could be related to different and more invasive *B. henselae* strains in the area[11] although it most likely is due to a higher index of suspicion by physicians in France.

Men and women were similarly affected. The syndrome affected all ages (mean, 45 yr), being more frequent in young adults. Most patients reported cat or dog exposure. Scratches were reported in only 35% of HS forms compared to 73% in CSD.[28] The importance of collecting this data and looking for this important sign should be emphasized.

Most patients had fever of less than 1 month duration. Fever could be the only clinical manifestation or could be associated with other signs or symptoms. When data from adults and children were compared, fever (86% vs 100%), abdominal pain (44% vs 68%), and weight loss (19% vs 42%) were less frequent in adults than in children, respectively. Percentages of constitutional symptoms were

TABLE 6. Summary of Patient Management and Antibiotic Treatment

Patient Management (n = 35)	N (%)	Duration of Treatment Mean (SD)/(Range), wk
No treatment	3 (9)	—
Surgical treatment	3 (9)	—
Surgical and antibiotic treatment	6 (17)	—
Antibiotic treatment	23 (66)	7.56 (7.95)/(1–24)
Antibiotic monotherapy	13 (45)	5.25 (5.58)/(1–20)
Antibiotic combinations	16 (55)	9.69 (9.37)/(2–24)

Abbreviations: N = number of patients, SD = standard deviation.

similar.[1,5,21,28,34] Peripheral adenopathies, which were detected in 85%–100% of typical CSD, were only present in 33% of HS forms. This proportion was similar in children. Hepatomegaly and splenomegaly were less frequent in adults than in children (14% vs 53%).[5,21] Leukocytosis was less frequent in adults (27% vs 79%), and the liver enzymes were raised in 38% of clinical cases herein reviewed. CRP and ESR were raised in both adults and children.[1,5,21]

Image studies were needed for the diagnosis of HS-CSD. CT scans were more frequently used for adults than for children (47% vs 5%, respectively). On the contrary, ultrasound scans were more frequent for children than for adults (68% vs 19%, respectively). Both imaging techniques were equally used with children and adult patients, and the percentages of discordances between these techniques were similar for both groups.[5] Therefore, it seems that CT scan is the radiologic image technique of choice for its greater sensitivity. Nevertheless, the low number of patients studied by MRI does not allow making conclusions about this imaging technique. A single lesion was found in 14% of adults. To our knowledge, this clinical sign has not been previously described in children. The simultaneous presence of abdominal adenopathies in both liver and spleen lesions was less frequent than previously reported.[1,5,19–21]

According to pathologic studies, most patients presented necrotizing granulomatous lesions (75%–91% depending on the affected organ). None of the patients showed vascular lesions suggesting peliosis. Silver staining, considered very specific for CSD, had sensitivity similar to that published in the literature, although it was rarely used since *Bartonella* infections were less frequently suspected in adults.[20,21]

Bartonella culture is the gold standard for diagnosis of *Bartonella*. Culturing of specimens can be performed by the centrifugation-shell vial technique with human endothelial cell monolayers or using Columbia sheep blood agar plates.[8] However, it was only performed in 2 cases, both with positive results. For most patients, microbiologic diagnosis was based on serologic assays. *B. henselae* IFA assays are accessible and can be performed in the majority of hospitals. Cross-reactions with *Bartonella* spp. (for example, *B. quintana*) or with *C. burnetii* are very frequent problems.[22] High titers or seroconversions are needed to confirm diagnosis. Molecular tools (specifically, PCR assays) enable rapid detection and identification of *Bartonella* species in blood samples and biopsy specimens and swabs of lesions, especially if sampled in patients with early stage CSD who have not received treatment.[2] Specific real-time reverse transcription-PCR assays targeting 16S-23S rRNA and pap31 genes have been demonstrated to be very useful for *Bartonella* detection in patients.[3]

The differential diagnosis should include other infections and neoplasia, such as lymphomas. There should be an initial effort to exclude these conditions that mimic HS-CSD.

Therapeutic approaches to HS forms of CSD are variable. No treatment was prescribed for some patients, whereas surgical procedures with or without antimicrobials were deemed necessary in other cases. In all cases, recovery from HS-CSD was satisfactory. Considering the reviewed cases, several surgical interventions could have been avoided if *Bartonella* spp. infections had been suspected. Splenectomy should only be performed in cases in which subcapsular lesions have high risk of rupture or when there is no clinical response to medical treatment. Antibiotics (in monotherapy or in combination) were used for 83% patients. Macrolides were the most frequently prescribed antibiotics in monotherapy, whereas tetracyclines, fluoroquinolones, and rifampicin were used in combination. Patients were treated as immunosuppressed patients with HS-CSD[31,34] since antibiotics were used for long periods of time and often in combination. In our patients, we only prescribed azithromycin (500 mg) every 24 hours for 5 days, as recommended by Bass et al.[7] Our patients achieved clinical resolution in 4 weeks, in contrast with the 9 weeks needed when other prolonged regimens were used. Nevertheless, the cure (radiologic resolution of the images) was slower with our regimen (5.7 vs 3.8 mo). Nevertheless, the clinical resolution was good in all cases (in our experience and according to the literature).[5,20,37] For these reasons, we think that a short course of azithromycin is a very good choice for immunocompetent patients when HS-CSD is not secondary to other conditions such as endocarditis and there is no other associated organ involvement (nervous system or bone).[31,34] We also recommend the use of CT scan and follow-up clinical evaluations when treatment is finished (after 4 weeks and 4 months) to be sure of the complete disappearance of the lesions.

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