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Splenic Cat-Scratch Disease in a Patient Receiving Etanercept: A Case Report and Review of Diagnosis, Management, and Risk of Persistent Imaging Findings

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Abstract: Cat-scratch disease (CSD), caused by *Bartonella henselae*, is most often a self-limited regional lymphadenopathy in immunocompetent hosts but can present with atypical, disseminated manifestations in immunosuppressed patients. We describe a 66-year-old woman with rheumatoid arthritis on etanercept who presented with a subacute febrile illness, severe hyponatremia, splenomegaly with multifocal splenic lesions, and laboratory features mimicking secondary hemophagocytic lymphohistiocytosis. Initial bone marrow and computed tomography (CT)-guided splenic biopsies were nondiagnostic, and an extensive infectious workup was unrevealing. After an exposure history identified close contact with outdoor cats, add-on broad-range polymerase chain reaction (PCR) on the previously obtained splenic tissue confirmed *Bartonella* species. She was treated with doxycycline and rifampin, etanercept was discontinued, and she had complete clinical recovery despite persistent sub-centimeter splenic lesions on follow-up imaging. This case highlights splenic cat-scratch disease as an important consideration in febrile patients on TNF-α inhibitor therapy with multifocal splenic lesions, the diagnostic value of broad-range tissue PCR, and the interpretation of residual radiographic findings after treatment.

Keywords: *Bartonella henselae*; cat-scratch disease; splenic lesions; etanercept; TNF-α inhibitor; immunocompromised host; hemophagocytic lymphohistiocytosis; granulomatous splenitis

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Highlights

- Splenic cat-scratch disease, caused by *Bartonella henselae*, should be considered in immunocompromised patients presenting with fever of unknown origin, splenomegaly, and multifocal splenic lesions, even in the absence of regional lymphadenopathy.
- Patients on tumor necrosis factor-alpha inhibitor therapy such as etanercept are at increased risk for disseminated and atypical forms of *B. henselae* infection, including hepatosplenic involvement, despite the typically benign course in immunocompetent hosts.
- Diagnosis frequently requires a combination of serology, tissue PCR, and exclusion of alternative infectious and neoplastic etiologies; blood and tissue cultures are usually negative due to the fastidious nature of the organism.
- Empiric β-lactam, trimethoprim-sulfamethoxazole, and fluoroquinolone regimens are not recommended in immunocompromised hosts due to high failure rates; doxycycline or azithromycin combined with rifampin is preferred for severe or disseminated disease.
- Persistent hypodense splenic lesions on follow-up imaging do not necessarily indicate treatment failure and may represent post-inflammatory granulomatous scarring; clinical and laboratory response remain the primary determinants of cure.

1. Introduction

Bartonella henselae is a fastidious, intracellular Gram-negative bacterium that is the causative agent of CSD. In immunocompetent individuals, typical CSD presents as self-limited regional lymphadenopathy following a cat scratch or bite, particularly with kittens serving as the principal reservoir and the cat flea (*Ctenocephalides felis*) functioning as the vector. However, *B. henselae* can cause a wide clinical spectrum that extends well beyond typical CSD, particularly in immunocompromised hosts, including prolonged fever of unknown origin, culture-negative endocarditis, neuroretinitis, granulomatous hepatitis and splenitis, bacillary angiomatosis, and bacillary peliosis hepatitis [1].

The introduction of tumor necrosis factor-alpha (TNF-α) inhibitors such as etanercept, infliximab, and adalimumab for rheumatologic and inflammatory bowel diseases has been accompanied by reports of granulomatous infections, including tuberculosis, histoplasmosis, and bartonellosis, presenting with atypical or disseminated features. TNF-α plays a central role in granuloma formation and macrophage-mediated containment of intracellular pathogens, and its pharmacologic inhibition has been associated with impaired control of *B. henselae* replication and increased risk for dissemination [2].

Splenic involvement in CSD is uncommon and may occur in isolation or as part of hepatosplenic disease. The differential diagnosis of multifocal splenic lesions is broad and includes pyogenic, mycobacterial, fungal, and parasitic infections, as well as lymphoma and other neoplastic processes [3]. We present a case of splenic CSD in a patient on etanercept therapy that initially mimicked secondary hemophagocytic lymphohistiocytosis (HLH) and required tissue-based broad-range PCR for definitive diagnosis. We review the epidemiology, clinical spectrum, diagnostic approach, and treatment of disseminated *B. henselae* infection, with particular attention to the interpretation of residual imaging findings.

2. Case Presentation

2.1. History of Present Illness

A 66-year-old woman presented with a two-week history of generalized malaise, poor appetite, and frequent falls. On presentation, she was febrile at 39.0 °C and required admission to the intensive

care unit due to severe hyponatremia (serum sodium, 117 mmol/L; reference range, 135–145 mmol/L). She was started on ceftriaxone 2 g intravenously every 24 h for presumed acute pyelonephritis.

2.2. Past Medical History

Her past medical history was significant for rheumatoid arthritis, for which she was receiving long-term etanercept therapy. She had completed QuantiFERON-TB testing in 2020 prior to the initiation of biologic therapy, which was negative.

2.3. Physical Examination

On examination, she was awake and oriented without evidence of meningismus. There was no palpable peripheral lymphadenopathy. Abdominal examination revealed mild tenderness in the left upper quadrant on palpation without rebound or guarding. Cardiac auscultation was unremarkable, and bedside transthoracic echocardiography demonstrated normal-appearing valves and preserved left ventricular contractility.

2.4. Laboratory and Imaging Studies

Laboratory studies were notable for elevated inflammatory markers, mild pancytopenia, and a constellation of findings raising concern for secondary HLH, including markedly elevated ferritin and soluble interleukin-2 receptor (sIL-2R) levels (Table 1). Contrast-enhanced CT of the abdomen and pelvis demonstrated splenomegaly with multiple subcentimeter hypodense splenic lesions.

Table 1: Laboratory findings on presentation.

Test	Result	Reference Range
CRP	89.8 mg/L	<5 mg/L
Total white blood cell count	3.0 $\times$ 10^9/L	3.4–9.6 $\times$ 10^9/L
Hemoglobin	8.8 g/dL	11.6–15 g/dL
Platelets	166 $\times$ 10^9/L	157–371 $\times$ 10^9/L
Liver function tests (ALT, AST, ALP, and total bilirubin)	Within normal limits	—
LDH	201 U/L	122–222 U/L
Ferritin	11,483 mcg/L	11–328 mcg/L
Fasting triglycerides	162 mg/dL	<150 mg/dL
Fibrinogen	247 mg/dL	200–393 mg/dL
sIL-2R	3831 pg/mL	<959 pg/mL

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CRP, C-reactive protein; LDH, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor.

2.5. Initial Diagnostic Workup

Bone marrow biopsy demonstrated reactive changes without evidence of malignancy or hemophagocytosis. Microbiologic evaluation of the bone marrow specimen, including cultures, PCR testing, and special stains, was not performed. Given the persistent diagnostic uncertainty, a

CT-guided splenic biopsy was subsequently obtained for histopathologic and microbiologic evaluation. A comprehensive infectious disease workup was performed and was unrevealing (Table 2).

Table 2: Initial infectious disease workup.

Test	Result
Blood cultures (2 sets obtained before initiation of antimicrobial therapy)	Negative
Histoplasmosis, blastomycosis, and coccidioidomycosis evaluation	Negative
Serum cryptococcal antigen	Negative
HIV Ag/Ab	Negative
QuantiFERON-TB Gold assay	Negative
Tick-borne pathogen panel	Negative
Francisella tularensis serology	Negative
Coxiella burnetii (Q fever) serology	Negative
Brucella species serology	Negative
Toxoplasma gondii serology	Negative
Splenic tissue bacterial culture and stain	Negative
Splenic tissue fungal culture and stain	Negative
Splenic tissue mycobacterial culture and stain	Negative

2.6. Hospital Course and Additional Workup

The patient improved clinically after five days of empiric ceftriaxone and correction of the hyponatremia and was subsequently discharged with planned outpatient infectious diseases follow-up. At the visit, a more detailed exposure history was obtained. She reported living with multiple outdoor cats and experienced frequent inadvertent scratches. She denied recent travel outside the United States, consumption of unpasteurized dairy products or raw meat, and direct contact with cattle or animal products of conception. She also reported no recent miscarriages among the cattle herd.

Given the patient's significant cat exposure history and an initially unrevealing diagnostic workup, serologic testing for *Bartonella* spp. was obtained. Immunoglobulin M (IgM) antibodies were negative; however, immunoglobulin G (IgG) antibodies were positive for both *B. henselae* (titer 1:16,384) and *B. quintana* ($\geqslant$1:2048). Whole-blood *Bartonella* PCR testing was negative. Transesophageal echocardiography was performed to evaluate for endocarditis and was unremarkable. Subsequently, broad-range bacterial PCR was performed on previously obtained splenic tissue and detected *Bartonella* species, thereby confirming the diagnosis of splenic cat-scratch disease.

3. Discussion

3.1. Epidemiology of Human–Pathogenic *Bartonella* Species

Three *Bartonella* species account for the majority of human disease worldwide. *B. bacilliformis* is transmitted by sand flies (*Lutzomyia*) and is endemic to the Andes Mountains of Peru, Ecuador, and Colombia, with humans serving as both reservoir and host [1]. *B. quintana*, transmitted by the human body louse (*Pediculus humanus*), is associated with homelessness, body louse infestation, and poor

sanitation. *B. henselae* has a worldwide distribution, with domestic cats serving as the principal reservoir and the cat flea (*Ctenocephalides felis*) functioning as the arthropod vector; transmission to humans typically occurs through cat scratches or bites, and kittens are more frequently bacteremic than adult cats [1]. Immunocompromised hosts, including patients with HIV, solid organ transplant recipients, and patients receiving biologic immunosuppression, are at increased risk for disseminated and atypical manifestations [1,2].

3.2. Clinical Spectrum of *B. henselae* Infection

The clinical spectrum of *B. henselae* infection differs substantially according to host immune status. In immunocompetent patients, typical CSD presents as a tender regional lymphadenopathy following a cat scratch or bite. Atypical manifestations include prolonged fever of unknown origin, culture-negative infective endocarditis, granulomatous hepatitis and splenitis, encephalopathy, and ocular involvement (neuroretinitis, Parinaud oculoglandular syndrome, choroiditis, and optic nerve granuloma). In profoundly immunosuppressed patients, the spectrum shifts toward chronic CSD with persistent bacteremia or fever of unknown origin, bacillary angiomatosis, bacillary peliosis hepatis, and culture-negative endocarditis [1].

Three entities deserve specific distinction because they share overlapping clinical and radiographic features but differ in pathology and host susceptibility (Table 3). Bacillary angiomatosis (BA) and bacillary peliosis hepatis (BP) occur almost exclusively in profoundly immunocompromised hosts, typically patients with HIV and CD4 counts below 50 cells/μL, and are characterized by vascular proliferative lesions or blood-filled, endothelial-lined cystic cavities, respectively. In contrast, hepatosplenic CSD is most often seen in immunocompetent or mildly immunosuppressed hosts and is histologically characterized by necrotizing granulomas with stellate microabscesses [1].

Table 3: Distinguishing features of bacillary angiomatosis, bacillary peliosis hepatis, and hepatosplenic cat-scratch disease.

Feature	Bacillary Angiomatosis	Bacillary Peliosis Hepatis	Hepatosplenic CSD
Host	Immunocompromised (typically HIV, CD4 < 50)	Immunocompromised (typically HIV, CD4 < 50)	Immunocompetent or mildly immunosuppressed
Species	*B. henselae* or *B. quintana*	*B. henselae*	*B. henselae*
Pathology	Vascular proliferative lesions; lobular capillary proliferation	Blood-filled, endothelial-lined cystic spaces (peliotic cavities) in liver/spleen	Necrotizing granulomas with stellate microabscesses
Primary site	Skin (most common)	Liver ± spleen	Liver ± spleen
Imaging/exam findings	Cutaneous lesions mimicking Kaposi sarcoma	Hepatic cysts/peliotic lesions on imaging	Multiple small hypoechoic/hypodense lesions on imaging

3.3. Differential Diagnosis of Multifocal Splenic Lesions

The differential diagnosis of multifocal splenic lesions in a febrile, immunocompromised patient is broad and must be approached systematically. Infectious etiologies include pyogenic bacteria

such as *Staphylococcus aureus* and *Streptococcus* species (typically in the setting of infective endocarditis, intravenous drug use, or hematogenous dissemination from skin and soft tissue infection); Enterobacterales (urinary or intra-abdominal extension); non-typhoidal *Salmonella* (gastroenteritis in immunocompromised hosts); fungi such as *Candida*, *Aspergillus*, *Cryptococcus*, and Mucorales in immunocompromised hosts; mycobacteria including *Mycobacterium tuberculosis* and non-tuberculous mycobacteria; melioidosis in patients with appropriate epidemiologic exposure; and bacillary angiomatosis and peliosis in patients with profound immunosuppression. Non-infectious considerations include sarcoidosis, lymphoma, vascular neoplasms, lymphangiomas, hamartomas, and metastatic disease [3].

3.4. Disseminated CSD in Patients on Anti-TNF Therapy

Reports of disseminated and atypical CSD in patients receiving TNF-α inhibitors have accumulated since the introduction of these agents. TNF-α is a key cytokine required for granuloma formation and for macrophage-mediated containment of intracellular pathogens; pharmacologic inhibition impairs this response and predisposes to disseminated *B. henselae* infection. Case reports have implicated etanercept, infliximab, and adalimumab, underscoring the need to consider *Bartonella* in patients on any TNF-α inhibitor presenting with fever, lymphadenopathy, or unexplained visceral lesions, even in the absence of recognized cat scratches [2].

3.5. Diagnostic Approach

The diagnosis of disseminated *B. henselae* infection requires a high index of suspicion and a combination of serologic, molecular, and histopathologic techniques. Serologic testing by indirect immunofluorescence assay (IFA) remains the most widely available diagnostic modality, with elevated IgG titers supporting the diagnosis, although seronegative cases occur, particularly in profoundly immunosuppressed hosts [4]. Blood cultures are typically negative due to the fastidious, slow-growing nature of *Bartonella* species, and *Bartonella* PCR on whole blood has variable sensitivity [4,5]. Tissue-based broad-range bacterial 16S ribosomal RNA PCR has emerged as a particularly valuable tool when conventional cultures and stains are unrevealing, as illustrated in the present case. Histopathology may demonstrate the characteristic necrotizing granulomas with stellate microabscesses, and Warthin-Starry silver stain may identify clusters of organisms within tissue [1].

3.6. Treatment

Antimicrobial selection in disseminated bartonellosis differs from that of typical CSD, in which spontaneous resolution often occurs, and antibiotic therapy may not be required. Rifampin, tetracyclines, and macrolides are the preferred agents [6–8]. Penicillins, first-generation cephalosporins, trimethoprim-sulfamethoxazole, and fluoroquinolones are not recommended [8]. For severe or disseminated disease, combination therapy with doxycycline or azithromycin plus rifampin is recommended [6–8]. Ceftriaxone is reserved as second-line therapy in pregnant patients when macrolides cannot be administered [6]; this partial activity may explain the initial clinical improvement observed in our patient during empiric ceftriaxone therapy during her hospitalization.

Treatment duration is informed by case series and expert opinion rather than randomized trials. For disseminated infection, bacillary angiomatosis, or hepatic peliosis, at least three months of antimicrobial therapy is often used [1,7,8]. The risk of relapse is highest in patients with AIDS, and continuous suppression with doxycycline or azithromycin for the duration of immunosuppression is advised in this population [1,7]. In patients receiving biologic immunosuppression for rheumatologic indications, temporary discontinuation of the offending agent during the acute treatment phase, with subsequent transition to or reintroduction of immunosuppression once clinical response has been established, represents a reasonable strategy in collaboration with the prescribing rheumatologist.

3.7. Interpretation of Persistent Imaging Findings

A practical question that frequently arises in the management of hepatosplenic CSD is whether residual hypodense lesions on follow-up imaging represent persistent active infection or post-inflammatory scarring. Long-term follow-up data are most robust in the pediatric literature. Scolfaro and colleagues reported seven pediatric patients with hepatosplenic granulomatous CSD, only one of whom was immunocompromised. The patients were treated for two to four weeks. Five had persistence of intraparenchymal liver or splenic lesions on imaging at follow-up of several months, presumed to represent residual fibrosis, and no patient relapsed during follow-up ranging from six months to four years [9]. Similarly, in the case of Schiffmann and colleagues describing splenic CSD on etanercept, persistent hypodense splenic lesions and peritoneal panniculitis were noted at three months despite clinical resolution. The patient had no recurrent symptoms after antibiotic completion [2]. In our patient, follow-up CT at three months demonstrated unchanged splenic subcentimeter lesions in the setting of complete clinical recovery, return of CRP to less than 3 mg/L, and resolution of the HLH-like laboratory profile, consistent with residual granulomatous changes rather than treatment failure.

3.8. Role of Antimicrobial Treatment of Cats

Owners of cats sometimes inquire whether treating their cat with antibiotics will eliminate the risk of *B. henselae* transmission, particularly in households with immunocompromised individuals. Experimental work by Regnery and colleagues demonstrated that antimicrobial therapy in cats with experimentally induced *B. henselae* bacteremia did not durably eradicate infection, with recurrence of bacteremia observed after challenge exposure and treatment [10]. For this reason, routine antibiotic treatment of cats is not recommended. Practical risk-reduction measures for households with immunocompromised individuals include avoidance of scratches and bites (particularly from kittens), flea control, prompt cleansing of any scratch wound, and avoidance of allowing cats to lick open wounds.

4. Case Resolution and Monitoring

The patient was treated with doxycycline plus rifampin for six weeks, followed by doxycycline monotherapy for an additional three months. Etanercept was discontinued at the time of hospitalization, and leflunomide was initiated at six weeks of therapy after clinical improvement had been clearly documented. Significant clinical improvement was noted one week after initiation of targeted therapy, and she returned to her baseline functional status at the six-week follow-up visit. Repeat CT of the abdomen and pelvis at three months demonstrated stable sub-centimeter splenic lesions that were unchanged from prior imaging. CRP at the three-month visit was less than 3 mg/L, and she remained afebrile and asymptomatic with no evidence of relapse.

5. Conclusion

Splenic CSD due to *Bartonella henselae* should be considered in the differential diagnosis of febrile multifocal splenic lesions in patients receiving biologic immunosuppression, particularly TNF-α inhibitor therapy. The initial presentation may mimic secondary HLH or other systemic inflammatory processes, and a careful exposure history, including ownership of and contact with cats and kittens, is essential. Conventional blood and tissue cultures are frequently unrevealing, and broad-range tissue-based PCR can be invaluable for establishing the diagnosis. Treatment with doxycycline plus rifampin followed by extended doxycycline monotherapy, in conjunction with temporary discontinuation of the implicated biologic agent during the acute phase, is likely to achieve a durable clinical cure.

Persistent residual splenic lesions on follow-up imaging are common and, in the setting of complete clinical and biochemical recovery, do not necessarily indicate treatment failure; clinical response and biomarker normalization, rather than radiographic resolution alone, should guide management decisions.

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References

1. Rose, S.R.; Koehler, J.E. Bartonella, including cat-scratch disease. In *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*, 9th ed.; Bennett, J.E., Dolin, R., Blaser, M.J., Eds.; Elsevier: Philadelphia, PA, USA, 2020; pp. 2824–2843.
2. Schiffmann, A.; Pers, Y.M.; Lukas, C.; Combe, B.; Morel, J. Mesenteric and splenic cat-scratch disease during etanercept therapy. *Rheumatology* **2009**, *48*, 1461–1462. [CrossRef] [PubMed]
3. Kamaya, A.; Weinstein, S.; Desser, T.S. Multiple lesions of the spleen: Differential diagnosis of cystic and solid lesions. *Semin. Ultrasound CT MRI* **2006**, *27*, 389–403. [CrossRef] [PubMed]
4. Kumar, A.; Abdulqader, M.; McBride, D.A. Utility of Polymerase Chain Reaction versus Serology-Based Testing in Immunocompromised Patients with *Bartonella henselae* Infection. *Open Forum Infect. Dis.* **2023**, *10*, ofad130. [CrossRef] [PubMed]
5. Vermeulen, M.J.; Diederen, B.M.W.; Verbakel, H.; Peeters, M.F. Low sensitivity of *Bartonella henselae* PCR in serum samples of patients with cat-scratch disease lymphadenitis. *J. Med. Microbiol.* **2008**, *57*, 1049–1050. [CrossRef] [PubMed]
6. Rolain, J.M.; Brouqui, P.; Koehler, J.E.; Maguina, C.; Dolan, M.J.; Raoult, D. Recommendations for treatment of human infections caused by *Bartonella* species. *Antimicrob. Agents Chemother.* **2004**, *48*, 1921–1933. [CrossRef] [PubMed]
7. Psarros, G.; Riddell, J., 4th; Gandhi, T.; Kauffman, C.A.; Cinti, S.K. *Bartonella henselae* infections in solid organ transplant recipients: Report of 5 cases and review of the literature. *Medicine* **2012**, *91*, 111–121. [CrossRef] [PubMed]
8. Bartonellosis: Adult and Adolescent OIs | NIH. clinicalinfo.hiv.gov. 2023. Available online: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/bartonellosis (accessed on 14 May 2026).
9. Scolfaro, C.; Leunga, G.K.; Bezzio, S.; Chiapello, N.; Riva, C.; Balbo, L.; Bertaina, C.; Tovo, P.A. Prolonged follow up of seven patients affected by hepatosplenic granulomata due to cat-scratch disease. *Eur. J. Pediatr.* **2008**, *167*, 471–473. [CrossRef] [PubMed]
10. Regnery, R.L.; Rooney, J.A.; Johnson, A.M.; Nesby, S.L.; Manzewitsch, P.; Beaver, K.; Olson, J.G. Experimentally induced *Bartonella henselae* infections followed by challenge exposure and antimicrobial therapy in cats. *Am. J. Vet. Res.* **1996**, *57*, 1714–1719. [CrossRef]