

A Case Report of *Bartonella henselae* Infection Causing Fever of Unknown Origin: Unveiling a Stealthy Pathogen

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Abstract

Bartonella species are bacterial pathogens responsible for Cat Scratch Disease (CSD) with various clinical manifestations, ranging from self-limiting febrile illnesses to severe systemic infections. Diagnosis is often challenging due to its insidious nature and variable presentation based on the body's immune status. Such a scenario emerged when a 25-year-old male presented to our hospital with nonspecific symptoms of Fever of unknown origin that were not responding to antibiotics until a timely diagnosis of *Bartonella* infection. This case report highlights the importance of considering *Bartonella* as a potential etiology in patients with prolonged Fever of unknown origin, especially in endemic regions.

Keywords

Bartonella henselae, Cat Scratch Disease, Lymphadenopathy, Immunocompetent, Cat, Endocarditis, Doxycycline, Rifampin

1. Introduction

Bartonella species are gram-negative, facultative intracellular bacteria that infect erythrocytes and endothelial cells, causing a spectrum of clinical diseases collectively known as bartonellosis. Although cat scratch disease (CSD) caused by *Bartonella henselae* is the most commonly recognized manifestation, other species like *Bartonella quintana* and *Bartonella bacilliformis* have been implicated in various clinical syndromes. *Bartonella* infections are often challenging to diagnose due to their nonspecific clinical presentation and the lack of routine diagnostic tests [1]. *Bartonella henselae*, the most common of the *Bartonella* species, has an annual incidence of about 12,500 infections and 500 hospitalizations

annually in the United States, with case density highest in the Southern United States. [2]

CSD clinically manifests as regional lymph node enlargement after a bite by a cat or scratch in the same area. Fever and inflammatory lymphadenopathy commonly appear within a few weeks after the injury, including a lesion of the skin, which develops at the injury site. The challenge for the physician is the dilemma of proving or invalidating the CSD etiology in the face of a patient with lymph node enlargement.

In most cases, the diagnosis must be based on clinical, epidemiological, serological, and histological data. Criteria for diagnosis of CSD usually require three of the following four criteria:

- 1) Contact history with a cat and the presence of a scratch or primary lesion of the skin, eye, or mucous membrane.
- 2) A positive cat scratch skin test reaction.
- 3) Negative laboratory testing for other causes of lymphadenopathy.
- 4) Characteristic histopathological findings in a lymph node biopsy specimen or at a site of systemic involvement.

However, these criteria must be sufficiently specific to establish a CSD diagnosis and differentiate between several infectious etiologies and especially aid in diagnosis where cases of seronegative *Bartonella* have been reported. [3] [4]

This case report aims to educate the scientific community on the suspicion, diagnosis, and treatment of *Bartonella* infections, especially in patients presenting with a fever of unknown origin and a history of exposure to cats.

2. Case Presentation

A 25-year-old Caucasian male, relatively healthy, presented to our emergency room with a chief complaint of 2 months of intermittent history of fevers up to 104 F measured at home. The Patient described his fevers as being intermittent, as high as 104 F, lasting for 2 - 3 days, and then stopping and recurring. The Patient mentioned having severe associated headaches with the fevers. He denies any sick contacts. He was a Student and liked playing video games and walking (however, he denied taking any hikes in the woods). He mentioned having no exposure to insect bites, exposure to Tuberculosis, or travel outside of the country.

Upon evaluation, his vitals were Temp-102°F, HR-108, BP-130/84, RR-22. His Physical examination revealed mild cervical lymphadenopathy and a faint maculopapular rash on the trunk but was otherwise essentially normal. His initial labs were pertinent for a white blood cell count of 9.6, platelets of 145, pro calcitonin of 0.06, ESR of 41, CRP of 78.5, and lactic acid of 0.9. (Refer to **Table 1**) A decision was made to admit Him for further workup of his Fever of potential infectious etiology.

On admission, the Patient underwent a drug screen that was negative for SARS-COV2, RSV (Respiratory Syncytial Virus), and Influenza A and B anti-

gens, which were negative. Subsequently, after he consented to an HIV antigen test, the Heterophile Antigen and RPR were non-reactive (Refer to **Table 2**).

Table 1. CBC with automated differential.

CBC WITH AUTOMATED DIFFERENTIAL	Reference Range & Units	Result
WBC	4.0 - 11.0 K/uL	9.6
RBC	4.40 - 6.00 M/uL	4.89
Hemoglobin	13.5 - 18.0 g/dL	13.5
Hematocrit	40.0 - 52.0 %	39.8 (L)
MCV	80 - 100 fL	81
MCH	27.0 - 33.0 pg	27.6
MCHC	31.0 - 36.0 g/dL	33.9
RDW	< 16.4%	14.4
Platelet Count	150 - 400 K/uL	145 (L)
Differential Type		Automated
Neutrophil %	%	66
Lymphocyte %	%	22
Monocyte %	%	10
Eosinophil %	%	1
Basophil %	%	1
Abs Neutrophil	2.0 - 8.0 K/uL	6.4
Abs Lymphocyte	1.0 - 5.1 K/uL	2.1
Abs Monocyte	0.0 - 0.8 K/uL	0.9 (H)
Abs Eosinophil	0.0 - 0.5 K/uL	0.1
Abs Basophil	0.0 - 0.2 K/uL	0.1
Sedimentation Rate (ESR)	0 - 15 mm/hr	41 (H)

Table 2. Negative serology for influenza, RSV, SARS-COV2 and Resp Pathogen.

Test	Reference Range & Units	Result
Influenza A RNA	Not Detected	Not Detected
Influenza B RNA	Not Detected	Not Detected
Respiratory Pathogen Panel, Na, Nasopharyngeal		Not Detected
RSV RNA	Not Detected	Not Detected
SARS-COV-2, NAA	Not Detected Not Detected	Not Detected Not Detected

Table 3. Negative Serology for autoimmune and atypical infections.

Test	Reference Range & Units	Result	Result	Result
Heterophile Mononucleosis Screen	Neg	Neg		
EBV (EPSTEIN BARR) ANTIBODY PANEL, QUAL	Neg		Neg	
RPR (MONITOR/TREATMENT) W REFLEX TITER	Neg			Neg
Anti-Nuclear Antibody (ANA)	Neg	Neg		
Rheumatoid Factor (RA)	0 - 15 IU/mL	< 5		

The Patient underwent a CT of the brain that was unremarkable and a CT of the abdomen and Pelvis with contrast that showed multiple small < 1 cm lymph nodes in the mesentery (Refer to **Figure 1**).

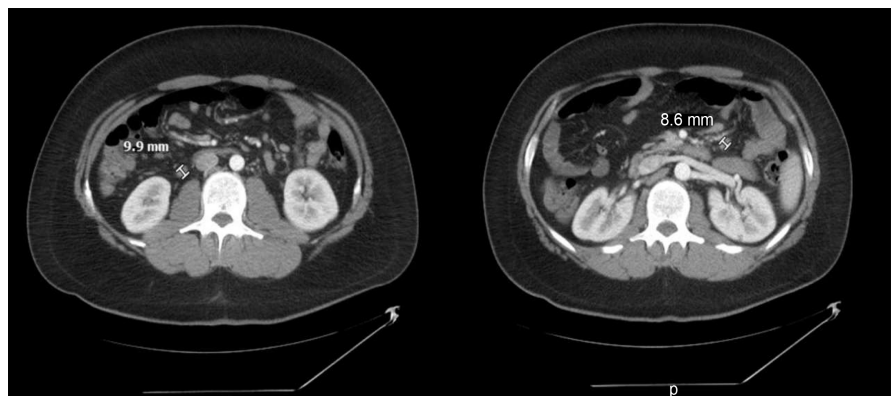


Figure 1. Axial views of CT abdomen and pelvis with contrast showing 9.9 mm on the left and 8.6 mm on the right Mesenteric Lymphadenopathy.

The Patient was started on IV ceftriaxone and doxycycline for empiric coverage for bacterial organisms. Over the next few days, he did not show any evidence of improvement and continued to have a fever in the range of 101°F. He continued fevers and headaches with Fever with no identifiable cause, a lumbar puncture was done that showed no evidence of any infection in CSF, and serologies for viral and atypical infections were sent out. (Refer to **Table 3**).

Due to no clear etiology of his Fever and lack of response to antibiotics, consultation with Infectious Disease for further evaluation was obtained for further workup of the Fever of Unknown origin. Upon Infectious disease consultation it was discovered that the Patient had three cats and two dogs. He had recently brought a cat home from the warehouse where his mom works. Cat had been having diarrhea last few months and has been living with them for six months. The cat was seen by a vet, who told us what was expected, but in the previous few months, it had lost weight and had diarrhea. He reported having recently

engaged in outdoor activities in a wooded area and exposure to stray cats. Given the history that he had acquired a new cat that had been sick for the past few months, he was then sent for a *Bartonella* antibody level detection. The Patient was switched over empirically to Levaquin 750 mg daily and monitored.

After the initiation of Levaquin, the Patient had no more episodes of fever and within 24 hours he was feeling better. His mesenteric Lymphadenopathy also raised the possibility of lymphoma so a hematology-oncology was consulted, who requested that the Patient have a bone marrow biopsy.

Patient underwent the bone marrow biopsy and the pathology showed a mildly hypercellular marrow with no evidence of lymphoma or leukemia. His chromosome analysis on bone marrow came back negative for any cytogenetic abnormality.

Patient remained afebrile and he was discharged home with Levaquin 750 mg for ten days and referred for an outpatient follow-up with infectious disease. After the Patient's discharge, His serologies for *Bartonella hens* came back positive (Refer to **Figure 2**). The Patient was started on Rifampin and doxycycline. He continued to show signs of improvement on these medications. However, after 2 weeks of being on these drugs, he developed a recurrence of Fever and a new onset of neutropenia, prompting him to be re-admitted to the hospital for further workup. Due to concern about endocarditis due to *Bartonella* Patient underwent a transthoracic followed by a transesophageal echo that showed no evidence of vegetation. After endocarditis was ruled out, a consultation with an infectious disease specialist recommended continuing on doxycycline and stopping the Rifampin due to the development of neutropenia.

Post the patient's discharge has did not have any recurrence of symptoms and was successfully treated for his *Bartonella* infection with 6 weeks of doxycycline treatment. No follow-up titres were available.

<i>B. henselae</i> IgM Titer-	1:80	REFERENCE RANGE: <1:20
<i>B. henselae</i> IgG Titer	1:128	REFERENCE RANGE: <1:64

Figure 2. Serology for *Bartonella* IgM and IgG.

3. Discussion

CSD (cat scratch fever) is an infection transmitted to Humans by bite or scratch of human mucous membrane by cats harboring the *Bartonella henselae* bacteria. In Immunocompetent individuals, it may remain dormant and self-resolve or typically present with a prolonged febrile illness accompanied by constitutional symptoms, lymphadenopathy, and sometimes a characteristic rash. These symptoms usually resolve without any lasting disease, and the majority of mild-to-moderate cases of CSD resolve without any antimicrobial therapy within a few months [5] [6].

Lymphadenopathy is the most common presentation seen in *Bartonella* infec-

tion, as was in this case with mild cervical lymphadenopathy clinically and mesenteric lymphadenopathy on CT scan. Histopathological examination of the lymph nodes reveals a granulomatous picture alongside micro-abscesses and focal necrosis when biopsied.

Dissemination of CSD is quite familiar with endocarditis, aseptic meningitis, and eye infections such as neuroretinal, uveitis, and choroiditis, being other manifestations that have been reported. [7] [8] Bartonella are mainly recognized as causative agents of culture-negative bacterial endocarditis. Reported cases of Bartonella endocarditis show that it tends to involve native valves due to their preference for mucous membranes. Subacute bacterial endocarditis due to Bartonella can also cause a false-positive ANCA (antineutrophilic cytoplasmic antibody) test, and clearly distinguishing both is useful because the misdiagnosis of an SBE as an ANCA-associated vasculitis can cause consequences in delay in initiating treatment [9]. As in this case, who presented with recurrent Fever after discharge, prompting workup for TEE, we highly recommended keeping SBE due to Bartonella as a diagnosis in patients having persistent Fever after treatment initiation.

The Diagnosis of CSD is suspected when patients give a positive history of contact with a cat supported by signs such as primary inoculation site wound or lymphadenopathy. This is often followed by the exclusion of other potential causes of subacute lymphadenopathy and *Bartonella henselae* antigen testing for definitive diagnosis [10].

Treatment approach varies based on the Patient's clinical manifestations and immune status. *In vitro*, Bartonella species can be susceptible to macrolides, tetracyclines expanded-spectrum cephalosporins, trimethoprim-sulfamethoxazole, Rifampin, and fluoroquinolones like ciprofloxacin. [11] [12] Clinically, the treatment depends on the presentation and level of involvement; Doxycycline and Rifampin are most commonly used, especially for mild infections, retinitis, and culture-positive bacterial endocarditis. We opted to use a combination of antibiotic Doxycycline and Rifampin as a treatment once the diagnosis was confirmed with good results however Azithromycin can also be used in milder forms of cat scratch disease. [13] [14] Other infections caused by Bartonella, such as Oroya Fever *Bartonella bacilliformis*, are endemic to populations of Peru and often affect tourists and transient workers. Rifampin, Ciprofloxacin, and Azithromycin can be used similarly with good results. [15] [16]

Prognosis is usually excellent, with most immunocompetent patients recovering within a few weeks of starting treatment. A double-masked, placebo-controlled study of azithromycin treatment of immunocompetent patients with uncomplicated CSD was reported by Bass *et al*. It showed an 80% decrease in the lymph node volume was documented in 7 of 14 azithromycin-treated patients but in only 1 of 15 placebo-treated controls during the first 30 days of observation (P = 0.026). No difference was found in any clinical outcome measurement except for the rate and degree of total lymph node volume decrease as determined by sonographic documentation. The study found that at 30 days, pa-

tients treated with azithromycin had a significantly greater reduction in the total lymph node volume, as demonstrated by sonography, compared to the total lymph node volume of the placebo group. Another study by Margileth *et al* retrospectively reviewed the effects of various antibiotics for treating 268 patients with typical CSD. The study found that the Efficacy of the 3 oral antibiotics in decreasing order was: rifampin 87%, ciprofloxacin 84%, trimethoprim-sulfamethoxazole 58% concluded that Antibiotic therapy be considered for patients with severe cat scratch disease while Conservative, symptomatic treatment is recommended for the majority of patients with mild or moderate CSD [17]. In most cases of *Bartonella henselae*, treatment with doxycycline with or without rifampin for a duration of 6 weeks is recommended for complete resolution [18].

This case report outlines the common challenges clinicians face in their approach to fever of unknown origin. During the time the patient continued to have fever, the source of the fever wasn't clear as since the patient was already on antibiotics and cultures were negative it was fitting a clear picture. The mesenteric lymphadenitis along with the history of cat bites fulfilled the criteria needed for CSD diagnosis and hence allowed for further testing for Bartonella that confirmed the diagnosis subsequently.

The gap that this case report hopes to fulfill in the scientific literature world is to highlight the importance of taking good social history, especially in working up patients with fever of unknown origin to allow for diagnosis of atypical infections such as CSD importantly in cases that have Non-specific findings like fever and lymphadenitis with absence of other cause like was encountered in this case.

4. Conclusion

Cat Scratch disease caused by *Bartonella henselae*, is a common infectious cause of lymphadenopathy and fever and should be considered in the differential diagnosis of patients with prolonged Fever, especially those with relevant exposure history of exposure to cats. Timely recognition and appropriate management are crucial to prevent complications and improve outcomes.

This pathogen is often overlooked and research is warranted to develop rapid testing techniques to aid in detecting and diagnosing optimal treatment strategies for Bartonella infections to minimize the potential organ damage such as retinitis, aspect meningitis and culture-negative endocarditis due to undetected infections in immunocompromised patients.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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