

Clinicocytopathologic Correlation in an Atypical Presentation of Lymphadenopathy With Review of Literature

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ABSTRACT

Objectives: To present a clinicocytopathologic correlation of an atypical case of cat scratch disease (CSD) involving retroperitoneal lymph nodes, with emphasis on communication between service teams for managing lymphadenopathy of unknown origin. We consider clinical and cytologic differential diagnoses and review the literature on atypical cases of CSD, with emphasis on abdominal presentation and cytologic findings.

Methods: Clinical services met with the cytology service to review clinical and pathologic features. Literature was reviewed via PubMed search (Harbor-UCLA subscriptions). Immunohistochemistry and Steiner silver stains were performed by Harbor-UCLA Department of Pathology. Enzyme-linked immunosorbent assay IgG and IgM Bartonella henselae titers were carried out by Quest Nichols Institute.

Results: Fine-needle aspirate Diff-Quik and Papanicolaou smears and H&E-stained cell block showed abundant histiocytes, monocytoid B cells, and numerous neutrophils associated with necrosis corresponding to a late stage of CSD infection. Silver stain was positive for clumps of pleomorphic organisms. IgM and IgG antibody titers were elevated.

Conclusions: The cytologic findings of CSD in an atypical abdominal presentation are similar to those of a classic presentation. Laboratory workup for atypical CSD should include at least two other modalities aside from cytomorphic features. Close clinical and cytologic correlation avoided potentially unnecessary and harmful surgery and enabled timely treatment.

Upon completion of this activity you will be able to:

- describe the pathologic agent and clinical management of suspected cat scratch disease.
- list the presenting symptoms of typical cat scratch disease and distinguish these from atypical presentations.
- compare the results of diagnostic tests depending on stage of infection.

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We present a case of visceral lymphadenopathy and a pathologic picture of necrotizing granuloma to emphasize the importance of maintaining a broad differential diagnosis and good clinical communication to reach a more timely diagnosis.

Case Report

The patient is a 19-year-old man who sought treatment from Harbor-UCLA Medical Center because of a 5-day history of abdominal pain, emesis, diarrhea, fever, night sweats, and anorexia. He reported an 8-pound weight loss since the onset of his illness. His medical history was significant for a positive tuberculin purified protein derivative for which he received monotherapy for 9 months. He was born in Mexico but has been living in Southern California since he was 3 months old. He denied any travel out of the area since that

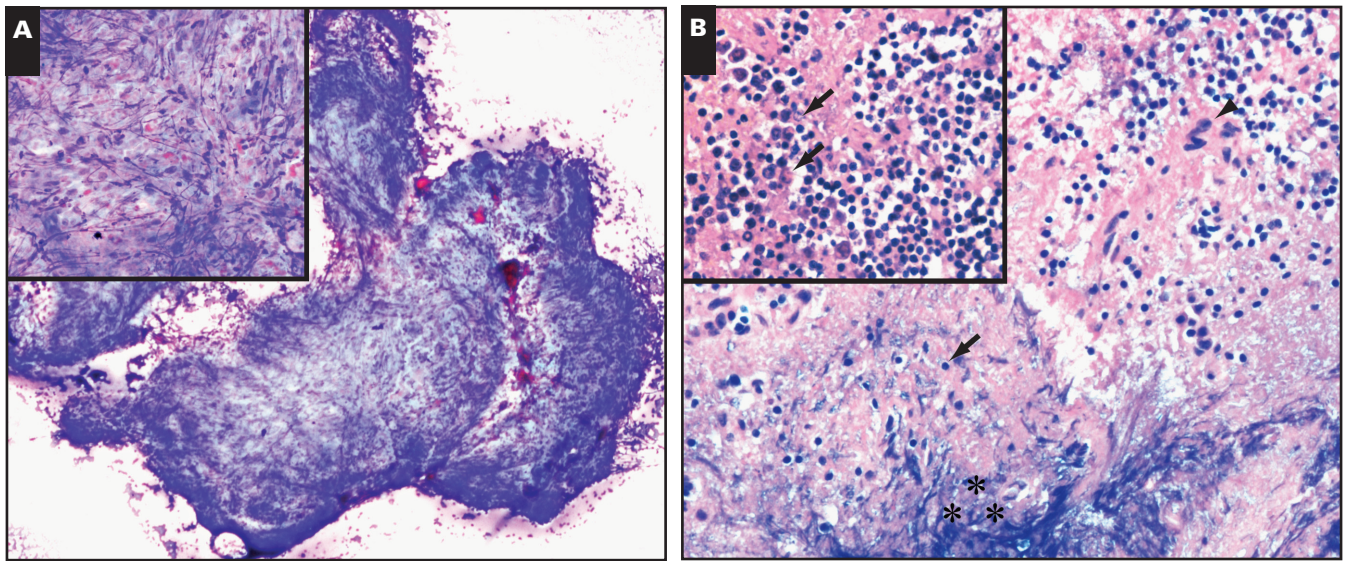


Image 1 **A**, Diff-Quik stain highlights the magenta-staining inflammatory exudate and necrotic tissue from a peripancreatic lymph node fine-needle aspirate (x50; inset, x125). **B**, H&E-stained section of the cell block (x320). Prominent necrotic, basophilic background (asterisks), with lymphocytes (arrow), degenerated neutrophils, and histiocytes (arrowhead). Inset: higher power view shows focal area of atypical lymphoid cells with monocytoid B cells (arrows; x640).

time. Since he graduated from high school nearly 2 years ago, he has worked as a restaurant dishwasher and other odd jobs, including a security guard job at a large music festival in a desert region 1 week prior to the onset of symptoms. He reported camping in a tent with one other person and eating fried rice and hot dogs. He denied eating raw or undercooked foods as well as unpasteurized dairy products. He also denied using tobacco, alcohol, and recreational drugs. He did not recall any insect bites, rashes, or animal contact. He was sexually active with one prior female partner, and he had previously tested negative for sexually transmitted infections. Physical examination was significant for tenderness at McBurney's point and positive psoas and obturator signs. He was febrile to 39.2°C and tachycardic with a heart rate of 120 beats per minute. His skin showed multiple comedones over the forehead, back, and arms. He had one tender axillary lymph node on the right that was about 2 cm in diameter. A complete blood count showed a WBC count of 11,000 per mm³ with a left shift of 17% bands. He also had an elevated sedimentation rate of 82 mm/h. Urine studies for infection were negative. The abdominal ultrasound was normal but did not visualize the appendix. Computed tomography (CT) of the abdomen was performed mainly to rule out appendicitis. The CT showed hypodense lesions in the liver and spleen, multiple enlarged lymph nodes, and a 2.8-cm soft tissue density. The latter was thought to be either an enlarged lymph node or a mass abutting the pancreatic head.

The patient was admitted to the inpatient unit and initially placed on metronidazole and ceftriaxone. Pediatric infectious diseases and hematology-oncology were

consulted for possible infectious and neoplastic etiologies. He continued to have fever and severe abdominal pain. He underwent an endoscopic ultrasound-guided fine-needle aspiration of the peripancreatic node on the third day of hospitalization. Diff-Quik- and Papanicolaou-prepared slides showed necrosis and granulomatous-type inflammation with polymorphous lymphocytes and histiocytes. Cell block revealed histiocytes, numerous neutrophils in a necrotic background, and occasional atypical lymphoid cells.

Image 1. Hematopathology was consulted and was unable to exclude low-grade B-cell type lymphoma. Since lymphoma was not in the original differential, RPMI solution for flow cytometry was not obtained. Cytomorphologic differential strongly included *Mycobacterium tuberculosis*. However, AFB and Kinyoun stains performed on deparaffinized sections were both negative. The QuantiFERON-TB Gold test (Quest Nicholls Institute, San Juan Capistrano, CA) was also negative. Human immunodeficiency virus antibodies, gonorrhea/chlamydia per urine polymerase chain reaction (PCR), *Clostridium difficile* toxin, stool ova and parasites, and blood and urine cultures were all negative.

The patient continued to be febrile and developed what appeared to be an acute abdomen the day after the biopsy. The antibiotics were then switched to piperacillin-tazobactam and vancomycin for broader antimicrobial coverage. Due to his worsening clinical course and a preliminary diagnosis, including necrosis, the pediatric primary team consulted pediatric surgery for exploratory laparoscopy to obtain fresh tissue for histology, mycobacteria culture, flow cytometry, and workup of other possible infectious agents.

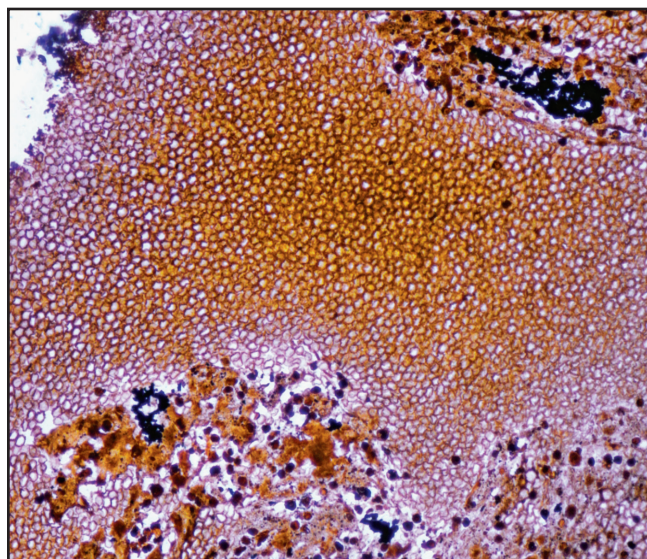


Image 2 Steiner stain of cell block (x320) shows positive staining and pleomorphic rod-shaped organisms in clumps, morphologically consistent with *Bartonella henselae*.

While the patient was in the surgical suite awaiting his procedure, the serology for *Bartonella henselae* resulted in an IgM titer of 1:40 and an IgG titer more than 1:1,024. Hence, the procedure was cancelled. Subsequently, Steiner silver stain performed on the cell block displayed pleomorphic, rod-shaped organisms in clumps morphologically consistent with *B henselae* **Image 2**. The patient was placed on azithromycin and a brief 3-day course of gentamicin due to hepatosplenic involvement. His pain improved significantly, and the fever resolved within 2 days of the new antibiotic regimen. The patient was discharged 4 days later, for a total 14-day hospital stay. Upon further questioning, the patient admitted to playing with a stray kitten and allowing it to stay in his car for several hours to shelter it from rain about 2 months prior to his illness. He denied any scratches or bites.

Review of Literature

Cat scratch disease (CSD) is reported in 9 to 10 per 100,000 persons per year, or approximately 32,000 annual cases in the United States. Most patients with CSD (88% per review of 1,312 cases diagnosed by skin antigen test¹) usually develop focal erythema with tender, nonpruritic papule(s) at the site of contact 3 to 10 days after contact with a feline. This is followed by gradual regional lymphadenopathy within a few weeks. The most common sites of lymphadenopathy are the head and neck, followed by the axillary, inguinal, and femoral areas. **Table 1** summarizes the typical CSD presentation.^{1,2} According to Moriarty and Margileth,¹ approximately 12% of cases have an atypical

Table 1
Summary of Documented Typical Cat Scratch Disease (CSD) Presentation^{1,2}

Cutaneous, tender, nonpruritic papules 3 to 10 days at inoculation site after contact with feline
Temperature >38.3°C for several days; ± malaise, fatigue, headache, sore throat
± Mild leukocytosis with neutrophilia and eosinophilia
Ipsilateral regional lymphadenopathy over 1 to 7 weeks
Multiple lymph nodes at multiple sites found in one-third of CSD cases
Most common lymphadenopathy sites: head and neck, axillary, inguinal, femoral
Self-limited course, usually resolves in 2 to 4 months

Table 2
Summary of Documented Atypical Cat Scratch Disease (CSD) Presentation

Extranodal involvement/lack of superficial regional lymphadenopathy/absence of any lymph node involvement
Mediastinal/retroperitoneal lymphadenopathy
Liver/spleen involvement (1%-2%) with almost 100% fever and ~70% abdominal pain³
Fever of unknown origin was the sole admitting diagnosis in 50% of hepatosplenic CSD
Systemic/bacteremic CSD¹: involvement of multiple organ systems with fever, rash, myalgia, arthropathy/arthritis^a
Rare manifestations
Osteomyelitis (2/96 patients with musculoskeletal manifestations)⁴
Neuroretinitis, encephalitis, transverse myelitis⁵
Presentations reported in immunocompromised patients
Skin: Kaposi sarcoma-like granuloma (epithelioid angiomatosis)⁶
Cardiac: aortic/mitral valve marantic vegetations⁷
Pulmonary: well-circumscribed pleural/parenchymal lesions⁸
Erythema nodosum⁴

^a Arthropathy/arthritis was found in 10% of 913 patients,⁹ predominantly presenting in older (>20 years) female patients with rash (erythema nodosum).

presentation **Table 2**.^{1,3-9} Intra-abdominal lymphadenopathy, as in this case, is considered one such atypical feature. However, atypical CSD can present with a wide range of symptoms. CSD reports include cases with or without lymphadenopathy, with single- or multiple-organ involvement, with fever of unknown origin, and without any skin evidence of feline contact.

Diagnosis

B henselae has been identified as the putative pathologic microorganism in CSD by studying tissue and blood samples of both patients^{10,11} and healthy cats and cat fleas.¹² They are facultative intracellular gram-negative rods that infect mainly erythrocytes and endothelial cells. Serology, PCR, immunohistochemistry (IHC) cytohistologic staining by silver, and cultures have all been used and found to have varying specificities and sensitivities.

Table 3 Summary of Histologic Findings in Various Infective Stages and in the Resolving Stage¹⁷

Early	Mid	Late	Resolving
Follicular hyperplasia with tingible body macrophages Sinus histiocytosis Increased monocytoid B cells/immunoblasts ± PCR and IHC positivity	Subcapsular microabscess progressing to central (stellate) necrosis Inner layer of histiocytes and outer rim of lymphocytes Immunostain/silver stain and PCR likely positive	Suppurative necrosis Increased neutrophils Granulomas (palisading histiocytes ± Langhans giant cells) Lymph node capsular fibrosis Decreased detection rate for <i>Bartonella henselae</i>	Scarred, resolving stellate granulomas with scant, residual neutrophil infiltration PCR likely negative ¹⁸

IHC, immunohistochemistry; PCR, polymerase chain reaction.

Table 4 Cytologic Findings in Fine-Needle Aspirates of Cat Scratch Disease

Monocytoid B lymphocytes Epithelioid histiocytes Neutrophils (late stages) ± Suppurative necrosis
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For example, in a study of biopsy specimens from 42 patients with histopathologic findings of CSD, 27 (64%) were positive by PCR, as were 23 (68%) of 34 patients with histologic and clinical CSD signs.¹³ In another review of 24 lymph node biopsy specimens consistent with CSD and with clinical suspicion, 11 (46%) were positive on silver stain, whereas only six (25%) were positive by immunostain.¹⁴ Seven cases positive by silver stain were negative by PCR, raising concern for false positivity by silver stain. Concordance between IHC and PCR was low, with four of six cases positive by IHC being negative by PCR. Because *B henselae* is a fastidious organism, the histologic results in atypical presentations should be interpreted cautiously and ideally confirmed by serology and/or PCR. In general, fresh tissue is more sensitive in suspected CSD cases than formalin-fixed, paraffin-embedded tissue.¹³ Indirect immunofluorescent antibody (IFA) or enzyme-linked immunosorbent assay (ELISA) *Bartonella* serology (titer >1:64) and PCR are considered diagnostic. ELISA serology is reported to be more sensitive than IFA.¹⁵ In 98 cases of serologically confirmed CSD by ELISA, 52 patients tested positive for anti-*B henselae* IgM antibody, whereas only 46 tested positive initially, indicating seroconversion.¹⁶ Within this cohort, 24 of 26 tested positive by PCR, and in the 24 PCR-positive cases, 83% were IgG positive and 58% were IgM positive. Hence, serology limitations must still be considered.

Histopathology of both typical and atypical CSD is found to follow the same three stages of manifestation Table 3.¹⁷ In their study, Margileth et al¹⁸ found that PCR detection rate was lower in cases considered late-stage infection. PCR was also negative in a case of prolonged hepatosplenic CSD with serologic positive *Bartonella* infection from biopsied liver tissue on the 66th day.¹⁹

The primary differential of granulomatous lymphadenopathy in the immunocompetent host is of CSD, tuberculosis, and neoplasm, primarily lymphoma. Rarer infectious etiologies should also be considered (sarcoidosis, tularemia, brucellosis, lymphogranuloma venereum, and sporotrichosis/other fungal infections). Granulomatous lymphadenitis with suppurative changes was primarily found in CSD, tularemia, and *Yersinia* infection. Monocytoid B lymphocytes (MBLs) were seen only in CSD and tularemia.¹⁷ In Asano's review¹⁷ of the literature on the histopathologic findings of granulomatous lymphadenitis, as in our case, MBLs and epithelioid histiocytes were features of CSD.

Cytology of typical CSD specimens is found to correlate closely with the classic histology Table 4.²⁰ In 13 fine-needle aspirates (FNAs) of CSD from the head and neck, there were granulomas identified in 77%, neutrophils in 62%, epithelioid histiocytes in 46%, and suppurative granulomas in 38%.²¹ Clinical suspicion was of neoplasia in 38%, and cytology differential was of bacterial abscess and lymphoproliferative disorder. Touch imprint from excised lymph nodes in eight cases diagnosed as CSD showed epithelioid histiocytes and monocytoid B cells.²² A PubMed search revealed no reported descriptions of FNA findings for abdominal CSD.

Treatment

While typical CSD is reported to resolve spontaneously in 2 to 4 months, atypical cases can have a variable course, and antibiotics are often administered. Azithromycin has been shown in a randomized controlled trial to be efficacious.²³ Erythromycin (500 mg qid), doxycycline, and rifampin are also commonly administered, with satisfactory outcomes.²⁴ Needle drainage may be therapeutic.²⁵ In a few studies of prolonged systemic disease, corticosteroid therapy has been attempted with resolution of hepatosplenic abscesses.^{26,27} These later cases were considered postinfectious with histopathologic findings of resolving inflammation. One such case reported by Bryant and Marshall¹⁹ showed negative PCR for *B henselae*.

Discussion

This case of late, diffuse abdominal CSD involvement is important for two reasons. First, it emphasizes the key role of a thorough history and communication between consulted services and the primary team and having a broad differential diagnosis for initial workup. *B henselae* serology was ordered as part of the differential diagnosis for lymphadenopathy despite negative animal exposure in the initial history. As in our patient, some patients do not recall any history of cat exposure.²⁸ Moreover, multiple teams were involved in the patient's care, and suspicion for infectious etiology was communicated to the gastrointestinal and cytopathology teams. Second, even when the clinical workup is incomplete, the cytology differential must remain broad. In this case, the diagnosis was not made prior to serologic evidence. While an atypical presentation, cat scratch lymphadenitis of the abdomen due to *B henselae* infection is well documented in the literature.^{29,30} Nevertheless, a literature review for FNA reports of abdominal lymph node or hepatosplenic CSD did not yield any results, and we believe this is the first case of FNA cytology of abdominal CSD to be reported. Key cytomorphologic findings were of necrosis, numerous neutrophils, granulomatous changes (epithelioid histiocytes and Langhans giant cells), and monocytoid B cells in the lymph node. The microscopic findings should prompt consideration of mycobacterial infection and *B henselae* infection among more rare infections in the immunocompetent host. The microscopic finding of suppurative necrosis and monocytoid B cells should prompt consideration of *B henselae*. Early-stage infection lacks prominent neutrophils and suppurative necrosis, showing only increased histiocytes and follicular hyperplasia. Late-stage infection shows abundant neutrophils and abscess formation, as in this case.

Conclusion

We report an atypical presentation of CSD with correlation of clinical and cytologic findings so far not reported in the literature. Laboratory workup for atypical CSD should include at least two other modalities aside from the cytomorphologic features. Ideally, there should be an accompanying positive serology or PCR test. Atypical clinical presentation of CSD should be kept in mind to avoid potential delay in diagnosis and treatment as well as unnecessary procedural interventions.

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