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Progressive Unilateral Cervical Lymphadenopathy With Elevated LDH in a School-Aged Female

Matthew Pertzborn, MD[1], and Alexandra Milloff Butler, MD[1]

Case Report

An 8-year-old previously healthy female presents with a 2-week history of an enlarging tender right-sided neck mass. The swelling was initially pea-sized, but over the 3 to 4 days immediately preceding her admission, the mass was noted to be enlarging. She had been seen 2 days prior to admission by her pediatrician and was prescribed sulfamethoxazole/trimethoprim, which she had been taking without improvement. In the 24 hours prior to admission she developed fever as high as 104°F, had decreased oral intake, and was complaining of neck pain. The patient had never been hospitalized before, had no known medical problems, and had no history of prior surgeries. Family history was significant for postural orthostatic tachycardia syndrome in the mother and paroxysmal atrial tachycardia in the father. The patient was in second grade, was very active, and was on the swim team. She had recently had contact with new kittens at her grandmother's home.

On initial examination the patient appeared ill but nontoxic. She had a 3-cm firm mobile mass located just beneath the pinna of her right ear with associated swelling, overlying erythema, and mild tenderness with palpation located in the upper anterior cervical chain. There was no fluctuance. She had slightly decreased range of motion of her neck when turning to her right. A <0.5 cm right supraclavicular lymph note was also appreciated. The remainder of the exam was normal.

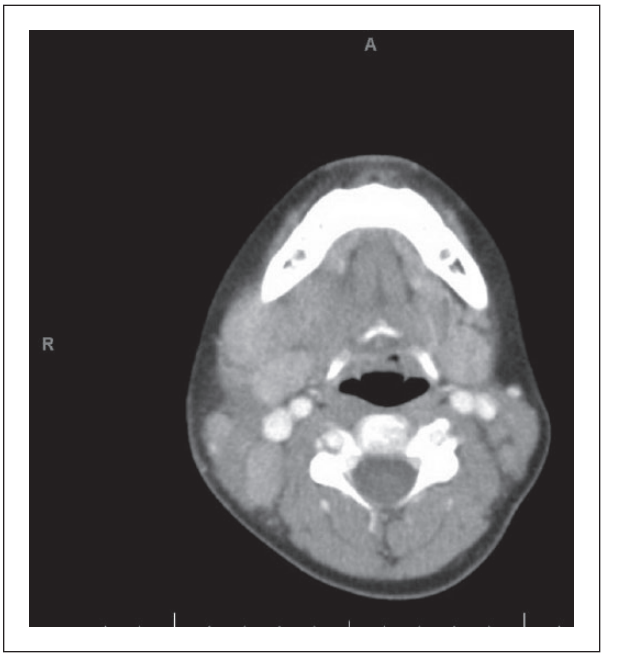

Figure 1. Right-sided Cervical Lymphadenopathy.

Final Diagnosis

Cat-scratch disease due to *Bartonella henselae*.

Hospital Course

Chest X-ray to evaluate for mediastinal lymphadenopathy was normal. Computed tomography (CT) scan of the neck with intravenous contrast demonstrated extensive swelling in the right neck secondary to right-sided cervical lymphadenopathy, with no fluid collection (see Figure 1). Given that there was no evidence of infectious source (no signs of dental or tonsillar infection) and that there was significant unilateral lymphadenopathy on the CT scan, there was concern for primary lymph node disorder or lymphoma in addition to atypical infection.

The patient was started on intravenous clindamycin 40 mg/kg/day and azithromycin 10 mg/kg on day 1 and 5 mg/kg for 4 additional days for empiric treatment of cellulitis and right cervical lymphadenitis as well as *Bartonella henselae* infection given her exposure to cats. As the CT scan findings were concerning for possible lymphoma, lactate dehydrogenase (LDH) was measured and was elevated to 641 U/L (upper limit of the reference

[1]University of Florida, Gainesville, FL, USA

Corresponding Author:
Matthew Pertzborn, University of Florida College of Medicine, 1600 SW Archer Rd, Gainesville, FL 32608, USA.
Email: matt.pertzborn@ufl.edu

range was 225 U/L). Uric acid was within normal limits. C-reactive protein was 91.8 mg/L. The white blood cell count was within normal limits as was the differential and peripheral smear. Minimal improvement in the right cervical adenopathy and in the firmness/erythema of the overlying area was noted after treatment with antibiotics for the first 2 hospital days, which was concerning for nonresponse to therapy. Due to the findings on CT scan and elevated LDH, pediatric hematology/oncology was consulted. The LDH had fallen to 272 U/L, and the C-reactive protein had fallen to 49.7 mg/L on day 3 of antibiotic therapy. Given laboratory improvement, concern for oncologic processes was lessened. The patient started to show clinical improvement with improvement of her neck swelling and erythema. Epstein–Barr virus and cytomegalovirus tests (Epstein–Barr virus viral capsid antigen IgG/IgM, cytomegalovirus DNA polymerase chain reaction, heterophile antibody/"Monospot" test) were negative. As she had clinically continued to improve with resolution of the fevers, she was discharged home with the remainder of the 10-day course of clindamycin and the remainder of the 5-day course of azithromycin.

After discharge, her *Bartonella henselae* titers returned positive (immunoglobulin M [IgM] at 1:128 and immunoglobulin G [IgG] at 1:512), thus confirming the diagnosis of cat-scratch disease (caused by *Bartonella henselae*).

Discussion

The differential for unilateral cervical lymphadenopathy is broad. Given the concern for infectious causes, the patient was treated for common bacterial causes of unilateral cervical lymphadenitis, such as group A streptococcus, *Staphylococcus aureus*, anaerobes, and *Bartonella henselae* infection. In this patient there was additional initial concern for oncologic etiology given imaging and elevated LDH, which is associated with cell turnover and commonly elevated in cancer. An important consideration on the differential, particularly when improvement of fever and lymphadenopathy is not noted with antibiotic therapy, is cancer (eg, lymphoma). Fevers, unilateral lymphadenopathy (demonstrated both on physical exam and on CT scan of the neck), elevated LDH, and nonresponse to antibiotics are all consistent with oncologic etiology such as lymphoma.

Bartonella henselae infection can present with all of these findings as well. *Bartonella henselae* can thus be confused for lymphoma and vice versa.[1,2] Four of the 8 patients in the study by Eymin et al had mildly elevated LDH (elevated to as high as 365 mg/dL, which was elevated but not as much as in our patient).[3] LDH is present in many different types of cells (not just lymphocytes or leukocytes), including but not limited to muscle cells and liver cells.[4] Nononcologic conditions can thus cause elevated LDH as well. Definitive diagnosis of cancer would require biopsy. Fortunately in this case, biopsy was not required as the LDH fell to near-reference range, the uric acid level was within reference range, and she was starting to demonstrate clinical improvement after about 72 hours of intravenous antibiotic therapy. Additionally, the positive *Bartonella henselae* titers noted after discharge confirmed the diagnosis and made oncologic etiology unlikely as her clinical course was, in fact, consistent with cat-scratch disease.

Fortunately when the *Bartonella henselae* titers resulted, she had already been empirically treated for this disease (with the azithromycin regimen). *Bartonella henselae* is a facultative intracellular bacteria.[5] It is an aerobic, oxidase negative, gram-negative bacilli.[6] It is a part of the proteobacteria class and closely related to the *Brucella* species in terms of taxonomy.[5] The bacteria has been found within the erythrocytes of infected felines and is transmitted to the cat only via the cat flea (*Ctenocephalides felis*).[5] The prevalence of positive antibody titer in cats in the United States is estimated to be between 28% and 51%, though this does vary regionally.[6,7] *Bartonella henselae* bacteria are typically transmitted to humans via feline saliva, a feline bite, or a scratch from the claws of a feline.[6] In the case of humans with the disease, the bacteria has been found intracellularly in vascular endothelium and macrophages, in erythrocytes (infects the young erythrocyte precursor cells in humans and does not infect the mature erythrocytes directly), and extracellularly in necrotic areas.[6] *Bartonella* can be isolated on either blood culture (via Warthin Starry silver impregnation stain or Brown–Hopps gram stain) or via polymerase chain reaction testing.[6,8] Blood cultures are frequently negative, however, even if *Bartonella* infection is present.[6] Isolation of *Bartonella* on blood cultures is very difficult, and sensitivities in vitro have poor correlation to sensitivities in vivo.[5] This poor correlation is hypothesized to be due to the intracellular location in which the organism typically dwells.[6] Of note, *Bartonella* IgG titers less than 1:64 are not suggestive of *Bartonella henselae* infection.[9] Titers greater than 1:256 are highly suggestive of the presence of an active or recent infection (the *Bartonella* IgG titer in our patient was 1:512).[9] Positive *Bartonella henselae* IgM correlates with acute disease (the IgM in our patient was positive).[9] Sensitivities of commonly available *Bartonella henselae* IgM assays range from 50% to 62%, and the specificities range from 87% to 96%.[10] Sensitivities of commonly available *Bartonella henselae* IgG assays range from 88% to 98%, and the specificities range from 69% to 89%.[10]

Cat-scratch disease can occur in multiple places throughout the world including, but not limited to, the United States, Japan, Australia, and New Zealand.[6] The months of July through October are noted to be when the incidence is highest in the United States.[6] The incidence is noted to be higher in warmer, more humid climates in general.[6]

The most common symptoms of cat-scratch disease are fever and local lymphadenopathy, though these symptoms do not have to necessarily be present.[3,6] In a case study of 8 patients serologically diagnosed with cat-scratch disease by Eymin et al, 7 of the 8 patients presented with fever and 7 of the 8 patients presented with tender lymphadenopathy.[3] Other conditions, such as lymphoma, can also present in this fashion. In our case, the unilateral mildly tender lymphadenopathy and elevated LDH on initial presentation were concerning for this (though further workup revealed that an oncologic etiology was unlikely). Other less common symptoms in mild-to-moderate *Bartonella henselae* infection can include myalgias, nausea, decreased appetite, malaise, and abdominal pain.[6] These are often the only symptoms in the case of mild disease.[6] The axillary and epitrochlear nodes are most commonly affected, followed by the head and neck nodes and then the inguinal nodes.[6] Lymph node biopsy, if performed, will typically demonstrate granulomas with microabscesses.[6] Suppuration of an involved lymph node has an incidence of 10%, and this requires drainage if it occurs.[6]

Most cases of cat-scratch disease will resolve on their own if left untreated.[6,8] Depending on the severity of the illness and the immune status of the patient, the symptoms can range from as few as 3 days to as many as 6 months.[3,6] *Bartonella henselae* can progress to more serious, disseminated disease.[3,6,8] Disseminated disease or involvement causing organ damage (including but not limited to endocarditis, neuroretinitis, encephalopathy, bacillary angiomatosis, pneumonia) require more than one antibiotic for treatment.[6,8] These more serious manifestations of cat-scratch disease occur in 5% to 14% of patients who contract this disease.[5] Azithromycin has been shown to improve the speed of resolution of lymph node swelling but has not been shown to prevent progression to disseminated disease, prevent organ damage in cases of more serious disease, or to be effective treatment for disseminated disease in immunocompetent patients.[5,6]

The use of antibiotic therapy in these patients is thus controversial. Antibiotic therapy is crucial, however, if the patient is immunocompromised. More serious manifestations of *Bartonella henselae* infections can generally be treated with doxycycline plus rifampin, particularly if retinal or central nervous system (e.g., encephalopathy) involvement is present for 4 to 6 weeks.[5,6] Endocarditis caused by *Bartonella* species should be treated with gentamicin for 2 weeks, ceftriaxone daily for 6 weeks, with or without doxycycline 6 weeks.[5] Other antibiotic regimens based on organ-specific involvement have been proposed and are available in the literature cited below.[6]

Conclusion

Bartonella henselae is an illness that is usually self-limited but has the potential to progress to more serious illness in a small number of cases. Clinicians should understand that cat-scratch disease may present atypically and should be considered in cases with fever, unilateral lymphadenopathy, and elevated LDH.

Author Contributions

MP contributed substantially to the design of this manuscript. He contributed substantially to the acquisition, analysis, and interpretation of the data. He drafted and critically revised the manuscript. AMB contributed substantially to the conception and design of this manuscript. She contributed substantially to the acquisition, analysis, and interpretation of the data. She critically revised the manuscript.

Declaration of Conflicting Interests

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