Persistent Cat Scratch Disease Requiring Surgical Excision in a Patient With MPGN

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abstract

We present the case of a 13-year-old immunosuppressed patient with unrelenting cat scratch disease despite 9 months of antibiotic therapy. The patient was being treated with mycophenolate and prednisone for membranoproliferative glomerulonephritis (type 1) diagnosed 13 months before the onset of cat scratch disease. Cat scratch disease was suspected due to epitrochlear lymphadenitis and an inoculation papule on the ipsilateral thumb, and the diagnosis was confirmed by the use of acute and convalescent titers positive for *Bartonella henselae*. The patient experienced prolonged lymphadenitis despite azithromycin and rifampin therapy, and she developed a draining sinus tract ~4 months after initial inoculation while receiving antibiotics. Acute exacerbation of the primary supratrochlear node prompted incision and drainage of the area, with no improvement in the disease course. Ultimately, excision of all affected nodes and the sinus tract 9 months after the initial diagnosis was required to achieve resolution. *Bartonella* was detected at a high level according to a polymerase chain reaction assay in the excised nodes. Persistent treatment with oral antibiotics may have prevented disseminated infection in this immunosuppressed patient. Surgical excision of affected nodes should be considered in patients with cat scratch disease that persists beyond 16 weeks.

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Dr Eldin provided commentary about the glomerular biopsy results; Dr Hicks provided the tissue pathology picture and discussion regarding the tissue pathology report; Dr Mazziotti provided a description of the patient's surgical care; Dr Starke provided the discussion about early management of the patient and provided the anatomic photograph; and Drs King and Michael wrote the manuscript. All authors participated in the care of the patient, commented on the manuscript, and agree to be accountable for all aspects of the work.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-2923

DOI: 10.1542/peds.2014-2923

Accepted for publication Feb 10, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Cat scratch disease is 1 of the most common causes of benign regional lymphadenopathy in children. The usual causative agent, *Bartonella henselae*, is a commensal organism found in cats and can be transmitted to humans through a scratch, bite, or contamination of an open wound or mucous membrane. Cat scratch disease usually resolves on its own in immunocompetent patients, whereas a limited course of enteral antibiotics is recommended to prevent systemic involvement in immunocompromised patients. The present article reports the unusual case of a mildly immunocompromised patient with persistent cat scratch disease despite prolonged antibiotic therapy. We discuss the utility of surgical excision for resolution of persistent cat scratch disease.

CASE DESCRIPTION

The patient was a 13-year-old Hispanic female diagnosed 13 months earlier with membranoproliferative glomerulonephritis (MPGN) type 1. She presented to the renal clinic with complaints of low-grade fevers, right elbow swelling, and pain of ~10 days' duration. She also reported a healing "scratch" on the dorsum of her right thumb for the previous 2 weeks. The family reported that they had 4 one-month-old kittens, 2 dogs, and 2 rabbits at home. The patient, who aspires to be a veterinarian, reported spending a great deal of time handling

all of these animals as well as gardening on a daily basis. She did not report any animal bites, consumption of unpasteurized foods, or unclean water.

The patient did not have HIV infection, inherited immunodeficiency, or a history of opportunistic infections that would prompt concern for immune defects. Her medical history was significant for MPGN type 1 confirmed according to biopsy results with complement 3 (C3)-dominant staining according to immunofluorescence and glomerular electron-dense deposits. The MPGN type 1 had been diagnosed ~13 months earlier, when the patient presented with edema, gross hematuria, elevated serum creatinine levels, and high blood pressure. The patient was initially treated with methylprednisolone pulse therapy (1000 mg weekly), oral mycophenolate (500 mg twice daily), and prednisone (40 mg every other day or ~1 mg/kg per dose), as well as 4 antihypertensive medications. She was initially slow to respond; the C3 levels remained very low (<10) for 3 to 4 months. However, with continued weekly methylprednisolone pulse treatment, she went into remission with sustained normal C3 levels and resolution of proteinuria and hematuria. When the patient presented with cat scratch disease, her doses of prednisone (20 mg every other day) and methylprednisolone (500 mg weekly) were both being weaned.

Results of the patient's examination were significant for an 8-mm papule with central eschar on the dorsum of her right thumb (Fig 1A); a 1.5-cm nontender, mobile, right epitrochlear lymph node; and several <1-cm right axillary lymph nodes. She had normal cognition and vision, and no hepatosplenomegaly. An ultrasound of the right arm revealed prominent right axillary and epitrochlear nodes that were not necrotic and not calcified; the largest measured 1.1 cm in diameter.

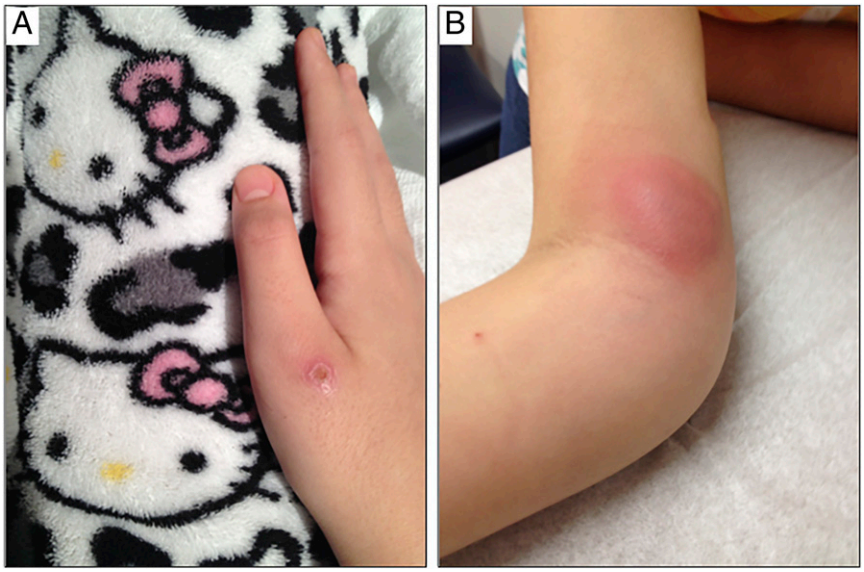

FIGURE 1
Results of the patient's examination. A, A classic inoculation papule was present on the dorsum of the hand at the time of initial presentation. B, Six months after initial diagnosis despite almost continuous treatment with dual antibiotic therapy, the patient presented with a large swollen epitrochlear node.

A presumptive diagnosis of cat scratch disease was made and confirmed 1 month later when the immunoglobulin M response to *B henselae* showed a definitive increase from <1:16 to 1:128 at a reference laboratory. Upon clinical diagnosis, the patient was treated with a 10-day course of azithromycin 5 mg/kg per day. Meanwhile, the methylprednisolone pulse therapy was decreased to 250 mg weekly × 3 and then stopped, and prednisone was continued at 20 mg every other day. However, the lymphadenopathy did not resolve and, 2 months later, she presented to the clinic with tender swelling of the right epitrochlear node, now measuring 3 × 3 cm, and a 1×1 cm axillary node. She was treated with azithromycin (10 mg/kg per day) plus trimethoprim/sulfamethoxazole (10 mg trimethoprim per kilogram per day) for 4 weeks, and the oral prednisone was tapered to 10 mg every other day. Trimethoprim/sulfamethoxazole was chosen as the second agent rather than rifampin because of a concern for drug interactions between rifampin and corticosteroids.

Four months after the initial diagnosis, the patient developed a draining sinus tract from her right arm. She was again given azithromycin (10 mg/kg per day), this time with rifampin (12 mg/kg per day) with some apparent reduction in drainage from the sinus tract. However, 2 months later, while still taking these antibiotics, the patient presented with a large acute swelling of the right epitrochlear node, which now measured 6 × 7 cm with fluctuance and increased tenderness (Fig 1B). She had limitation in range of motion in the right elbow and was admitted for incision and drainage of the infected node. She was treated for a presumed bacterial superinfection of the lymph node, but abscess fluid from the inflamed region grew no organisms. A portion of the abscess fluid was submitted for polymerase chain reaction (PCR) assay for *Bartonella*, and results of this testing were positive.

After incision and drainage, the patient continued on the azithromycin and rifampin treatment regimen. However, 1 month later, she

had persistent drainage from the right elbow sinus tract and experienced an increase in size of a right axillary node. Subsequently, 9 months after her original diagnosis, the patient underwent excision of all affected lymph nodes and the draining sinus tract. The previous incision and drainage procedure made excision of the epitrochlear nodes difficult. Hence, 3 separate incisions were used to excise nodes between the elbow and the axilla, including fibrous tracts. A large axillary node was also excised as the final step for removal of all palpable disease. Microscopic examination of the submitted lymph nodes and soft tissue revealed numerous necrotizing granulomas (Fig 2) involving lymph nodes and soft tissue. Results of histochemical staining for bacteria (ie, Gram stain, Steiner and Steiner silver stain), fungus (ie, periodic acid Schiff stain), and mycobacteria (ie, acid-fast bacilli, Fite stain) were negative on all tissue submitted. Results of microbiologic cultures were also negative. Results of the PCR for *Bartonella* performed on sections from the submitted tissue were positive and confirmed persistent *Bartonella* infection. Two weeks after the surgery, the patient's antibiotics were stopped, and she maintained progressive improvement with no palpable lymph nodes and gradual healing of the surgical wounds.

Of note, the patient never developed neutropenia or leukopenia throughout the course of the illness. She was compliant with her medications according to self-report and parental report. At no point in the treatment course did she demonstrate hepatosplenomegaly, persistent abdominal pain, hepatitis, or retinitis. The results of an abdominal ultrasound performed at the end of therapy were normal, and the MPGN remained in remission.

DISCUSSION

Regional lymphadenitis due to *B henselae* or *Bartonella quintana* infection is a common disease of childhood, with a worldwide distribution and an annual incidence estimated at between 3.7 and 9.3 per 100 000 persons.[1] *Bartonella* are Gram-negative extracellular bacilli that are difficult to culture; diagnosis is usually made by using serologic testing, ideally with demonstration of an increase between acute and convalescent titers.[2] PCR can distinguish between *B henselae* and *B quintana* with high specificity, but the sensitivity of this test is lower than serology results. In our case, PCR was useful in demonstrating that the pathogen was persistently present in excised tissue.

Cat scratch disease is usually a self-limited condition with resolution of tender lymphadenopathy within 2 to 8 weeks.[2,3] In 1 prospective trial, 90% of patients had resolution of lymphadenopathy after 16 weeks.[4] In murine studies, *B henselae* is mostly cleared by cell-mediated immunity, with significant induction of a Th1 cytotoxic T-cell response.[5] Immunocompetent children almost invariably control dissemination of the disease, with few exceptions.[6]

The efficacy of antibiotics in speeding the resolution of *Bartonella*-associated lymphadenitis is uncertain. A placebo-controlled study found that a 5-day course of azithromycin treatment was efficacious in decreasing the size of the affected lymph nodes within the first 30 days of treatment, but patients exhibited similar resolution beyond 30 days regardless of treatment.[4] Azithromycin is the most commonly used antimicrobial agent, but other antibiotics with efficacy include clarithromycin, rifampin, ciprofloxacin, and trimethoprim/sulfamethoxazole.[7] Parenteral gentamicin is also effective.[8] The American Academy of Pediatrics' Committee on Infectious Diseases recommends a 5-day course of azithromycin as a treatment option in immunocompetent children with no complications.[8] This treatment regimen is recommended for all patients with painful adenitis, hepatic or splenic involvement, or immunocompromised status.

Most of the concern for immunocompromised patients centers on dissemination of disease, which has been reported in transplant patients.[9,10] Dissemination can include a range of manifestations, including encephalitis, retinitis,

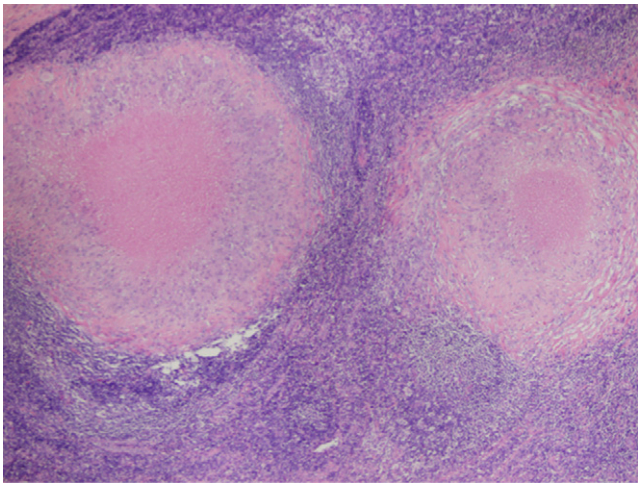

FIGURE 2
Necrotizing granulomatous inflammation involving an epitrochlear lymph node (hematoxylin and eosin staining; original magnification 100×). Results of the PCR assay performed on tissue sections from this lymph node were positive for *Bartonella*.

bacillary angiomatosis, and peliosis. Persistent adenopathy is rare, even among immunocompromised patients.[11,12] Indeed, our hospital treats a high volume of immunocompromised patients; we are unaware, however, of other cases of *Bartonella* adenitis persisting for such an extended period of time despite prolonged antibiotic treatment. To the best of our knowledge, no similar cases have been reported in the literature. Our patient, while immunosuppressed, had a relatively intact immune system. Although she was receiving small doses of prednisone, she was never neutropenic and showed no signs of T-cell suppression, such as reactivation of herpes simplex virus, cytomegalovirus, or *Candida* mucositis. Our patient showed no signs of systemic disease, perhaps because she was persistently maintained on antibiotic therapy. Further studies are needed to determine whether she had an unusual pathogenic variant or a subtle immune defect that caused her prolonged disease.

For regional lymphadenopathy, surgical incision and drainage have been associated with development of draining sinus tracts and are therefore not recommended.[13] However, an excisional biopsy can be performed if adenopathy persists or if the diagnosis is unclear. Excisional biopsy offers the dual benefit of diagnostic studies for confirmation of tissue infection with elimination of concern for other infectious agents and a favorable outcome.[14] In the present case, complete excisional biopsy of all palpable nodes was the only intervention that led to resolution of the disease. We therefore suggest that unrelenting *Bartonella* lymphadenitis beyond 16 weeks should prompt consideration of surgical excision of affected sites.

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Pediatrics 2015;135;e1514
DOI: 10.1542/peds.2014-2923 originally published online May 11, 2015;

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