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CLINICAL VIGNETTE

Head and Neck Lymphadenopathy in a Young Man

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A 30-year-old male veteran without significant past medical history presented to primary care with a 2 week history of a progressively enlarging right-sided neck mass. The mass appeared about one week after suffering a right elbow abrasion from a fall from his bicycle. It was initially non-tender and pea-sized, but subsequently doubled in size and became painful. He reported feeling feverish twice during the past two weeks, but had not taken his temperature. He denied weight loss, night sweats, respiratory symptoms, throat pain, or ear infection. He noticed that his eyes were both red, speculating that it might be due to wearing the same pair of contact lenses for a prolonged period, but denied pain, irritation or pruritis. He also denied recent sick contacts or travel history. His family history was unremarkable. He smoked one pack of cigarettes weekly starting from age 21. He did not use alcohol or illicit drugs. He served one tour each in Afghanistan and Iraq. His only medication was an acetaminophen-aspirin-caffeine combination for pain.

On physical examination, he was well appearing and afebrile; heart rate was 63 beats per minute and blood pressure 139/88 mmHg. His conjunctiva were moderately injected bilaterally and his oropharynx was clear and moist, without exudates or erythema. Neck exam was notable for a 2.5 cm firm, mobile, and tender node located in the inferior aspect of the right posterior cervical lymph node group. There were no overlying skin changes or fluctuance. No other lymphadenopathy was noted. Cardiopulmonary exam was unremarkable and he had no hepatosplenomegaly. A healed abrasion over the right elbow was noted. Initial hematological and metabolic laboratory studies showed only a slightly elevated lactate dehydrogenase (184; normal range 87-165).

Given concerns for lymphoma, the patient was referred to Otolaryngology clinic. However, he returned to primary care within 2 days, stating that his neck mass had become larger and more tender, and that a second smaller lump behind his right ear had developed. During this visit, a history of cat and puppy ownership was elicited, though he denied ever being scratched or bitten. Repeat exam was unchanged except for a new sub-centimeter nodule

located in the right occiput that was firm, mobile, and tender. Cat scratch disease was now added to the differential along with malignancy, and new lab studies were ordered, including Epstein-Barr virus and Bartonella henselae serologies. He was empirically prescribed azithromycin, and a CT scan of the neck was ordered.

Patient was evaluated in Otolaryngology clinic six days later. His neck masses had become non-tender, but remained stable in size. A flexible laryngoscopy was performed but unremarkable. A fine needle aspiration of the masses was scheduled, and the patient was encouraged to proceed with the previously ordered CT scan.

The patient was seen back in primary care clinic one month after the initial visit. He had not completed the CT or biopsy but his neck masses had resolved after taking azithromycin. Follow-up on laboratory studies revealed positive Bartonella henselae serologies, with IgG titer >1:1024 and IgM titer = 1:320.

Discussion

Cat scratch disease (CSD) generally causes a benign, self-limited, regional lymphadenopathy, though other manifestations including central nervous system, ocular, and hepatosplenic involvement may often occur^{1,2,3}.

CSD is caused by Bartonella henselae bacterium, a fastidious, intracellular, Gram-negative rod also implicated in other diseases including bacillary angiomatosis and peliosis hepatis. These latter diseases are often but not exclusively seen in immunocompromised individuals¹.

Transmission

Domestic cats serve as a major asymptomatic reservoir for the organism⁴. Horizontal transmission between cats is believed to be by the cat flea, Ctenocephalides felis⁵ but not via direct transmission⁶, suggesting that arthropod vectors are required⁷. Ownership of kittens and cats with fleas has been linked most closely to CSD, and inoculation

into humans is thought to occur via a scratch or bite from an infected cat^{1,8}, with subsequent introduction of contaminated cat saliva or flea feces into the skin⁹. However, despite the name, CSD can be transmitted through other modalities including dog scratches¹⁰, and there is controversial evidence to suggest that arthropods, including fleas and ticks, may potentially be culprits for direct transmission of *B. henselae* into humans as well¹¹.

Clinical manifestation

Approximately three to ten days following inoculation of *B. henselae* into the skin, patients generally develop a cutaneous lesion at the site of the scratch or bite, known as the primary inoculation lesion^{1,3}. The lesion ranges from 0.5 to 1 centimeters in size and progresses through vesicular, erythematous, and papular phases. Systemic symptoms such as low-grade fever and malaise may occur in up to half of patients, along with headache, anorexia, weight loss, nausea/vomiting, and splenomegaly³. The cutaneous lesion is followed by lymphadenopathy, which emerges proximal to the primary inoculation lesion approximately one to two weeks after inoculation¹. In a series of 1200 patients, 85% of cases involved a single node, though when regional lymphadenopathy occurs, generally two to three enlarged nodes are affected¹. Lymph nodes usually range from one to five centimeters in size, occasionally enlarging up to eight to 10 centimeters¹². Affected nodes are tender and may occasionally suppurate or become erythematous.

The location of lymphadenopathy depends on the primary inoculation site, though common areas include axillary, epitrochlear, cervical, supraclavicular, and submandibular nodal groups. The most common site of lymphadenopathy has been variably described, with one author suggesting axillary lymph nodes were most commonly affected, comprising 48.8% of 1200 patients¹, and another study suggesting that the neck was the most commonly affected area, comprising 43% of 246 patients¹³. Overall, though, CSD is one of the most common causes of head and neck lymphadenopathy, with a frequency of 13.4% in a study group of 454 patients, suggesting that CSD should be strongly considered in the differential for head and neck masses¹⁴.

Unusual, self-limiting manifestations of CSD may also occur. Encephalopathy, initially presenting as a convulsion followed by coma or combative behavior, may last for days to weeks¹. Hepatosplenic

involvement may include masses in the liver or spleen yielding granulomas on biopsy¹⁵. Musculoskeletal manifestations can include myalgia, arthritis or arthralgia, tendinitis, osteomyelitis, and neuralgia¹⁶. Ocular manifestations include Parinaud's oculoglandular syndrome, neuroretinitis, and focal retinochoroiditis¹⁷. Parinaud's oculoglandular syndrome occurs subsequent to inoculation of the bacterium near or in the eye, either through cat bite or lick, or by self-inoculation from another site. This syndrome presents as eye redness/conjunctivitis, foreign body sensation, and often a serous discharge that can occasionally become purulent. Ocular symptoms are accompanied by ipsilateral preauricular lymphadenopathy^{1,17, 18}.

Diagnosis

CSD is often suggested by its typical clinical picture. Traditionally, the presence of three of four criteria must occur for diagnosis: traumatic cat contact, a positive skin-test response to the CSD antigen, characteristic histopathological findings, and lack of other causes for lymphadenopathy². However, definitive diagnosis is through laboratory studies. The *B. henselae* bacterium is fastidious and slow growing, which makes culturing difficult. PCR of lymph nodes or pus is highly sensitive and specific for detecting DNA of the bacterium, though the invasive nature of this method is a drawback¹⁹. Serology for *B. henselae* is often sent for CSD diagnosis especially in cases of atypical clinical manifestations. A positive IgM is strongly associated with active disease, though the window for positive IgM is narrow as its production is brief; testing within the first six weeks of symptoms onset is most optimal. Testing for IgG is thought to be less useful, as populations with a high seroprevalance yield a lower sensitivity and specificity¹⁹. Tissue examination of lymph node biopsies may reveal nonspecific findings consistent with a granuloma formation¹. Warthin-Starry silver stain may be applied to visualize *B. henselae* bacilli.

Treatment

CSD is usually self-limited and resolves within one to six months. The decision to treat with antibiotics thus remains controversial. The 2005 Infectious Diseases Society of America practice guidelines are equivocal about antibiotic treatment in typical CSD, though, if antimicrobial therapy is chosen, a short course of azithromycin is recommended²⁰. This recommendation was based on the findings of one randomized double blind study that showed significant improvement in lymph node size within

the first 30 days of azithromycin treatment as compared to placebo, though after 30 days, the rate or degree of lymph node volume resolution became insignificant²¹. Other authors, however, remain less convinced about antimicrobial therapy for immunocompetent patients with mild to moderate manifestations of CSD. One paper recommended against antibiotics in typical CSD as the data for treatment is sparse, and that antibiotics have a risk of adverse drug reactions and of promoting resistant flora. However, if patients manifest large bulky adenopathy, azithromycin is a viable option²². Other less well studied antibiotics for CSD include rifampin, ciprofloxacin, trimethoprim/sulfamethoxazole, and gentamicin²³. In the case of complicated CSD, including ocular, neurologic, and visceral manifestations, treatment would be indicated, and combination therapy with doxycycline and rifampin is recommended²².

Summary, case wrap up

In assessing for possible CSD, the clinical picture is most important. Serologies may be useful, depending on the clinical presentation. Manifestations of CSD vary, and can include visceral, neurologic, and ocular syndromes. Guidelines for treatment of CSD are sparse, and the decision to use antimicrobials should be based on the individual case, recognizing that CSD is often self-limiting.

In our patient, we were initially concerned about Hodgkin's Lymphoma because of the enlarging, rubbery lymph nodes (without an initial history of pet exposure). Subsequent evaluation by Otolaryngology also raised their concern for malignancy. Hence, even in more experienced hands, the diagnosis of neck lymphadenopathy is not always clear, though serendipitously the diagnosis became obvious in retrospect. Interestingly, the patient may have had Parinaud's oculoglandular syndrome, though this remains speculative.

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