Abstract:
A 17-year-old male adolescent presented to the emergency department initially with abdominal pain and headache which progressed to neck swelling and vision changes over a period of several weeks. He was noted to have a 4 cm by 4 cm right supraclavicular lymph node and visual acuity of 20/200 in the right eye and 20/70 in the left eye. Further testing, imaging, and a thorough history revealed the source of his illness and unusual ophthalmologic findings.

Keywords:
cat scratch disease; Bartonella henselae; neuroretinitis; macular star

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Hindsight Is 20/20

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A 17-year-old male adolescent with no significant medical history presented to the emergency department (ED) with a chief complaint of abdominal pain with a duration of 2 weeks. He described the pain as bilateral lower quadrant cramping which migrated from right to left. The pain fluctuated throughout the day but did not seem to be associated with any specific movement. He had tried occasional nonsteroidal anti-inflammatory drugs without relief. He had been eating a regular diet without issue and denied constipation, diarrhea, nausea, or vomiting. He also complained of 2 days of chest pain and headache. His chest pain was located in the left parasternal area without radiation, both dull and sharp, and occurring at both rest and with exertion. There was no increase in work of breathing, diaphoresis, or syncope. His headache was bilateral frontal in location, slightly worse on the right. There was no trauma, blurred vision, aura, or previous history of similar headache. On review of systems, the patient did have some intermittent, bilateral upper extremity numbness and weakness which mostly occurred with overuse at work. The patient denied constitutional symptoms of fever, weight change, chills, or night sweats. The remainder of the review of systems was negative, in particular, no genitourinary symptoms, sexual activity, rash, or melena. The patient did have a surgical history of inguinal hernia repair at age 5 years. He denied taking any medications other than nonsteroidal anti-inflammatory drugs, including herbal supplements and over the counter products, and had no reported allergies. There were no obvious exposures to potential gastrointestinal pathogens such as contaminated food, unpasteurized products, or unpurified water sources. He denied all drug, tobacco, and alcohol use. His family history was positive for

multiple myocardial infarctions (all >50 years of age) and hypertension.

His physical examination revealed an obese male in no apparent distress. Vital signs were normal with temperature 36.7°C, heart rate 74/min, blood pressure 124/76 mm Hg, and respiratory rate 20/min. His height was 182 cm, weight was 129 kg, and body mass index was 38.9 kg/m^2. The remainder of his physical examination was unremarkable with the exception of tenderness in the lower bilateral quadrants of the abdomen without rebound, guarding, or abnormal bowel sounds. No masses or hepatosplenomegaly was noted. Chest and abdominal radiographs, as well as an electrocardiogram, were obtained and interpreted as normal. Serum lipids and troponin were normal. No other laboratory work was ordered. The treating physician felt that abdominal radiographs demonstrated a large stool burden, so the patient was discharged home with the diagnosis of constipation, precordial catch syndrome, and acute chest pain.

The patient returned to the ED 21 days later with the chief complaint of right-sided neck swelling which started 1 week after the initial ED visit and had been gradually increasing in size. The swelling would also fluctuate in size with manipulation to the area such as putting on a shirt overhead. The area was tender to palpation with some overlying erythema but no drainage. There was no history of trauma to the area or similar swelling in the past. He now reported blurred vision in the right eye for 2 days prior to presentation. He had previously worn contact lenses, which he had not been wearing for several months; however, he felt his vision was worse than before. There was no dizziness, diplopia, or syncope. The predominant features of his initial visit had improved, with resolution of headache, chest pain, abdominal pain, and weakness of the extremities. He reported no fevers. Additional exposure history revealed he had lived in the lower Mississippi River Valley region for the majority of the past year and had traveled to North Carolina to go camping for a brief period. He denied tick exposure, cave exploration, animal contact, or consumption of unpurified water. Vital signs were again within normal limits. His physical examination was notable for a tender, nonfluctuant, freely mobile, right-sided supraclavicular swelling measuring 3 cm by 4 cm without overlying erythema. No visual examination was documented. The patient had a repeat chest radiograph that was normal. Laboratory studies, including a comprehensive metabolic profile, lactate dehydrogenase (LDH), uric acid, and complete blood count, were completed and were within normal limits. He had a tuberculin skin test placed and was discharged with a diagnosis of right-sided supraclavicular lymphadenopathy, with a referral to the outpatient surgery clinic for the lymphadenopathy.

He returned to the ED 3 days later to have the tuberculin skin test read (negative); however, he was found to have significant worsening of his vision on the right, now with progression to the left eye. He described the vision in the right eye as having "two large dark spots on the side with a normal line in the middle." He described the vision in the left eye as slightly blurry. The patient also had worsening, recurrent headache symptoms, primarily on the right side. His headache was notably worse in the morning but improved throughout the day. He had no nausea or vomiting. Bilateral upper extremity weakness and numbness had returned as well with more frequent episodes that occurred with just normal activity. Vital signs were within normal limits with the exception of his temperature of 38.1°C. Physical examination was notable for an increase in the previously noted tender, right-sided supraclavicular swelling, now measuring 4 cm by 4 cm. He had upper extremity weakness of 4/5 with an otherwise normal neurologic examination. Visual acuity testing revealed 20/200 in the right eye and 20/70 in the left eye without correction. Comprehensive metabolic profile, complete blood count, LDH, and uric acid were again normal. Erythrocyte sedimentation rate was elevated at 25 mm/h (normal 0-10 mm/h), and C-reactive protein was elevated at 45 mg/L (normal <9 mg/L). Rapid plasma reagin was negative. Toxoplasmosis and Lyme serologies were sent out for measurement. The patient had an ultrasound of the neck swelling which was interpreted as demonstrating right supraclavicular lymphadenitis with central calcification. Ophthalmology consultation revealed 3+ optic head edema with a hemorrhage along the superotemporal border of the disc and intraretinal edema extending to the macula in the right eye. There was nasal sectoral optic nerve head edema of the left disc with a small hemorrhage inferonasally. No afferent pupillary defect was noted. Magnetic resonance imaging of the brain and orbits was completed, demonstrating normal brain matter with some elevation of the right optic nerve head (Figure 1) and flattening of the left optic nerve head, suggestive of papilledema. A lumbar puncture in the lateral decubitus position was completed with an opening pressure of 36 mm and closing pressure of 28 mm. Cerebrospinal fluid analysis was normal without pleocytosis, and the culture was negative for growth after 3 days. He was admitted to the hospital for further workup.

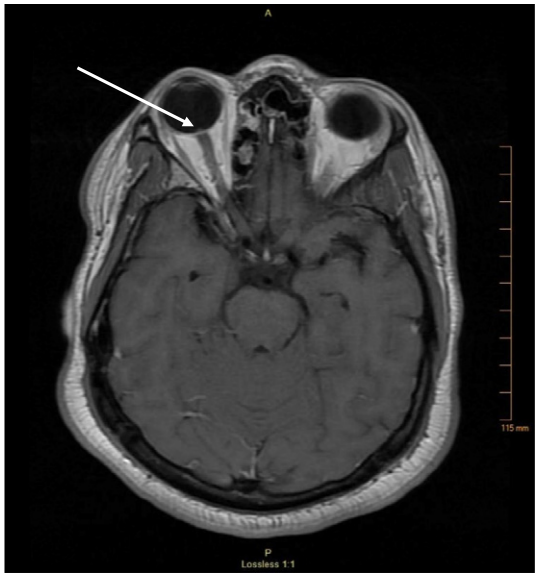

Figure 1. Magnetic resonance imaging of the brain revealing elevation of the right optic nerve head.

DIFFERENTIAL DIAGNOSIS

Patients presenting with multisystem problems such as headache, lymphadenopathy, and visual changes are most concerning for systemic illnesses including infectious diseases, inflammatory conditions, and malignancy. In children, infections comprise the predominant etiologies for such illnesses. Although the differential for unilateral lymphadenopathy is fairly limited, the presence of visual changes encompasses other less common etiologies.

Lyme disease is a tick-borne illness caused by the bacterial family of Borreliaceae primarily occurring in New England and the eastern Mid-Atlantic regions of the United States.[1] Typical presentation includes erythema migrans at the site of inoculation, followed by systemic signs and symptoms of arthralgias, headache, fatigue, fever, and regional lymphadenitis. Lymphadenitis is not typically unilateral or supraclavicular. Neurologic involvement is varied and may include meningitis and peripheral neuropathy. Visual changes have been reported in cases of pediatric Lyme disease due to inflammation of the optic nerve (optic neuritis, perineuritis or papillitis), posterior uveitis, as well as secondary to increased intracranial pressure.[2,3]

Histoplasmosis is the most frequently diagnosed endemic fungal infection in the United States and is highly prevalent in the Mississippi River Valley region.[4] Following inhalation, histoplasma spreads from the lungs throughout the reticuloendothelial system via alveolar macrophages. Hilar or paratracheal adenopathy is typically seen; however, concomitant peripheral adenopathy, particularly of supraclavicular nodes, can be seen as they drain into mediastinal nodes. Disseminated infection is generally limited to immunocompromised individuals; however, immunocompetent patients may be symptomatic during the acute phase of infection. Symptoms include fever, fatigue, bone marrow suppression, lymphadenopathy, and hepatosplenomegaly. Patients with disseminated histoplasmosis typically have some pulmonary involvement ranging from pneumonitis to respiratory failure, and as many as 70% have gastrointestinal manifestations.[5] On ophthalmologic examination, patients may have chorioretinitis with yellow-white punched out round spots (histospots) in the retina. Ocular symptoms may include distorted vision; however, most patients are visually asymptomatic.

Tuberculosis must be considered in all cases of unexplained supraclavicular adenopathy because it could be a manifestation of scrofula. This is caused by *Mycobacterium tuberculosis*, and although pulmonary tuberculosis is most common, many other locations of infection may occur. Patients may present with abdominal symptoms, adenitis, cardiac involvement, constitutional symptoms, vertebral infiltration, or ocular involvement. The most common extrapulmonary sites of infection in children are the central nervous system and lymphadenitis.[6] Non–tuberculosis mycobacterium infections are more commonly seen in the United States and can cause unilateral lymphadenopathy, which is often mistaken for mass due to indolent progression. Patients are usually young children with anterior cervical rather than supraclavicular lymphadenopathy but typically do not have visual changes. It is important to have a knowledge of local epidemiological data and take a history of risk factors that might lead to exposure to tuberculosis.

Several viral diseases are known to present with constitutional symptoms and have ocular involvement as well. Most common are the herpes viruses (herpes simplex 1 and 2), measles, influenza, varicella, human immunodeficiency, Epstein-Barr virus, West Nile virus, and cytomegalovirus. All may present with headache, fever, malaise, lymphadenopathy, and elevated inflammatory markers. However, unilateral lymphadenopathy is rarely seen. Ocular involvement can be seen during the acute infection or postinfectious immune-mediated phenomena and can manifest as chorioretinitis; neuromyelitis optica; neuroretinitis; optic neuritis; papillitis; or, as a late finding, optic disc atrophy. There has been some benefit observed with antiviral therapy and corticosteroid treatment, but occasionally, visual damage may be permanent despite treatment.[7]

It is critical to rule out malignancy in patients presenting with signs of systemic illness, and although supraclavicular lymphadenopathy can be due to other causes, malignancy is the most common cause of adenopathy at this location.[8] Lymphoma may present with constitutional symptoms and diffuse lymphadenopathy; however, this is typically nontender. This is the most common cancer in the adolescent period, so exclusion is critical.[9] Uric acid and LDH are frequently elevated. Diagnosis requires confirmatory biopsy usually performed by a surgeon or interventional radiologist. Mediastinal masses are frequently involved, so chest radiograph should be completed especially if there are respiratory abnormalities. Acute forms of leukemia can result in ocular and central nervous system complications. Optic nerve edema may result from leukemic infiltration of the optic nerve head or increased cerebrospinal fluid pressure. Direct leukemic infiltration of the optic nerve with a reduction in vision is a visual emergency requiring immediate local radiotherapy.[10]

CASE PROGRESSION AND DIAGNOSIS

After admission, further questioning revealed the patient had received a new kitten 6 months prior to the onset of symptoms and had been scratched multiple times on the hands. The kitten was healthy, so the family did not feel the need to report this exposure on initial interviews. *Bartonella henselae* serology was sent, and due to high degree of suspicion of bartonellosis, the patient was started on doxycycline 100 mg twice a day and rifampin 300 mg twice a day and was discharged from the hospital. It was theorized that the patient may have developed hepatosplenomegaly early in the illness course causing abdominal pain, which could have been missed on examination because of the patient's body habitus. He then went on to develop lymphadenopathy and ocular findings which resulted in the diagnosis. *Bartonella* titers resulted positive with an IgG of 1:512 and IgM of 1:40. Seven days after discharge, the patient was seen in neuro-ophthalmology clinic where he was noted to have neuroretinitis of the right eye with stellate macular exudate (macular star) as shown in Figure 2. The infectious disease team recommended a treatment course of 4 weeks with both doxycycline and rifampin. Two months after discharge from the hospital, the patient was seen again in neuro-ophthalmology clinic, and he was noted to have complete resolution of initial ophthalmic findings. Visual acuity returned to 20/20 in the right eye and 20/50 in the left eye, which was consistent with his baseline vision. The patient was prescribed corrective lenses for his previous astigmatism but was otherwise cleared from the neuro-ophthalmology service. All other symptoms had resolved, and the patient was discharged from outpatient follow-up.

CASE DISCUSSION

Cat scratch disease (CSD) is typically a mild, self-limited, infectious disease which involves regional lymphadenopathy in immunocompetent hosts but can progress to disseminated disease and involve

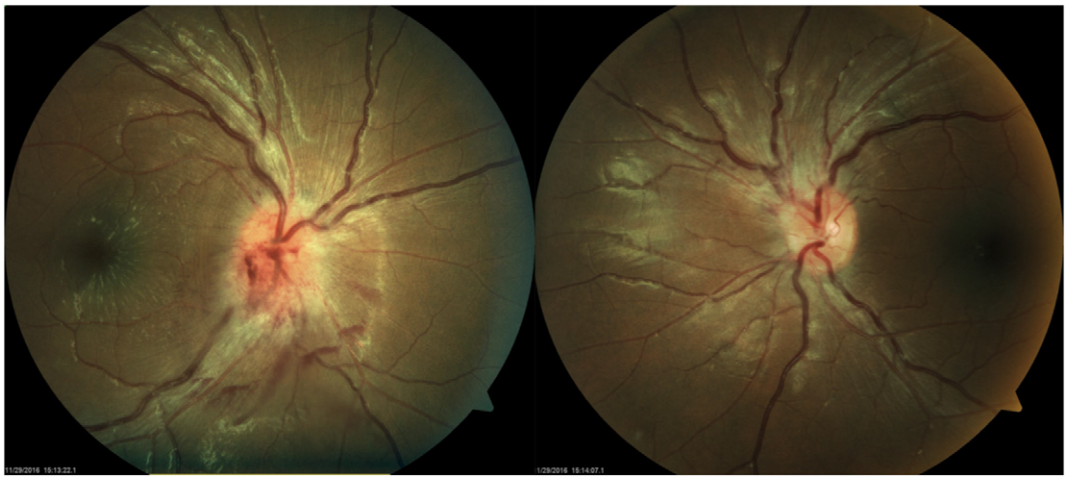

Figure 2. Fundus photos of the right and left eye, respectively. The right optic nerve has high-grade edema with associated disc and preretinal hemorrhages, marked disruption of the retinal nerve fiber layer, and intraretinal edema extending to the macula. There is evidence of a macular star. The left optic nerve has sectoral swelling superonasally with associated retinal nerve fiber layer disruption. There is no macular star noted in the left eye.

multiple organ systems. Infection is caused by the gram-negative, intracellular pathogen *B henselae*.[11] The primary reservoir for this organism is cats, with an overwhelming majority being asymptomatic despite being bacteremic. Kittens are frequently the source of infection and are more likely to be bacteremic, with one California study finding 90% of domestic felines less than 1 year of age with positive *B henselae* serology.[12] Transmission can occur from a scratch or bite of an infected cat, direct contact with fluids at mucosal surfaces or breaks in the skin, or bites from fleas who have fed on bacteremic cats.

Organisms are taken up by macrophages and circulated in the reticuloendothelial system. Cytokine release results in inflammation and angiogenesis, which causes the classic features of tender lymphadenopathy, fever, and elevated inflammatory markers.[13] This typically presents as localized lymphadenitis proximal to the inoculation site. A primary lesion is often noted 3-10 days after inoculation, and regional lymphadenopathy may manifest anywhere from 2 weeks to 2 months from exposure. The most common site of inoculation are the hands, which results in the most common location of lymphadenopathy being the axillary and epitrochlear lymph nodes. Patients may develop fever, malaise, or abdominal pain, but symptoms are generally minimal and self-limited. Unusual presentations are thought to be due to disseminated infection, and although this is most commonly seen in immunocompromised individuals, it may be seen in immunocompetent patients as well. Visceral organ involvement may result in hepatosplenomegaly, and granulomas can often be seen on abdominal imaging. Patients may have musculoskeletal findings such as arthralgias, arthritis, myalgias, and even osteomyelitis. Neurologic manifestations include cerebellar ataxia, encephalitis, radiculitis, status epilepticus, and transverse myelitis. Other rare presenting symptoms include hypercalcemia, thrombocytopenic purpura, pneumonia, prolonged fever, endocarditis, and septic shock.

There are 2 common types of ocular involvement. Granulomatous conjunctivitis with regional lymphadenopathy is an uncommon condition called *parinaud oculoglandular syndrome* which affects approximately 22 000 people annually in the United States.[14] The disease is transmitted when there is exposure on or near the eye and often involves pain, swelling, and excessive tearing. Patients typically have inflammation of the conjunctiva and eyelid and often have preauricular, submandibular, or anterior cervical lymphadenopathy. One to two percent of all cases of CSD demonstrate neuroretinitis, making it the most common infectious cause of neuroretinitis. Visual loss is often accompanied by symptoms of floaters or ocular pain and usually follows a prodrome by 2 to 4 weeks.[15] Early in the disease course, patients may have a swollen disc (papillitis) with peripapillary retinal striae extending from the disc toward the macula. Later, a star-shaped pattern of macular exudate (macular star) becomes more prominent. An afferent pupillary defect may be present if there is asymmetric inflammation of the anterior portion of the optic nerve.

Diagnosis is made by having a high degree of clinical suspicion. Serological testing to detect serum antibodies to *B henselae* can aid in making a diagnosis. IgM production can be easily missed because it is transient. An IgG titer of >1:256 is considered to signify acute infection. Low positive IgG titers between 1:64 and 1:256 should be repeated in 2 weeks. Blood culture and polymerase chain reaction testing are of limited value given the fastidious nature of the organism.

Treatment of CSD is frequently debated and mostly based on immune status of the patient and severity of disease. For patients with classic CSD, most studies show no benefit from treatment and that illness will resolve over 4 to 6 weeks. Some experts elect to treat painful lymphadenopathy with azithromycin due to a randomized, controlled trial which demonstrated more rapid reduction in node size, but no difference in time to complete resolution was observed.[16] Treatment is also warranted in immunocompetent patients with evidence of disseminated disease, particularly hepatic, splenic, or retinal involvement. All immunocompromised patients should be treated. Incision and drainage are not recommended because these pose a risk for the formation of a chronic draining sinus tract. Common drug regimens include azithromycin plus rifampin, or doxycycline (if age > 8 years) plus rifampin. In cases of ocular involvement, doxycycline and rifampin (regardless of age) are preferred because of their central nervous system and intraocular penetration. Corticosteroids are sometimes used as adjuvant therapy, but their benefit is questionable. Follow-up should be closely maintained with ophthalmologist, and prognosis is generally favorable if treatment is started early.

SUMMARY

Patients presenting to the emergency department with headache, lymphadenopathy, and visual changes raise concern for systemic illness which requires investigation. Patients with visual complaints should always have a visual examination documented with evaluation of the optic nerve. If there is concern for ocular pathology, ophthalmologic consultation is recommended. When screening for potential sources for CSD, always ask directly about cats, specifically

kittens, as these can be an unrecognized exposure to the patient or their family. Although most cases of CSD are self-limited, treatment may be warranted in certain instances. ✚

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