Case Challenge

A Persistently Febrile Adolescent with Headache and Vision Changes

Alexandra Milloff Butler, MD; Vini Vijayan, MD; Colette Meehan, MD; Rochelle Wilson, MD; and Michele Lossius, MD

A 15-year-old, previously healthy Hispanic male presented with a 6-week history of intermittent fevers associated with night sweats, a 10-pound weight loss, and fatigue. Initially, his fever occurred at intervals of 2 to 4 days, but in the 2 weeks prior to admission his fever occurred daily. Fever was associated with chills and rigors, and severe frontal retro-orbital headache. He reported intermittent diplopia and blurry vision. There was no altered mental status. The patient also developed cough, shortness of breath, and upper abdominal pain in the days preceding admission. His activity was severely restricted due to these symptoms, and he had missed more than 1 week of school.

The patient’s past medical history was significant for mild intermittent asthma. Family medical history was significant for a mother with hepatitis C. The patient had moved to Florida from Massachusetts 6 months prior to presentation, and lived with his mother, stepfather, and two siblings. He denied any sexual activity, tobacco use, drug use, or substance use. His vaccinations were up to date.

At presentation, the patient’s vital signs were notable for a temperature of 39.3°C, heart rate of 126 beats per minute, and respirations of 22 breaths per minute with saturation of 98% on room air. His weight was 50.3 kg, which was at the 17th percentile for age, and it was noted to be 3.5 kg lower than that recorded at his pediatrician’s office 1 month before admission. The patient’s physical examination was notable for a frail-appearing boy with rigors. Ophthalmologic exam was normal. Oropharynx was mildly erythematous without exudates, and mucous membranes appeared dry. Chest auscultation demonstrated decreased air entry bilaterally with expiratory wheezing and scattered bi-basilar crackles. Abdomen was diffusely tender with guarding but without rebound. The rest of the exam was unremarkable.

Laboratory evaluation revealed a white blood cell count of 28,200/mm³, hemoglobin of 11.3 g/dL and platelets of 403,000/mm³ with 87% neutrophils, 6% lymphocytes, 4% monocytes, and 3% eosinophils. Basic metabolic panel and liver panel were within normal limits. He was found to have elevated liver enzymes.

Editor’s note: Each month, this department features a discussion of an unusual diagnosis. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at pedann@Healio.com.
erythrocyte sedimentation rate (ESR, 98 mm/hour) and C-reactive protein (CRP, 189.3 mg/L). Chest X-ray was normal. Abdominal ultrasound was within normal limits. His cerebrospinal fluid (CSF) analysis was unremarkable as were blood, urine and CSF cultures. Viral respiratory panel was negative.

Computed tomography (CT) of head was negative for intracranial pathology. The patient continued to be febrile 48 hours after admission, and his headache and visual complaints continued to worsen despite empiric antibiotic therapy with ceftriaxone. Doxycycline was added to broaden coverage for rickettsial diseases and Mycoplasma pneumoniae (Mp) while studies were pending.

Laboratory testing for Lyme disease, babesiosis, Rocky Mountain spotted fever, as well as enterovirus, cytomegalovirus, Legionella, Ebstein-Barr virus, syphilis, herpes simplex virus, and HIV were negative. A purified protein derivative was placed and subsequently determined to be negative. Bone marrow aspiration and biopsy with flow cytometry were negative for malignancy. Ophthalmological examination was negative for optic neuritis and CSF studies were negative for markers of multiple sclerosis.

Magnetic resonance imaging of the brain showed ischemic demyelination in the watershed areas of the anterior and middle cerebral arteries, prompting a CT angiogram that demonstrated multiple bilateral branched vessels that were proximally smaller in caliber than the more distal aspect, with mild irregularity, indicative of vasculitis of the middle cerebral arteries (Figure 1). An evaluation for autoimmune vasculitis was negative. Given his persistent symptoms and the discovery of vasculitic changes, he additionally received methylprednisolone 20 mg/kg for one dose as well as intravenous immunoglobulin (IVIG) at a dose of 1g/kg over 24 hours.

Diagnosis:

*Mycoplasma Pneumoniae-Associated Central Nervous System Vasculitis*

The patient’s Mp immunoglobulin M serology was determined to be positive at 1.16 U/L (range, < 0.76 U/L), and this was confirmed with convalescent titers that increased over fourfold within 3 weeks. The patient’s symptoms resolved within 48 hours of administration of doxycycline, IVIG, and steroids. He was discharged home in good condition, and continued to do well at his 6-month follow-up.

**DISCUSSION**

Mp typically causes upper and lower respiratory infections, and is transmitted by aerosols. Mp infection
usually presents with a cough as well as constitutional symptoms including fever and malaise, although Mp is also known to cause a wide array of extra-pulmonary symptoms involving almost every organ system, including the central nervous system (CNS).

These extra-pulmonary symptoms may resemble other disease processes, so the diagnosis may be delayed or missed. The diagnosis of extra-pulmonary Mp disease is difficult for several reasons, even when the clinician considers it in the differential. The organism is very difficult to grow in culture conditions, and often the diagnosis is made over several weeks by noting a fourfold increase in serological testing between paired acute and convalescent samples. Clinicians must have a high suspicion in children with neurological symptoms who do not have clear diagnoses.

Both neurologic and vascular complications from Mp are common in the literature; however, they are still thought to be under-reported. Multiple neurological complications have been reported in association with Mp, with meningoencephalitis and encephalitis being the most common. Additionally, transverse myelitis, Guillain-Barre syndrome, seizures, cerebellar ataxia, psychosis, and aseptic meningitis can also occur. Interestingly, both neurological and vascular symptoms seem to occur in patients who do not have the typical respiratory manifestations of Mp, and so clinicians must have a high index of suspicion for Mp in patients who may have atypical clinical features.

The pathogenesis of CNS disease associated with Mp is unclear. Direct invasion of the CNS by Mp has been implicated, but toxin-mediated disease has also been suggested. Immune-mediated damage caused by either Mp-induced autoimmune processes or immune complex formation and subsequent inflammatory reactions are also described in the pathogenesis. Mp may locally affect a vascular wall by inducing cytokines and chemokines such as tumor necrosis factor-alpha, interleukin (IL)-6, and IL-8 resulting in vascular occlusion without systemic hypercoagulability.

The treatment of Mp-associated CNS disease has not been established. The benefit of using antibiotics for treatment of CNS conditions associated with Mp has been variable. Macrolides are the antibiotics of choice, however, tetracyclines and fluoroquinolones are also effective. Steroids have been used in patients with severe CNS syndromes, based on the presumed role of cytokines in inflammation. Additionally, if given in the acute phase of the illness, steroids may accelerate recovery. Steroids, in addition to high-dose IVIG, have been associated with improved outcomes in cases of stroke related to Mp infection in children. CNS manifestations associated with Mp are generally considered self-limiting with a favorable outcome, as in our patient, and the drastic improvement noted with immune-modulating therapy further suggests the pathogenesis is immune mediated.

CONCLUSION
Our case highlights the importance of considering the association of intracranial vasculitis with Mp infection and also emphasizes the need for increased familiarity with CNS manifestations of Mp. Clinicians should have a heightened awareness of the association of Mp and several CNS manifestations, including vasculitis.

REFERENCES