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Eosinophilic Meningitis in a Previously Healthy 13-Year-Old Child

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A previously healthy 13-year-old male developed acute onset of a bi-temporal headache. The headache persisted, and two weeks later, he was diagnosed with sinusitis and was given amoxicillin. On illness day 17, he experienced worsening headache, slurred speech, transient left facial droop, right hand numbness, and dizziness. At a local emergency department (ED), magnetic resonance imaging (MRI) of the brain showed no significant abnormalities, though images were obscured by artifact from his orthodontic hardware. He was discharged without a specific diagnosis after his neurologic symptoms had resolved. On illness day 19, the patient had return of hand tingling and slurred speech and presented to the Children's Hospital Colorado ED. He was diagnosed with an atypical migraine and was treated with ketorolac, diphenhydramine, and prochlorperazine. His symptoms improved, and he was discharged.

On illness day 20, the patient experienced severe right eye pain and recurrence of his headache. He returned to his local ED and was hospitalized after minimal clinical improvement with treatment for migraine. At that time, his Romberg sign was abnormal, he was ataxic, and he had diplopia. On illness day 22, he underwent a lumbar puncture (LP) because of concern of pseudotumor cerebri. The cerebral spinal fluid (CSF) showed white blood cell count (WBC) of 763/mm^3 (with a differential of 80% lymphocytes, 15% monocytes, and 5% eosinophils), red blood cell count (RBC) of 2/mm^3, protein of 49 mg/dL, and glucose of 54 mg/dL. Intravenous acyclovir was started but was discontinued when polymerase chain reaction assay (PCR) of the CSF for herpes simplex virus returned negative. Bacterial and fungal cultures of the CSF were negative. He was discharged home after a three-day hospitalization.

Over the next several weeks, he remained stable but continued to have intermittent headaches and ongoing diplopia. Then, forty-seven days after initial onset of illness, the patient developed severe right eye pain and photophobia and returned to the local ED. Repeat LP showed an opening pressure of 44 cm H_20, WBC of 347/mm^3 (with a differential of 53% lymphocytes, 26% monocytes, 21% eosinophils), RBC of 3/mm^3, protein of 127 of mg/dL, and glucose of 35 mg/dL. He was subsequently transferred to Children's Hospital Colorado.

On admission, the patient was afebrile and had normal vital signs. Physical examination showed papilledema with splinter hemorrhages, left esotropia with subjective diplopia, and no signs of meningismus. Complete blood count (CBC) showed WBC of 9,100/mm^3 (with differential of 44% neutrophils, 33% lymphocytes, 11% monocytes, 12% eosinophils), hemoglobin of 16.1 g/dL, hematocrit of 47.1%, and platelet count of 320,000/mm^3. Repeat lumbar puncture on day 50 of illness showed an opening pressure of 34–35 cm H_20, WBC of 273/mm^3 (with a differential of 46% lymphocytes, 46% eosinophils, 5% monocytes, 3% macrophages), RBC of 32/mm^3, protein of 107 mg/dL, and glucose of 38 mg/dL. A brain MRI, performed after removal of the patient's braces, was normal. Additional blood testing was negative, including: EBV PCR, *Bartonella henselae* IgG/IgM, *Bartonella quintana* IgG/IgM, *Blastomyces* antibody, *Coccidioides* IgG/IgM, *Histoplasma* antibody, HIV 1/2 antibodies, *Cryptococcus* antigen, *Toxocara* antibody, and *Toxoplasma* IgG/IgM. CSF acid-fast bacillus stain, cryptococcal antigen, and mycobacterial, fungal, aerobic and anaerobic cultures were also negative.

Upon further questioning, the patient reported that he and his family had traveled to their vacation home in Kauai, Hawaii for the two weeks directly preceding the onset of symptoms. They had not stopped on any other Hawaiian island. During the trip, the family had found a dead rat in their hot tub, though the patient had not been in it. They had consumed organic lettuce from a local vendor and fresh produce from their herb garden. The patient denied exposure to seafood, mollusks or other exotic cuisine. The family had stopped in Los Angeles on their return trip home but had not ventured outside of the city. The patient denied any other travel, animal contact, or known insect bites.

The patient's exposure history prompted additional testing of the CSF, which confirmed the etiology of his eosinophilic meningitis.

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CSF samples from times days 47 and 50 of illness were sent to the Centers for Disease Control and Prevention (CDC), and both tested positive for *Angiostrongylus cantonensis* DNA using a specific real-time PCR, confirming the diagnosis of eosinophilic meningitis due to *A. cantonensis*. The patient was provided supportive care, and within 10 days of diagnosis, his headache completely resolved, and he no longer had diplopia or photosensitivity. One month later, fundoscopic exam showed complete resolution of papilledema. Approximately 5 months after diagnosis, the patient had his first of 3 seizures occurring in a period of several months. A repeat lumbar puncture and brain MRI were normal. An initial electroencephalogram (EEG) showed subtle slowing over the left

hemisphere, but a subsequent EEG was normal. He was treated with anticonvulsant therapy, which he currently continues.

Although eosinophilic meningitis can be caused by infections (parasitic, fungal, or bacterial), malignancies, medications, or intracranial hardware, *A. cantonensis* is the most common cause worldwide.[1] *A. cantonensis*, also known as the rat lung worm, is a nematode that lives primarily in the pulmonary arteries of rats, where the adult female worm lays its eggs. After the eggs hatch, the larvae migrate to the rat's gastrointestinal (GI) tract, are excreted in the feces, and then are eaten by mollusks, which serve as the intermediate host in the lifecycle. From mollusks, the larvae can be transmitted to paratenic hosts such as shrimp and land crabs. Humans become infected as incidental hosts by either consuming colonized intermediate or paratenic hosts, or by eating the larvae directly from contaminated produce. Once ingested by humans, the larvae migrate through the GI tract until they finally reach the central nervous system, resulting in eosinophilic meningitis.[1]

The first human infection from *A. cantonensis* was described in Taiwan in 1945.[2] Since that time, there have been over 2,800 cases reported worldwide. Only 25% of these documented cases have occurred in pediatric populations.[1] *A. cantonensis* is endemic in south Asia, especially China and Thailand, as well as the Pacific islands, Australia, and the Caribbean islands.[1] Though rats in New Orleans have been shown to be infected carriers of *A. cantonensis*,[3] human cases of *A. cantonensis* on the continental United States are rare. Almost all reported cases in the US have occurred in Hawaii. A systematic statewide review of laboratory data and medical charts in Hawaii revealed 24 cases of eosinophilic meningitis between 2001 and 2005 that were attributed to *A. cantonensis*. Of those 24 cases, 11 occurred on the island of Oahu, 9 on the Big Island, 3 on Maui, and 1 on Lanai.[4] To our knowledge, this case represents the first published report of a person contracting this disease on the island of Kauai.

A review of clinical signs and symptoms of 114 pediatric patients infected with *A. cantonensis* by Wang et al. showed that 84% of patients had headaches, 82% had nausea and vomiting, 82% had somnolence, 80% had fever, 76% had constipation, 34% had abdominal pain, 15% had muscle extremity weakness, and 10% had blurry vision or diplopia.[1] The symptomatology was similar among adult patients, but adults were much less likely to have nausea and vomiting, fever, somnolence, and abdominal pain. A separate review in Taiwan found that children generally develop more severe disease compared with adults: 23% of pediatric patients had papilledema on fundoscopic exam and 28.7% developed meningoencephalitis compared with 12% and 5% respectively among adults.[5,6]

The diagnosis of angiostrongyliasis is usually based on consistent clinical symptoms and exposure history in the setting of laboratory findings demonstrating eosinophilia in the peripheral blood and CSF. During infection, eosinophils may account for 7–36% of peripheral WBC,[1] and eosinophilic meningitis, defined as the presence of greater than 10% eosinophils or greater than 10 eosinophils/mm^3 in the CSF,[7] is present. As occurred in our case, the CSF may not meet the definition of eosinophilic meningitis based on the percentage of eosinophils, but calculation of the absolute eosinophil count (AEC) can still

point to the diagnosis. Our patient's initial CSF contained only 5% eosinophils, but the CSF AEC of 38 eosinophils/mm^3 nevertheless fulfilled the definition of eosinophilic meningitis.

Definitive diagnosis of *A. cantonensis* can only be made upon direct visualization of worms in the CSF, but this is a very rare event. Immunologic assays are available in a few laboratories around the world; however, none is available commercially in the United States. The PCR performed at the CDC in this case was originally developed and validated to detect *A. cantonensis* in host animals.[8] Based on testing of CSF samples from six patients with serologically-confirmed angiostrongyliasis, the sensitivity of this real-time PCR was 83%. Ongoing specificity testing indicates that this test detects only *A. cantonensis* and no other causes of meningitis.[9] Although this PCR assay is still undergoing clinical validation, to our knowledge, our patient represents the first PCR-confirmed case of *A. cantonensis* in a pediatric traveler returning to the continental United States.

Since angiostrongyliasis is rarely fatal, treatment with anti-helminthic drugs, such as albendazole or mebendazole with or without corticosteroids, remains controversial. A randomized controlled trial of 71 patients with eosinophilic meningitis showed a statistically significant decrease in headache duration from 16.2 to 8.9 days with albendazole treatment compared with placebo.[10] Still, other studies report exacerbations of neurologic symptoms when anti-helminthic drugs are used alone for treatment, likely due to an inflammatory response to the dying parasite.[11] Further studies to define the optimal treatment strategy are needed.

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