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The Brief Case: *Angiostrongylus cantonensis* Eosinophilic Meningitis in a Returned Traveler

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CASE

A 22-year-old male without significant prior medical history presented to the hospital with headache and double vision of 1 month's duration. He reported a trip to the island of Hawaii 1.5 months prior, where he spent time on the beach, including in the ocean, and ate various types of seafood, including sushi, crab, mahimahi, and shrimp. No other close contacts from his travel became ill. His symptoms began 2 weeks after his return, with headaches, malaise, red eyes, and ear pain. All of these symptoms resolved with a short course of oral antibiotics except the headache and malaise. Approximately a week from his initial symptoms, he developed fevers, and a lumbar puncture was performed, showing 270 white blood cells (WBC)/μl, 2 red blood cells (RBC)/μl, 85% mononuclear cells, 12% eosinophils, and 3% polymorphonuclear cells (PMN). Cerebral spinal fluid (CSF), bacterial culture, and Epstein-Barr virus (EBV) and herpes simplex virus (HSV) real-time PCRs were all negative, and he was assigned a presumptive diagnosis of viral meningitis. Two weeks later, he developed double vision. He was referred to ophthalmology, where an ophthalmologic exam revealed papilledema and bilateral cranial nerve 6 palsy. A noncontrasted brain computed tomography was performed, which was normal. Magnetic resonance imaging of the brain showed a markedly abnormal appearance of the brain and optic nerves, with a T2 hyperintense signal and enhancement in the bilateral optic nerves suggestive of acute inflammation. Additionally, scattered cerebral cortex-based nodular foci of enhancement with a T2 signal abnormality were seen. Lumbar puncture was repeated, with an opening pressure of 28 cm H_2O, 588 WBC/μl, no RBC, 61% eosinophils, 29% lymphocytes, 9% monocytes, 1% PMN, protein of 343 mg/dl, and glucose at 36 mg/dl. CSF was tested by PCR for HSV and varicella-zoster virus (VZV), and direct staining and culture were performed for aerobic organisms, fungi, and acid-fast bacillus; all were negative. Serum HIV testing was also negative. CSF flow cytometry showed marked acute inflammation with abundant eosinophils. No malignant cells were identified. A CSF cysticercosis IgG enzyme-linked immunosorbent assay (ELISA) was positive. A CSF sample was sent to the CDC for an *Angiostrongylus cantonensis* real-time PCR, which was positive. The patient was diagnosed with *Angiostrongylus cantonensis* eosinophilic meningitis with likely exposure from consumption of undercooked crab or shrimp in a known region of endemic *Angiostrongylus cantonensis* on the big island of Hawaii. He was started on prednisone and had several additional therapeutic lumbar punctures for treatment of increased intracranial pressure, with significant improvement in his clinical symptoms at the 2-month follow-up.

DISCUSSION

Eosinophilic meningitis is a rare, underrecognized clinical entity with a distinct differential diagnosis. It is defined by the presence of $\geq$10% eosinophils/μl of the total

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For answers to the self-assessment questions and take-home points, see page 3147 in this issue (https://doi.org/10.1128/JCM.02429-16).

CSF leukocytes and thus can easily be missed if it is not the predominant cell type. One of the most common causes of eosinophilic meningitis, *Angiostrongylus cantonensis*, is the rat lungworm first described in 1935 by H. T. Chen, who named it after Canton, China, where it was recovered. The adult worms inhabit and lay eggs within the pulmonary arteries of a variety of rodents. Once hatching occurs, the first-stage (L1) larvae enter the alveolar space, migrate up the trachea and down the alimentary tract, and finally are excreted in the feces. Slugs, as well as land planarians and terrestrial and aquatic snails, serve as the intermediate hosts, either by L1 larval penetration into the mollusk or by the ingestion of contaminated rodent feces. Larval development continues within the mollusk, where the third-stage (L3) infective larvae develop. Following ingestion by rodents, the L3 larvae migrate to the brain, where they develop into young adults before migrating to the subarachnoid space. From there the young adult enters the venous system and finally undergoes sexual maturation within the pulmonary arteries. Humans serve as an accidental host and thus develop infection through ingestion of slugs, snails, land planarians on vegetables contaminated with infective larvae, or paratenic hosts, such as crabs or shrimp. Larvae are unlikely to survive within humans, and most will die in the central nervous system (CNS). Some larvae may reach the eye chamber; however, they are unlikely to migrate to the lungs.

A. cantonensis was first seen in the United States in 1987, when it was isolated from the rat species *Rattus norvegicus*, introduced to the gulf coast of New Orleans, LA, from docked ships. Since then, it has expanded to rodent populations outside the known habitat of rats as well as to a new rat host species. In 1995, the first human case of *A. cantonensis* in the United States was described in an 11-year-old from New Orleans who became ill after ingestion of a raw snail (1). Most recently, in Houston, TX, there were two human cases without apparent known risk factors of travel or a classic mollusk ingestion (2).

Although the parasite was first recognized in Hawaii in the early 1960s, human cases were rarely reported until late 2004, when a cluster of infections was seen on the island of Hawaii. Consumption of fresh produce, particularly unwashed, homegrown produce, rather than mollusk ingestion, was implicated in this epidemic. These may relate to changes in snails/slugs, particularly the introduction and the increasing number of *Parmarion martensi* organisms, which were first discovered on the island of Hawaii in 2004. The juvenile forms of *P. martensi* tend to be smaller than other slugs/snails and less noticeable on produce; they also result in a higher proportion of the population being infected, carry a higher parasite load, and more frequently enter human habitats than adult *P. martensi* (3). Hawaii is now the epicenter for *A. cantonensis*, where it has remained a reportable disease since 2005 (4). The patient in this case had traveled to a region of Hawaii where the organism is endemic and had ingested potentially infected paratenic hosts (shrimp and crabs).

The clinical presentation of angiostrongyliasis ranges from self-limiting meningitis, eosinophilic meningitis, encephalitis, and radiculomyelitis to permanent neurologic injury or even death. Symptoms are mostly attributed to larval migration through the CNS and eye or by the inflammatory reaction provoked by the dying worm, which results in increased intracranial pressure. Prodromal symptoms, including enteritis, cough, or sore throat, may occur as the larvae pass through different organ systems. Fever and malaise, though nonspecific, may also occur prior to the development of CNS disease (5). Peripheral eosinophilia was observed in 66 to 68% of cases, and CSF eosinophilia of $\geq$10% was noted in approximately 70 to 95% of cases (5, 6). Thus, the laboratory finding of serum and especially CSF eosinophilia is an invaluable laboratory marker for *A. cantonensis* infection in the absence of other adjunct laboratory diagnostics. Both *Baylisascaris procyonis* and *Gnathostoma spinigerum* infection can induce CSF eosinophilia; however, the clinical syndrome is typically characterized as meningoencephalitis, which is a rapid and fatal clinical course and can cause intracerebral hemorrhage or subarachnoid hemorrhage, particularly in the case of gnathostomiasis. Importantly, neither of these organisms has been reported from Hawaii and therefore would not generally be considered in the differential diagnosis for this case.

The definitive laboratory-based diagnosis of angiostrongyliasis remains challenging. Identification of larvae in CSF or the vitreous humor confirms the diagnosis but is rarely ever seen. The ultimate identification of the larvae should be performed only by an experienced parasitologist, as the larvae can be mistaken for *Strongyloides stercoralis*. Serologic testing for *A. cantonensis* is severely limited. Reagents (ELISA, immunoblot, or dot-immunogold assay reagents) are not commercially available in the United States, and the CDC does not offer this testing. Real-time PCR detection of *A. cantonensis* can be used to detect the nematode from CSF samples; however, it is currently available only in the United States through the CDC. About 12% of cases show intermittently positive and negative real-time PCR results, indicating that levels of *A. cantonensis* DNA in CSF may fluctuate during the course of illness (7). This suggests that both PCR and immunodiagnosis or recollection of CSF for PCR on subsequent days may be necessary to establish the diagnosis. The patient in this case likely had a false-positive cysticercosis IgG ELISA antibody result, as the patient had no known risk for cysticercosis. While cross-reactivity between cysticercosis and *Echinococcus granulosus* is well characterized, no direct cross-reactivity between cysticercosis and *A. cantonensis* has been observed to date. It is important to note that cross-reactivity for cysticercosis IgG ELISAs is known to include other helminths, including filarial infections, and thus this case also emphasizes the importance of appropriate parasite serology utilization.

A. cantonensis should be considered in the differential diagnosis of a patient presenting with eosinophilic meningitis, especially those with travel or epidemiological links to regions of endemic *A. cantonensis*, even if a history of classic mollusk exposure is absent. The diagnosis of angiostrongyliasis is challenging. However, it is an important subject for clinicians and laboratories, as it is no longer simply a sporadically imported tropical disease and requires esoteric testing beyond documenting CSF eosinophilia.

SELF-ASSESSMENT QUESTIONS

1. Which of the following options is the most likely diagnosis for a returning traveler from Hawaii with a headache, a stiff neck, photophobia, fever, and a CSF profile of WBC at 270/μl, RBC at 2/μl, mononuclear cells at 85%, eosinophils at 12%, and PMN at 3%?
   A. *Leptospira* spp.
   B. *Angiostrongylus cantonensis*
   C. Herpes simplex virus 2
   D. *Trichinella spiralis*
2. Which one of the following pathogens can also induce CSF eosinophilia?
   A. *Acanthamoeba*
   B. *Taenia saginata*
   C. *Baylisascaris procyonis*
   D. *Trichostrongylus*
3. Which of the following is well known to generate cross-reactive IgG antibodies to *Taenia solium* (cysticercosis) antigens?
   A. *Toxocara canis*
   B. *Entamoeba histolytica*
   C. *Echinococcus granulosus*
   D. *Endolimax nana*

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