Eosinophilic Meningitis due to *Angiostrongylus* and *Gnathostoma* Species

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Eosinophilic meningitis can be the result of noninfectious causes and infectious agents. Among the infectious agents, *Angiostrongylus cantonensis* and *Gnathostoma spinigerum* are the most common. Although angiostrongyliasis and gnathostomiasis are not common in the United States, international travel and immigration make these diseases clinically relevant. Both *A. cantonensis* and *G. spinigerum* infection can present as severe CNS compromise. Diagnoses of both infections can be challenging and are often clinical because of a paucity of serological assays readily available in the United States. Furthermore, there are conflicting recommendations about treatment for angiostrongyliasis and gnathostomiasis. To further explore the emerging nature of these helminthic infections, a case description and review of *A. cantonensis* and *G. spinigerum* infections are presented. The clinical severity of eosinophilic meningitis and diagnosis of these infections are highlighted.

CASE DESCRIPTION

A previously healthy 44-year-old man presented with progressive myalgias, paraesthesias, and headache. His symptoms started after a 5-week vacation to the South Pacific, where he ate seafood, drank stream water, and was exposed to insects and bats. Three days after returning to the United States, he had fevers (maximum temperature, 38.9°C) and upper respiratory symptoms. He then developed trunk and right extremity neuropathic pain that generalized to his whole body. He was noted to have peripheral eosinophilia. He was admitted to the hospital for pain control and evaluation.

On the day of hospital admission, the patient developed a headache with severe photophobia. A complete blood count was notable for a WBC count of 12.2 cells/μL with 9% eosinophils. He had a normal erythrocyte sedimentation rate and C-reactive protein level. An initial lumbar puncture revealed a normal opening pressure, a WBC count of 55 cells/μL (with 96% lymphocytes), a glucose level of 54 mg/dL, and a protein

level of 97 mg/dL. Head and cervical spine MRI findings were normal. The patient was empirically treated with ceftriaxone and acyclovir.

Because of a worsening headache and ongoing migratory hyperesthesia, a follow-up lumbar puncture on hospital day 7 revealed an opening pressure of 49 mm water (normal, <21 cm water) and a WBC count of 754 cells/μL, with an automated differential of 44% neutrophils, 35% lymphocytes, 10% plasma cells, and 11% monocytes. Manual reevaluation of the CSF smear revealed 44% eosinophils with no neutrophils. Findings of repeat head MRI were normal, and an ophthalmologic evaluation revealed left-sided papilledema.

Because of the patient's peripheral and CSF eosinophilia and travel history, he received a diagnosis of helminthic meningoencephalitis. He initiated dexamethasone treatment secondary to the elevated intracranial pressure; his headache and photophobia improved, but there was no change in his paraesthesias. He did not receive antihelminthics because of concern for an inflammatory reaction to dying parasites.

The patient was readmitted to the hospital 1 month later, because he developed tender nonmigratory nodules on his lower extremities. Because of continued concern for a helminthic infection in the context of continued neurologic compromise and new dermatologic lesions, he was given a 28-day course of albendazole therapy. A lumbar puncture 2 months after his initial presentation revealed a normal opening pressure,

a WBC count of 118 cells/μL (with 16% eosinophils), an RBC count of 689 cells/μL, a glucose level of 48 mg/dL, and a protein level of 99 mg/dL. Findings of lower extremity MRI were normal.

Serum and CSF samples were sent to the Faculty of Tropical Medicine, Mahidol University (Thailand) for helminthic immunoassay. The acute-phase serological and CSF specimens collected during the patient's initial hospitalization tested negative for angiostrongyliasis and gnathostomiasis. The convalescent-phase serum and CSF samples, collected 76 and 66 days after presentation, respectively, tested positive for antibodies against an *Angiostrongylus cantonensis* 31-kDa antigen by immunoblot assay.

REVIEW

It is estimated that 20%–70% of people who travel to resource-poor settings will have an illness associated with their travels [1]. Although many of these patients will have self-limited febrile, gastrointestinal, or dermatologic diseases, some patients present with more-severe infections [1]. *Angiostrongylus* and *Gnathostoma* species, common causes of eosinophilic meningitis, are infectious agents that can cause severe disease.

Eosinophilic meningitis is defined as the presence of ⩾10 eosinophils/μL in CSF or at least 10% eosinophils in the total CSF leukocyte count [2]. In a series of 217 samples from patients with meningitis, CSF eosinophilia was reported in 2.3% of samples [2]. Because eosinophils are not normally found in the CSF, their presence is suggestive of a number of different etiologies that can be divided into infectious and noninfectious categories [3]. Although this article will focus on angiostrongyliasis and gnathostomiasis, other infections, including *Baylisascaris* infection, toxocariasis, and neurocysticercosis; malignancies; medications; and the presence of intracranial foreign bodies can produce eosinophils in the CSF [3].

Because eosinophilic meningitis is caused by few etiologic agents, the laboratory identification of CSF eosinophilia is important [2]. Eosinophils can be distorted or destroyed during CSF processing and can be mistaken for neutrophils if CSF analysis is automated [2]. Also, eosinophils are more detectable with Wright or Giemsa staining [2].

ANGIOSTRONGYLIASIS

A. cantonensis is the most common parasitic cause of eosinophilic meningitis outside Europe and North America [4]. Human cases of angiostrongyliasis, a neurotropic helminthic infection, have been reported in the South Pacific, Asia, Australia, and the Caribbean [4, 5]. In the United States, case series have been reported from Hawaii, where *Angiostrongylus* infection is endemic [5]. There have also been reports of rats infected with *Angiostrongylus* species in Louisiana [6].

The life cycle of this worm includes an adult form that lives and lays eggs in the pulmonary arteries of rodents [7]. *Angiostrongylus* species reproduce when the eggs hatch and the larvae migrate into the pharynx, are swallowed by the rodent, and are passed in a larval stage in the stool [7]. The larvae become second- and third-stage larvae when they are swallowed or penetrate a mollusk species [7]. Humans acquire the infection when they ingest these infected intermediate hosts or a variety of paratenic hosts, including prawns, crabs, and frogs, or when they eat raw vegetables containing material from the intermediate or paratenic hosts (e.g., shells and secretions) [7]. The larvae then enter the systemic circulation after passage through the gastrointestinal tract and migrate to the CNS, where they mature and cause disease in nonrat hosts [7].

Clinical manifestations of angiostrongyliasis usually occur 1 week to 1 month after exposure and include fever, headache, and painful paresthesias [4]. The clinical spectrum can range from mild disease to meningitis or, uncommonly, encephalitis [4]. The most common clinical manifestations in a case series of 34 patients were a bitemporal or frontal headache (in 90% of patients), stiff neck and vomiting (56%), paresthesias (54%), and fevers (41%) [5]. The predominance of migrating painful paresthesisas is particularly noteworthy in the context of angiostrongyliasis. Less common presentations include cranial nerve palsies, most commonly of nerves 7 and 8 [8]. In addition, visual disturbances can occur secondary to a direct larval invasion of the ocular structures [7]. The natural course of the disease often involves spontaneous resolution of symptoms after 1–2 weeks, although the headaches and paresthesias can persist for weeks to months [4, 5, 9].

The diagnosis of angiostrongyliasis is based largely on the history of possible exposure, clinical presentation, and CSF eosinophilia [3]. Peripheral eosinophilia can be present. CSF findings indicative of angiostrongyliasis include cloudy CSF, elevated opening pressure, an increased protein level, a normal glucose level, and an elevated absolute leukocyte count with eosinophilia [4, 9]. Angiostrongyliasis does not usually produce focal lesions on head CT or MRI [3].

Although angiostrongyliasis is often a self-limited disease, treatment options consist of symptomatic interventions, steroid therapy, antihelminthic therapy, or a combination of these strategies. Symptomatic treatment includes serial lumbar punctures, to alleviate increased intracranial pressure, and analgesics [10]. In a prospective study, Punyagupta et al. [11] found a >60% resolution of headaches with analgesia alone in a cohort of patients who had received a clinical diagnosis of eosinophilic meningitis. Because the severity of angiostrongyliasis is thought to be secondary to the host inflammatory reaction, steroids have been studied as a potential treatment [12]. The benefit of steroids in relieving headaches was shown in a prospective trial of patients with clinical eosinophilic meningitis treated with prednisone over a 2-week period [13]. A number of studies

have not found steroids to be helpful in the treatment of *Angiostrongylus* infection [11, 13].

Although 2-week treatment courses with anthelmintics have been effective in animal models of angiostrongyliasis, the role of this treatment in humans is controversial [10, 11]. Jitpimolmard et al. [15] designed a randomized prospective study involving patients with eosinophilic meningitis who were treated with albendazole for 2 weeks. In the treatment group, there were fewer patients with persisting headaches after 2 weeks (21% vs. 41%) and the duration of symptoms was shorter (8.9 days vs. 16.2 days), compared with the control group [15]. An inflammatory reaction to dying parasites has not been found in animal or human studies [3, 4].

A number of studies have evaluated combination treatment with steroids and anthelmintics. Chotmongkol et al. [10] studied the treatment of eosinophilic meningitis with albendazole and prednisilone for 2 weeks. They found that, with this combination treatment, the median duration of symptoms was 4 days and that 11.5% of patients had continued headache after treatment [10]. Although albendazole is the drug of choice for treating angiostrongyliasis, combination treatment with prednisilone and mebendazole has been studied in serologically confirmed cases of *Angiostrongylus* infection [14]. Among patients treated with prednisilone and mebendazole for 2 weeks, the median duration of headaches was 3 days, and 10% of patients had unresolved headache [14].

GNATHOSTOMIASIS

G. spinigerum infection is endemic in Southeast Asia, particularly in Thailand; the prevalence of such infection is increasing in Mexico and Central and South America [8, 16]. The definitive hosts of *Gnathostoma* species are dogs and cats [8, 16]. After ingestion of third-stage larvae, the helminths mature in the stomach of the host, and eggs are passed in the feces [8, 16]. The larvae that hatch can develop into the second stage when they are ingested by crustaceans of the genus *Cyclops*. These crustaceans are then eaten by a range of paratenic hosts, including fish, frogs, pigs, snakes, fowl, and eels [8, 9, 16]. The helminth matures into the third phase when it migrates to host muscle tissue and encysts [17]. Infection can be passed between paratenic hosts, including humans, when infected muscle is ingested [17]. Humans become infected through ingestion of raw or undercooked paratenic hosts or, rarely, through direct larval penetration of the skin [8, 9, 16].

In humans, the ingested third-phase larvae do not mature but are aggressive migrators [9]. The destructive nature of this infection is thought to occur through direct mechanical- and toxin-mediated injury, as well as a local host-inflammatory reaction to *Gnathostoma* larvae [8, 9].

Infection with *Gnathostoma* species is typically categorized into cutaneous, visceral, and CNS forms [16]. *Gnathostoma*

infection can cause symptoms that recur for 10–12 years, whereas *Angiostrongylus* infection can cause symptoms that recur for several months [7, 8]. The intermittent nature of symptoms can be diagnostically challenging [16].

The dermatological manifestations of *Gnathostoma* infection include panniculitis, creeping eruptions, and pseudofurunculosis with a predilection to the trunk [8]. These lesions are associated with recurring pain, pruritis, and erythema [8]. In addition, because this parasite can migrate through superficial and deep tissues, involvement of most organ systems is possible. Similar to *Angiostrongylus* infection, *Gnathostoma* infection can directly invade the eye and cause pain, uveitis, increased intraocular pressure, and blindness [8].

Although *Gnathostoma* infection is not neurotropic, it can invade the CNS [9]. In the CNS, *Gnathostoma* infection is often more severe than *Angiostrongylus* infection [3]. CNS gnathostomiasis usually presents with radicular pain and paresthesias of the trunk and extremities and, less frequently, with paresis or paralysis [3, 8]. These symptoms are thought to result from direct migration of the worm along cranial or peripheral nerves into the spinal cord [3, 8]. The usual progression of symptoms is radicular pain followed by onset of headaches; weakness or paralysis may occur in some cases [8]. Direct burrowing of the organism into neural tissue can result in meningeal inflammation, myelitis, or encephalitis, and damage to the cerebral vasculature can result in subarachnoid hemorrhages [3, 8]. In addition, cranial nerve palsies of nerves 2–12 have been described [8].

Diagnosis of gnathostomiasis is challenging. The presence of peripheral and CSF eosinophilia, history of travel to regions with high risk of infection, and progression of symptomotology are suggestive of this diagnosis. The absence of peripheral eosinophilia, however, has been reported in a small subset of patients with *G. spinigerum* infection [8]. Analysis of CSF specimens from patients with gnathostomiasis usually reveals xanthochromia, an elevated opening pressure in one-half of infected patients, pleocytosis with eosinophilia, normal glucose levels, and normal or elevated protein levels [8, 18]. Head CT may reveal nodular lesions, areas of hemorrhage with tracks, and even hydrocephalus [8, 18].

Treatment of gnathostomiasis differs on the basis of the location of infection. For cutaneous disease, albendazole and ivermectin therapy have been effectively used, although multiple courses are needed for some patients [18]. Two studies revealed cure rates of dermatologic gnathostomiasis of 94.1% and 93.8% after 21 days of albendazole treatment [19, 20]. For dermatologic gnathostomiasis, a 21-day treatment course of ivermectin was found to be as effective as a 21-day treatment course of albendazole [19]. A single dose of ivermectin had a lower cure rate than did a 21-day course of albendazole (76% vs. 92%), although the difference was not statistically significant

[21]. Treatment of neurological gnathstomiasis is primarily supportive, because the role of steroids and antihelminthics in CNS gnathostomiasis has not been clearly defined [8, 9, 17]. Similar to angiostrongyliasis, there is concern that the inflammatory reaction to dying helminths may worsen the clinical course of gnathostomiasis [3].

DIAGNOSIS OF ANGIOSTRONGYLIASIS AND GNATHOSTOMIASIS

The definitive diagnosis of both angiostrongyliasis and gnathostomiasis requires identification of the organism in host tissue. However, organism isolation in CNS is difficult and lacks sensitivity [5, 17].

For angiostrongyliasis, direct identification of the parasite in host samples has seldom been described [6]. Therefore, a number of serologic assays have been developed for angiostrongyliasis [3, 17, 22, 23]. The specificity and sensitivity of these assays vary greatly and are limited by cross-reactivity with other parasitic infections [24]. Different antigen preparations against the third and fifth larval stages have been used for Western blot analysis [4]. Monoclonal antibodies have also been developed for testing of patient samples [24]. Recently, a multiple dot–blot ELISA using unpurified *Angiostrongylus* antigen and human serum was developed, with some noted cross-reactivity to *Gnathostoma* species [23].

A range of tests for *Gnathostoma* infection, including skin testing, precipitation testing using different developmental stages of *G. spinigerum* mixed with human serum, radioimmunoassay, complement fixation, and indirect fluorescent antibodies have been developed [25]. More recently, ELISA and Western blot have also been used [17]. Previous studies have used both crude *G. spinigerum* larva extracts and a purified 24 kDa antigen to measure total and IgG subclasses [26]. Nopparatana et al. [22] purified a 24-kDa *Gnathostoma*-specific antigen from larvae with a reported specificity and sensitivity of 100%. Measurement of specific IgG subclass antibody production has been assessed as a diagnostic tool [26]. Nuchprayoon et al. [26] found that IgG1 and IgG2 antibody to whole *Gnathostoma* L3 samples had the highest sensitivity and specificity, respectively. Development of diagnostic immunoassays for *G. spinigerum* has been limited by cross-reactivity to other nematodes, including *A. cantonensis;* this highlights the need for *G. spinigerum*–specific antigen development [26].

DISCUSSION

Increasing globalization and changes in travel, migration, and international commerce are expanding the range of potential infectious diseases that might be encountered in the inpatient and outpatient settings. In the case presented here, the presence of peripheral and CSF eosinophilia in the context of a recent trip to the South Pacific made *G. spinigerum* and *A. cantonensis*

likely etiologic agents. However, there were a number of challenges in the diagnosis. An automated CSF cell count initially misidentified a large number of eosinophils as neutrophils, which if not revised, would have made the diagnosis of the patient's infection difficult. Therefore, if there is a suspicion for eosinophilic meningitis, the sample should be properly stained, and the stain should be manually read [2].

Because of the limitations of pathological and serological diagnostics, clinical features are important for the diagnosis of gnathostomiasis and angiostrongyliasis (table 1). Unlike gnathostomiasis, angiostrongyliasis is usually a self-limited clinical entity consisting of headaches, photophobia, and paresthesias. *Angiostrongylus* infection can also involve the cranial nerves and the eye [5]. In comparison with angiostrongyliasis, gnathostomiasis can persist for many years and presents with cutaneous, visceral, or neurological manifestations [16]. Migrating panniculitis, eruptions, and pseudofurunculosis are common dermatologic manifestations of *Gnathostoma* infection [8]. Neurologic manifestations of gnathostomiasis usually include radiculomyelitis, encephalitis, paralysis, and hemorrhage [3, 8]. Similar to *Angiostrongylus* infection, *Gnathostoma* infection can involve the cranial nerves and eye [8].

Although there are a number of clinical differences between angiostrongyliasis and gnathostomiasis, this case illustrates that these differences can sometimes be difficult to distinguish [2]. Clinically, our patient's prominent parasthesias and headache made angiostrongyliasis a plausible diagnosis. Although there have been case reports of patients with severe and long-term neurologic involvement after *A. cantonensis* infection, the continuation of symptoms for 8 months in our patient, as well his lower extremity nodules (although nonmigrating), are more common with gnathostomiasis [27]. Clinically, it is unclear whether this patient had angiostrongyliasis or gnathostomiasis.

In these clinically challenging scenarios, fast and accurate serodiagnosis of helminthic infection is important. Accuracy of immunodiagnosis is confounded by potential false-positive results because of cross-reaction of helminthic antigens. In addition, the timing of obtainment of samples can affect diagnosis. In this case, the acute-phase serum and CSF samples were negative for *Angiostrongylus* species, but the convalescent-phase samples were positive for *Angiostrongylus* species. The 2-month span between obtainment of CSF and serum samples likely reflects the time required for seroconversion. In a case series of acquired *A. cantonensis* infection in 12 patients, only 1 patient had a positive acute-phase serum sample, compared with 10 patients with a positive convalescent-phase serum sample [4]. Therefore, when there is a clinical index of suspicion for angiostrongyliasis, it is important to obtain serological data on convalescent-phase samples.

There are limited controlled trials that outline the benefit or harm of using antihelminthics for treatment of *A. cantonensis*

Table 1. Comparison of features of *Angiostrongylus* and *Gnathostoma* infection with the case description.

Variable	*Angiostrongylus cantonensis*	*Gnathostoma spinigerum*	Case description
Exposure	Consumption of contaminated crustaceans, mollusks, prawns, crabs, frogs, and/or vegetables; contact with rats	Consumption of contaminated poultry or fish	Consumption of seafood and contaminated water; contact with mosquitoes and bats
Geographical distribution	South Pacific, Australia, Africa, the Caribbean, Hawaii, and Louisiana	Southeast Asia, Japan, China, Mexico, Central and South America, Africa, and the Middle East	Fiji, Vanuatu, and Thailand
Onset of symptoms	Days to ~1 month	Days to months	First symptoms 3 days after return to United States
Duration of symptoms	A few months	10–13 years	>5 months
Clinical features	Headaches, photophobia, stiff neck, vomiting, parasthesias/hyperesthesias, fever, cranial nerve 8 palsy, and ocular involvement	Cutaneous: migrating, panniculitis, eruptions, and pseudofurunculosis; visceral: any organ; CNS: radiculomyelitis, encephalitis, paralysis, hemorrhage, and cranial nerve/ocular involvement	Cutaneous: nonerythematous, nonmigrating, tender nodules; systemic: self-limited fever; CNS: headache, photophobia, and paresthesias/hyperesthesias
Laboratory features	Peripheral eosinophilia, CSF: involvement, elevated open pressure, elevated WBC count, eosinophilia, elevated protein level, and normal glucose level	Peripheral eosinophilia, CSF: xanthrochromia, elevated open pressure, elevated WBC count, eosinophilia, elevated protein level, and normal glucose level	Peripheral eosinophilia, CSF: clear (2 weeks after return to United States); open pressure, 49 mm water; WBC count, 754 cells/μL; 44% eosinophils; protein level, 110 mg/dL; and glucose level, 42mg/dL
Imaging	Head MRI and CT findings usually normal	Head CT and MRI findings: hemorrhage and hydrocephalus	Head and neck MRI findings normal; extremity MRI findings normal
Serological assays	Immunoblot	Immunoblot	CSF and/or serum immunoblot assay positive for *Angiostrongylus* species
Treatment	Serial lumbar punctures and analgesics; consider steroids and antihelminthics	Cutaneous: albendazole, ivermectin; CNS infection: supportive therapy (consider steroids); no evidence for antihelminthics	Serial lumbar puncture, analgesics, steroids, and 28-day course of albendazole

and *G. spinigerum* CNS infection [3, 17]. Because of our patient's severe neurologic symptoms and progressive course of infection, he received a 28-day course of albendazole therapy, with no clinical change. Importantly, some eosinophilic meningitis treatment trials include patients who receive a diagnosis of *Angiostrongylus* infection on the basis of local epidemiology and symptomotology but not serological testing. It is possible that some treatment trials are confounded by patients with eosinophilic meningitis secondary to a different helminthic infection, given the overlap in the geographic distribution of *Gnathostoma* and *Angiostrongylus* species.

Although previous studies revealed a potential benefit of treating angiostrongyliasis with antihelminthics and steroids, the breadth of studies does not exist for neurologic gnathostomiasis. A review of the literature yielded no case series evaluating the role of antihelminthic treatment specifically for neurologic gnathostomiasis.

Finally, prevention of disease when traveling to areas of endemicity cannot be overemphasized. Although travel vaccinations and prophylaxis are important, anticipatory guidance regarding the use of appropriate clothing, limiting animal exposure, and precautions about consumption of contaminated food or water should be a mainstay of travel medicine.

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