A Severe Case of Angiostrongylus Eosinophilic Meningitis with Encephalitis and Neurologic Sequelae in Hawai‘i

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Abstract
Angiostrongylus eosinophilic meningitis is caused by infection with larvae of the rat lungworm, Angiostrongylus cantonensis. We report the case of an adult who ingested a raw, giant African snail (Achatina fulica) on the island of O‘ahu in Hawai‘i and developed an eosinophilic meningoencephalitis with severe headache, confusion, sixth cranial nerve palsy, ataxia, limb weakness, and paresthesia. He was treated with lumbar punctures to relieve pressure, high dose corticosteroids, and 14 days of albendazole. He had a prolonged convalescence, requiring 3 months of prednisone, and still had evidence of motor nerve weakness 4 months after exposure. A field investigation at the site of exposure yielded 5 of 9 Achatina fulica snails with evidence of A. cantonensis DNA by PCR. Cerebrospinal fluid samples from the patient were negative acutely but positive on day 15 of symptoms, using an investigational, real-time PCR assay. We discuss clinical management of this case in light of the current medical literature.

Keywords
Achatina fulica, Alibendazole, Angiostrongylus cantonensis, Angiostrongylus eosinophilic meningitis, Case report, Cerebral angiostrongylia, Corticosteroid, Eosinophilic meningitis, Hawai‘i, Human, Meningoencephalitis, Neuroangiostrongylia, Radiculomeningoencephalitis, Snail

Introduction
Rat lungworm infection of the human central nervous system can have devastating consequences. Although often described as a self-limited meningitis requiring no treatment, there is a spectrum of disease, and severely affected patients may suffer from encephalitis, radiculomyelitis, permanent neurologic injury, or even death. The etiologic nematode, Angiostrongylus cantonensis, persists in the pulmonary veins of the rat, its primary host, and is perpetuated by snails, its intermediate hosts. Humans are accidental hosts and acquire the infection through eating raw or poorly cooked snails and slugs, or by eating paratenic (transport) hosts such as freshwater shrimp, frogs, monitor lizards, and flatworms (Planaria), or inadvertently through eating vegetables contaminated with these hosts. Infectious larvae migrate to the central nervous system where they undergo two molts, emerging as young adult worms in the subarachnoid space. Because humans are not definitive hosts, most worms die before reaching the pulmonary arteries. Symptoms are caused by larval migration through the central nervous system and the resulting axonal damage, inflammatory reaction, and increased intracranial pressure.

The condition is often termed “angiostrongylia,” but a related nematode, Angiostrongylus costaricensis, causes a distinct gastrointestinal syndrome, so throughout this text we will use the term Angiostrongylus Eosinophilic Meningitis (AEM) for the spectrum of neurologic disease caused by A. cantonensis, from meningitis through severe encephalitis. The disease appears to have expanded from Southeast Asia and Taiwan to Australia and across the Pacific Basin during the last century. Over 2800 cases in 30 countries have been reported worldwide, including recently in the Caribbean, China, and Latin America. Several cases have been reported in travelers to endemic areas and in military personnel. Angiostrongylus cantonensis is present in the Hawaiian Islands and researchers in Hawai‘i were instrumental in proving that the nematode was a cause of eosinophilic meningitis. Over the past decade this infection has been increasingly recognized in Hawai‘i, and the State made angiostrongylia a reportable disease in 2005, after five cases of AEM were reported within a four-month period.

The diagnosis of AEM is generally made when eosinophilia is noted in the cerebrospinal fluid (CSF) in the setting of appropriate neurologic symptoms and a history of accidental or intentional consumption of molluscs or other hosts. Specific diagnostic testing for A. cantonensis is only available from certain research laboratories, and results are usually not available during the acute phase of the illness. The appropriate treatment remains controversial although several recent studies from Thailand have given some guidance. Intentional consumption of hosts might be reduced if more people were informed of the devastating results that can occur with this infection. To provide a clear picture of this rare but serious disease, we present a case of AEM with severe symptoms and prolonged neurologic sequelae in a military member serving on the island of O‘ahu. We discuss the case in light of the current medical literature.

Case Report
During the autumn of 2010, a previously healthy 22-year-old service member presented to his local clinic with a 4-day history of arthralgias and 2 days of profuse night sweats and generalized myalgia involving his trunk and limbs. He had a leukocytosis of 17,500/µl with an absolute eosinophil count of 2100/µl, and was treated symptomatically with analgesics. Two days later he returned with new onset headache, was noted to be confused, and was referred to the regional medical center.

In the emergency department, the patient denied any recent trauma or exposure to toxins, illicit substances, sick people, arthropods, or rodents. Two weeks prior to presentation, he had participated in a field training exercise on O‘ahu, but was unaware of anyone else from his unit who was ill. His past
medical history was otherwise noncontributory; he was taking no other medications, and had no known drug allergies.

Physical examination revealed a 22-year-old, Caucasian male, alert but in moderate distress from generalized pain. Blood pressure was 152/78 mmHg, pulse 93 bpm, respirations 17/min, and oral temperature 98.2 °F (36.8°C), with an oxygen saturation of 98% on room air. There were no meningeal signs and the rest of his physical examination was unremarkable. Hematology revealed a leukocyte count of 11,700/µL with 14% eosinophils (absolute eosinophil count 1670/µL). Hematocrit, electrolytes, liver function tests, and urinalysis findings were within normal limits. A non-contrast, head computed tomography (CT) was negative. A lumbar puncture (LP) was performed, and CSF analysis revealed 338 WBC/µL, with a differential of 68% lymphocytes, 20% mononuclear cells, 15% eosinophils, and 0% neutrophils. The CSF protein was 117 mg/dL and glucose was 51 mg/dL; Gram stain was negative for bacteria; fungal stain was negative for Cryptococcus, and no worms were seen. The CSF opening pressure was not recorded. A diagnosis of eosinophilic meningoitis was made.

The patient was admitted to hospital and started on 60 mg daily intravenous prednisolone for possible AEM. CSF cultures from admission were sterile. Magnetic resonance imaging (MRI) on hospital day (HD) 3 revealed subtle, leptomeningeal enhancement consistent with meningitis. The patient improved and was discharged next day with a prescription for oral prednisone.

Five days after discharge, which was day 14 post onset of symptoms (POS), the patient returned to the emergency department with complaints of feeling strange and a worsening headache. He had become confused, agitated, anxious, and not oriented to place or time. His blood pressure was 158/95 mmHg and his temperature was 100.6 °F. Physical examination was unremarkable, but WBC was 18,000/µl (absolute eosinophil count 900/µl). A CT scan without contrast was again unremarkable. Upon LP, intracranial pressure was > 55 cm H₂O, and CSF analysis yielded 1248 WBC/µL with 57% lymphocytes, 27% eosinophils, 15% mononuclear cells, and 1% neutrophils. He was re-admitted to hospital, prednisone was increased to 60 mg daily, and albendazole 600 mg orally, twice daily, was added.

The morning after readmission (day 15 POS) the patient was noted to have a left sixth cranial nerve (abducens) palsy with diplopia. Over the next 2 days his mental status worsened; he underwent a therapeutic LP and improved. Over the next several days, his confusion slowly continued to improve, but he developed ataxia, difficulty coordinating complex movements, limb paresthesias, and weakness in the intrinsic muscles of both hands and in his lower legs. On HD 7 (day 20 POS), magnetic resonance angiography demonstrated leptomeningeal enhancement with punctuate foci of restricted diffusion within the right Sylvian fissure and scattered white matter lesions with increased signal on T2-weighted and fluid attenuated inversion recovery images, consistent with inflammatory or ischemic change.

Symptoms and signs peaked on HD 9 (day 22 POS) after which the patient gradually improved, with clearing sensorium and increasing strength. He was discharged on HD 12, walking with assistance, with diplopia because of persistent abducens palsy, 4/5 right triceps strength, weakness in the intrinsic muscles of both hands, and lower extremity ataxia.

Two days after discharge, he completed 14 days of albendazole, twice daily, and a rapid prednisone taper was begun. Ten days after discharge (day 35 equivalent) the patient reported worsening of headache; so, a more gradual taper was used. By 5 weeks after discharge, the patient had greatly improved, but some motor weakness persisted. At three months, his deficits had decreased to diplopia at far leftward gaze and mild grip weakness. His gait had normalized, and while he continued to undergo physical and occupational therapy, he was able to carry on normal activities including running, although at a reduced pace. His clinical course is summarized in Table 1. The final diagnosis was AEM with encephalitis and radiculitis, probably secondary to A. cantonensis infection following ingestion of a raw snail.

Although asked at the first emergency department visit, a history of snail ingestion was not obtained until HD 6 of the second hospitalization. His symptoms had begun approximately 9 days after ingestion of the snail. During follow up the patient related that, during the field exercise on O‘ahu prior to his illness, he had swallowed an entire raw snail, un-chewed, as part of a wager.

**Field Investigation**

The case was reported to the local military public health officer. A field team, including a Hawai‘i Department of Health epidemiologic investigator and an entomologist from U.S. Army Garrison Hawaii-Schofield Barracks, conducted an environmental investigation in the area where the patient’s exposure occurred. Molluscs were readily observed, and 9 giant African snails (Achatina fulica) and one Cuban slug (Veronicella cubensis) were collected.

**Laboratory Testing**

Clinical and environmental samples were sent by Hawai‘i Department of Health as part of an ongoing research collaboration with the Division of Parasitic Diseases and Malaria, Centers for Disease Control and Prevention (CDC), for testing using real-time polymerase chain reaction (PCR). The testing protocol was originally developed for host tissue testing (rats and molluscs); validation for testing clinical specimens is ongoing.

Five (56%) of 9 A. fulica snails and the one slug were found to harbor A. cantonensis DNA. The patient’s CSF specimen collected 6 days POS (acute sample) was negative, whereas the sample collected day 15 POS (mid-course sample) was positive for A. cantonensis DNA by real-time PCR.

**Discussion**

We report a severe case of AEM with encephalitis and prolonged neurologic sequelae in an adult. The infection was acquired on the island of O‘ahu in Hawai‘i, by ingesting a raw giant African snail (Achatina fulica). Although the likely diagnosis was considered at admission to hospital, some doubt remained because the patient did not admit until 19 days after onset of illness to
Table 1. Clinical Events and Laboratory Results in a 22-Year-Old Male with Angiostrongylus Eosinophilic Meningitis.

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<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>Approximate time of snail ingestion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>9</td>
<td>4</td>
<td>Myalgias begin</td>
<td>Analgesics</td>
<td>17.5/12%</td>
<td>2100</td>
<td></td>
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<tr>
<td>13</td>
<td>6</td>
<td>First hospital admission</td>
<td>Prednisolone 60mg/d</td>
<td>11.7/14%</td>
<td>1670</td>
<td>338/15%</td>
<td>Negative</td>
</tr>
<tr>
<td>17</td>
<td>8</td>
<td>Lumbar puncture; MRI</td>
<td></td>
<td>13.2</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>18</td>
<td>9</td>
<td>First discharge</td>
<td>Prednisone 20mg/d</td>
<td>16.6/12%</td>
<td></td>
<td></td>
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<tr>
<td>20</td>
<td>11</td>
<td>Treated in ED</td>
<td></td>
<td>21.9/9%</td>
<td></td>
<td></td>
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<tr>
<td>23</td>
<td>14</td>
<td>Second hospital admission</td>
<td>Prednisone80mg/d; begin albendazole</td>
<td>18.0/5%</td>
<td>860</td>
<td>1248/27%</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>15</td>
<td>Abduscsens palsy</td>
<td></td>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26^</td>
<td>17</td>
<td>Mental status worse</td>
<td>Prednisone 80mg/d + albendazole continue; therapeutic lumbar puncture</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>28</td>
<td>19</td>
<td>Staff learns of snail ingestion</td>
<td></td>
<td></td>
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<tr>
<td>29</td>
<td>20</td>
<td>MR angiogram</td>
<td></td>
<td></td>
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<tr>
<td>30</td>
<td>21</td>
<td>Ataxia, paresthesias</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>32</td>
<td>23</td>
<td>First signs of clinical improvement</td>
<td></td>
<td></td>
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<tr>
<td>34</td>
<td>25</td>
<td>Second discharge</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>28</td>
<td>First outpatient follow up visit</td>
<td>Finish albendazole; begin prednisone taper</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>44</td>
<td>35</td>
<td>Headache worse</td>
<td>Prednisone 80mg/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>57</td>
<td>48</td>
<td>PCR data received</td>
<td>Tapering prednisone more slowly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>85</td>
<td>76</td>
<td>Diplopia resolved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>99</td>
<td>90</td>
<td>Mild abduscsens and limb weakness persists</td>
<td>Off prednisone</td>
<td></td>
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^days post ingestion of snail. ^days post onset of symptoms. "no further laboratory data available

eating the snail. _Achatina fulica_ from the area of ingestion were later confirmed to carry _A. cantonensis_. A real-time PCR assay, currently under validation for diagnosis of clinical samples, amplified _A. cantonensis_ DNA from the patient’s mid-course, but not acute CSF. Therapeutic LPs, corticosteroids, and antihelminitics were all used for treatment. The patient required a month of high dose steroids plus a 2-month taper and still had residual weakness 4 months post exposure.

In making the diagnosis of AEM, a history of potential or actual ingestion of raw or poorly cooked hosts is important, but the history elicited from a patient may be unreliable, because the patient has no memory of eating the usual hosts, the host was chopped up in contaminated raw food such as inadequately washed salad, or the patient is too embarrassed to admit it. Our patient revealed eating the snail only after his condition had severely worsened. However, we knew he had touched the snails, and that _A. cantonensis_ is present in the Hawaiian Islands. The Hawai’i Department of Health has received reports of 38 cases of autochthonous AEM from 2005 through 2011 (SY Park, 2011, unpublished). In addition, AEM has been seen previously in military personnel serving in Hawai’i. Neurologic symptoms and signs at presentation are generally non-specific, but more characteristic signs, such as cranial nerve palsies, limb weakness, paresthesias, and ataxia may occur. This patient had headache, myalgias, and confusion on day 6 POS, but developed a characteristic abduscsens nerve palsy on day 15 POS, and then paresthesias, limb weakness, and ataxia evolved over the next week. CT usually does not show abnormalities in patients with AEM, but MRI may show subtle findings. In our case, the MRI on day 8 POS had only subtle leptomeningeal enhancement, but magnetic resonance angiography on day 20 POS showed somewhat more characteristic, although non-specific, changes. Diagnosis and treatment of AEM are more thoroughly discussed elsewhere in this issue.

Because of the nonspecific initial presentation and the rather wide differential for eosinophilic meningitis, there is a need for specific laboratory testing to confirm the diagnosis of AEM. Dot blot ELISA and Western Blot assays based on a 31 kDa protein from adult _A. cantonensis_ have proven useful to detect antibodies against the organism in infected patients but are not widely available. PCR has recently been developed as an alternative to morphological identification of infectious larvae in mollusc tissue, and this real-time PCR assay was used in our field study. The 56% parasitism rate of _A. cantonensis_ in molluscs collected from the site where the patient ingested the snail is in agreement with recent estimates of infectivity rates among molluscs from Hawai’i. PCR has recently been adapted for human testing in abdominal angiostrongyliasis caused by _A. costaricensis_. Acute and mid-course CSF specimens from this case were tested with the same real-time PCR assay used to
detect *A. cantonensis* in molluscs. *Angiostrongylus cantonensis* DNA was not amplified from the day 6 POS (day 15 post ingestion) sample but was amplified from the day 15 POS sample. Although this test has not been standardized for diagnostic purposes, it was reassuring to the treating physicians that there was evidence of *A. cantonensis* DNA in the patient’s CSF. By using PCR to amplify even small quantities of parasite DNA in patient samples, the potential exists to detect organisms and thus confirm the diagnosis sooner compared with antibody tests.

There is currently no clear consensus on the best therapy for AEM. Several investigators have reported that high volume LPs improve headaches temporarily, probably by reducing intracranial pressure. Therapeutic LPs were helpful in our patient for symptomatic relief. Steroids have been used to help decrease intracranial pressure and blunt the immune response. One double-blind, placebo-controlled, randomized trial demonstrated that high dose corticosteroids, given for 2 weeks, reduced duration of illness in Thai adults with AEM. These patients, however, appear to have had milder illness than the present patient, because most patients treated with prednisone had resolution of symptoms by day 5. Therapy of severe disease has not been studied systematically, and further studies are needed to determine the best treatment for severe disease. Our patient was treated with high dose corticosteroid, and initially improved, then worsened temporarily before recovering.

It has been suggested that anthelmintic therapy might cause harm by the rapid killing of worms and a subsequently worsened immune response, but this has not been seen in mouse studies. Unlike the case in neurocysticercosis in which worm cysts are immobile, in AEM there is a theoretical advantage to killing worms because they migrate through the CNS and cause axonal damage according to autopsy studies. There is one double-blind, placebo-controlled, randomized trial of albendazole given without steroids in the treatment of Thai adults with AEM. It showed a reduction in days of symptoms that just reached statistical significance, and there were no adverse effects. However, most clinicians would give corticosteroids concomitantly with an anthelmintic such as albendazole in treating neuropsychiatric conditions. Recently several investigators have reported using a combination of corticosteroid, and albendazole to treat AEM, but no double-blind, placebo-controlled, randomized trial has been reported. In general, unblinded studies have shown cure rates in patients receiving both prednisolone and albendazole similar to those with prednisolone alone. It is possible that the effects of albendazole may be masked due to the efficacy of the steroids. When our patient was re-admitted, albendazole was added to prednisone based on the rationale that the anthelmintic might prevent further axonal damage from live worm migration, although the clinical evidence to support this intervention is not strong. After this, his condition continued to worsen for 7 days before significant improvement was noted. It is not clear whether the worsening was due to addition of albendazole or to the further progression of the disease. Animal studies have shown that albendazole is most effective when given early in the disease, before the larvae molt to young adults. This last molt occurs approximately 11-13 days post ingestion in the animal model, which would have been 2-4 days POS in the present patient. Thus, it is possible that the albendazole the patient received on days 14-28 pos may have been more effective if given earlier in the patient’s course.

AEM is often described as a mild, self-limited condition. However, severe cases including fatalities have been reported. The present patient had an unusually long persistence of neurologic symptoms and clearly had encephalitis, but was never comatose. Other severe cases have been associated with *A. fulica* ingestion. Pediatric patients also tend to present with worse disease. It has been postulated that the severity of infection may be related to the size of the inoculum of infective larvae relative to the mass of the patient. Although the human infective dose is not known, 50 infective larvae have been used to infect each rodent in experiments. *Achatina fulica* were found to harbor a median of 5200 larvae in a study from American Samoa, and one snail contained 90,800 larvae. A quantitative assessment of larval burdens in the *A. fulica* snails collected from the area of ingestion in this case is presented elsewhere in this issue. The present patient swallowed a large, raw *A. fulica*, yet his squad mate chewed one and spit it out without becoming ill. Although the inoculum in the specific snail the patient swallowed is unknown, it is possible that the severity of his illness may have been related to the ingestion of a high number of infective *A. cantonensis* larvae.

The host range of *A. cantonensis* has been expanding, and intermediate hosts such as the giant African snail are becoming invasive in new areas. Travelers to areas where the rat lungworm is present can also be exposed. Clinicians should have a high index of suspicion for AEM with any case of eosinophilic meningitis. For treatment, high volume LPs as needed, and prednisolone or prednisone 60mg daily for 2 weeks are now accepted therapy for adults. After 14 days, corticosteroids can be tapered gradually as symptoms allow. One might consider adding albendazole 7.5 mg/kg twice daily for 2 weeks in addition to corticosteroids, although the evidence for albendazole benefit is not as strong as that for steroids, and further trials are needed.

**Conflict of Interest**

None of the authors identifies any conflict of interest.

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