EOSINOPHILIC MENINGITIS CAUSED BY *ANGIOSTRONGYLUS CANTONENSIS* AFTER INGESTION OF RAW FROGS

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Abstract. *Angiostrongylus cantonensis* is the most common cause of eosinophilic meningitis in humans after ingestion of raw or inadequately cooked intermediate hosts or food contaminated with infective third-stage larvae. Frogs are known to be a paratenic host of *A. cantonensis*, but have never been reported as the infectious source of human angiostrongyliasis in Taiwan. We report the first case of eosinophilic meningitis caused by *A. cantonensis* after ingestion of raw frogs (*Rana plancyi*).

INTRODUCTION

*Angiostrongylus cantonensis*, also known as rat lungworm, is prevalent in the Pacific islands and Southeast Asia and is the most prevalent cause of eosinophilic meningitis in humans in areas endemic for the parasite. Chen first found this parasite in rat lungs in Canton, China in 1935, and Nomura and Lin described the first human case of eosinophilic meningitis caused by *A. cantonensis* in 1945. The definitive hosts of *A. cantonensis* are various species of rats, and humans are infected by ingestion of raw or inadequately cooked intermediate hosts, or food contaminated with the infective third-stage larvae. Snails and slugs are the major intermediate hosts in which first-stage larvae molt in to infective third-stage larvae.

In Taiwan, the major intermediate hosts are African giant land snails (*Achatina fulica*) and golden apple snails (*Ampullaria canaliculata*). Eosinophilic meningitis caused by ingestion of raw snails has been reported. In Thailand, ingestion of raw *Pila* snail may be the major source of *A. cantonensis* infestation. Planaria, crabs, shrimp, fish, frogs, and toads are also known as paratenic or transport hosts, but whether they serve as a source of infection to human is unknown. Two human cases of angiostrongyliasis probably caused by ingestion of fresh toad liver have been reported. We report a case of eosinophilic meningitis caused by *A. cantonensis* after ingestion of raw frog muscles and bones as Chinese medicine.

CASE REPORT

A 70-year-old man came to our emergency room with headache, bilateral upper abdominal pain, and generalized weakness for one week. The headache was not accompanied by nausea, vomiting, or vertigo. The patient had repeatedly visited other hospitals but only had transient relief of the symptoms after medication. The symptoms persisted and became severe, necessitating the current consultation. At the emergency room, he had a body temperature 36.8°C, respiration rate of 18 beats/minute, a heart rate of 72 beats/minute, and a blood pressure of 160/96 mm of Hg. Results of a physical examination were unremarkable except for tenderness over the bilateral upper abdominal area. No obvious focal neurologic sign was detected.

Laboratory tests showed a white blood cell count of 11,010/µL (45% neutrophils, 25% lymphocytes, 26% eosinophils, and 4% monocytes). Results of renal and liver function tests were normal, and levels of electrolytes were all within normal limits. Except for mildly dilated ventricles, no space-occupying lesion or other abnormalities were found by computed tomography of the brain (Figure 1A).

After admission, lumbar puncture was performed, and a tentative diagnosis of meningitis was made. The opening pressure was 256 cm of H2O. Results of cerebrospinal fluid (CSF) examination showed a white blood cell count of 647/cm³ (3% neutrophils, 25% lymphocytes, 60% eosinophils, and 12% monocytes), a red blood cell count of 4/cm³, a protein level of 155 mg/dL, a glucose level of 52 mg/dL (serum glucose level = 153 mg/dL), and a lactate level of 25.8 mg/dL (reference range = 10.8–18.9 mg/dL). The serum IgE level was 44 IU/mL. Eosinophilic meningitis was diagnosed.

On review of history, the patient had ingested raw frogs approximately one month prior to admission. He had done this because he was told that eating raw muscles and bones of frogs as Chinese medicine was beneficial to human bones. Accordingly, he caught eight frogs that were approximately 4–5 cm in size, cut off their heads and distal limbs, flayed the skin, and removed the viscera and intestines. He then minced the muscles and bones, seasoned them with soy sauce, and ingested them in raw with a drink. The patient recognized the frogs he ate were *Rana plancyi* after carefully reviewing an atlas of frogs. The patient denied eating any other raw food or fish in the last three months.

On the basis of the history, clinical presentation, and examinations, *A. cantonensis* infestation associated eosinophilic meningitis was suspected. Mannitol, acetaminophen, and diclofenac were administered for relief of the headache. The CSF and serum were both positive for antibodies to *A. cantonensis* by enzyme-linked immunosorbent assay. Levels of antibodies to *A. cantonensis*, levels of serum IgE, and blood eosinophil counts are summarized in Table 1. Magnetic resonance imaging (MRI) of the brain showed dilated ventricles. Meningeal enhancement or increased signal intensity within the globus pallidus were not found (Figure 1B). Bilateral upper abdominal pain resulting from paresthesia in bilateral T-9
dermatomes was suspected because the patient denied any history of trauma and no apparent abdominal lesion, and no intra-abdominal lesion was found by abdominal ultrasonography. Spinal MRI showed enhancement of the cervical and thoracic cord surface on contrast-enhanced T1-weighted imaging (T1WI) (Figure 1C and D).

The headache and paresthesia improved gradually. However, the patient refused repeat lumbar puncture as monitoring for the response to treatment. He was discharged after 10 days of treatment and was followed-up for three weeks after discharge. The patient had no headaches, abdominal pain, or other discomforts.

**DISCUSSION**

Frogs and toads are known paratenic hosts of *A. cantonensis*. Ash first recovered the third-stage larvae from frogs (*Hyla aurea*) and found that larvae from muscle were generally alive and infective to experimental rats. In contrast, larvae collected from the alimentary tract or liver were often dead. After the report of two human cases of angiostrongyliasis probably caused by swallowing fresh toad liver, Asato and others examined toads and frogs and found that larvae were most frequently found in the stomach, intestinal wall, and mesentery, with some in the liver and muscles but

<table>
<thead>
<tr>
<th>Antibody to <em>A. cantonensis</em>†</th>
<th>Examinations</th>
<th>Duration from ingestion of frogs to examinations (day)</th>
<th>28</th>
<th>34</th>
<th>38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum (positive control &gt; 0.92, negative control &lt; 0.17)</td>
<td>0.64</td>
<td>NT</td>
<td>1.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF (positive control &gt; 0.61, negative control &lt; 0.12)</td>
<td>0.88</td>
<td>NT</td>
<td>NT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum IgE level (IU/mL)</td>
<td>444</td>
<td>539</td>
<td>520</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood eosinophil count (×10³)</td>
<td>2,863</td>
<td>2,434</td>
<td>2,109</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*NT = not tested.
† Antibody levels are expressed as optical density at 630 nm after detection by enzyme-linked immunoabsorbent assay.
none in the heart and lungs.\textsuperscript{13} Oku and others first described that tadpoles might act as an intermediate host of \textit{Angiostrongylus cantonensis} because first-stage larvae could develop into the second-stage in infected tadpoles.\textsuperscript{14} Their subsequent study reported that as infected tadpoles mature into frogs, first-stage larvae develop into infective third-stage larvae that are found in the liver, pancreas, gastrointestinal wall, and muscles.\textsuperscript{15} Thus, ingestion of raw frogs containing infective larvae could cause \textit{A. cantonensis} infection.

Ottsura and others studied definitive, intermediate, and paratenic hosts of \textit{A. cantonensis} in the southwestern islands of Japan and Taiwan and found that larvae were present in \textit{Bufo asiaticus} (36 of 107, 33.6%), \textit{Rana plancyi} (6 of 28, 21.4%), \textit{R. latouchi} (3 of 14, 21.4%), \textit{R. catesbeiana} (7 of 44, 15.9%), \textit{B. melanostrictus} (1 of 12, 8.3%), and \textit{R. tigrina} (3 of 94, 3.2%).\textsuperscript{16} The most common frog used for food in Taiwan is \textit{R. catesbeiana}, but it is often eaten after being cooked. Catching frogs and eating the muscles of legs is a common game among children in rural Taiwan, but the viscera and intestine are usually removed and the frogs are fried before ingestion.

Our patient ate raw frog (\textit{R. plancyi}) muscles and bones because he believed that they were beneficial to human bones. He might have acquired the \textit{A. cantonensis} infection by two routes. First, the patient was infected directly by ingesting frog muscles that contained infective larvae because he removed the head, distal limbs, and viscera. Second, he was infected indirectly by hands or implements contaminated with the debris of viscera when he prepared the frogs. The latter is similar with the route reported in southern Taiwan, where children are infected during the preparation of snails or playing with them, rather than by eating them.\textsuperscript{19} However, in studies of larval infectivity of frogs, infected rats were fed with larvae directly, not with infected viscera or muscles.\textsuperscript{12,13,15} Thus, although results in this case are definitive, whether the ingestion of raw frog muscles results in human angiostrongyliasis requires further investigation.

Results of computed tomography of the brain and MRI of eosinophilic meningitis caused by \textit{A. cantonensis} vary from normal to non-specific. The major findings of computed tomography of the brain include normal images, cerebral edema, or ventricular dilatation.\textsuperscript{4} Results of brain MRI are more protean.\textsuperscript{17–19} Kanipattaya and others found a prominence of the subcortical enhancing lesions on T1WI and high T2 signal lesions in the peri-ventricular regions are predominant abnormalities.\textsuperscript{17} Tsai and others reported high signal intensities over the globus pallidus and cerebral peduncle on T1WI, in which signal intensity is correlated with severity of headache. CSF pleocytosis, and eosinophilia of CSF and blood. In addition, lepto-meningeal enhancement, ventriculomegaly, and abnormal enhancement within the cerebral and cerebellar hemisphere are found on contrast-enhanced T1WI.\textsuperscript{18} Jin and others found multiple enhancing nodules in the brain and linear enhancement in the lepto-meninges as the main features, with stick-shaped enhancement as the characteristic sign of the disease on contrast-enhanced T1WI.\textsuperscript{19} In contrast to these reports, our patient had no meningeal enhancement or other abnormalities detected by brain MRI except for ventricular dilatation. This might be the result of larvae in frog muscles that were eaten, which is relatively lower compared with those of snails or other intermediate hosts.

Despite spinal cord involvement, findings of spinal MRI in patients with angiostrongyliasis are rarely described. Multiple enhanced-nodules in the spinal cord or nerve roots,\textsuperscript{20} diffuse lepto-meningeal enhancement of the nerve root sheaths at the level of the cauda equina and lepto-meningeal covering of the spinal cord,\textsuperscript{20} as well as intra-medullary spinal cord mass lesions,\textsuperscript{21} have been reported. Unlike these reports, linear enhancements of the spinal cord surface over cervical and thoracic levels were found in our patient (Figure 1C and D). These abnormalities might indicate an inflammatory process of the pia matter or engorgement of the coronal venous plexus of the involved spinal cord. In humans, third-stage larvae penetrate the intestinal wall and migrate to the capillaries of the brain and spinal cord surface through the bloodstream, thereby inciting an inflammatory reaction. Although there was no MRI showing a resolution of the spinal lesions, we believe that abnormalities resulted from an inflammatory reaction to \textit{A. cantonensis} infection because the hyperesthesia in the bilateral thoracic dermatomes was found clinically and subsided together with relief of the headache.

In summary, ingestion of raw intermediate hosts, mainly snails and slugs, is the major cause of human angiostrongyliasis. Frogs, previously recognized as paratenic hosts of \textit{A. cantonensis}, may cause human angiostrongyliasis if they are eaten raw. The linear enhancement of spinal cord surface on contrast-enhanced T1WI spinal MRI may expand the image findings of this infection.

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REFERENCES


