Title

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Journal

American Journal of Tropical Medicine and Hygiene, 95(6)

ISSN

0002-9637

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Publication Date

2016-12-07

DOI

10.4269/ajtmh.15-0902

Peer reviewed

Am. J. Trop. Med. Hyg., 95(6), 2016, pp. 1424–1427
doi:10.4269/ajtmh.15-0902

Case Report: Cerebral Paragonimiasis Presenting with Sudden Death

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Abstract. A 58-year-old Korean-born woman with a history of seizures and psychiatric issues was found dead at home. Autopsy was notable for large, calcified nodules that had nearly replaced her right temporal lobe. Histologic examination revealed the presence of *Paragonimus* eggs. This case demonstrates a rare manifestation of an aberrantly migrated lung fluke that resulted in epilepsy and sudden death years after the initial infection.

INTRODUCTION

Paragonimiasis refers to a parasitic pulmonary infection caused by lung flukes of the trematode genus *Paragonimus*. Human infection is acquired via ingestion of metacercariae, the immature forms of the parasite, in undercooked, raw, or pickled freshwater crabs or crayfish. Although chronic pulmonary disease is the most common manifestation of disease, aberrant migration of juvenile flukes can lead to extrapulmonary involvement, the most serious of which is cerebral paragonimiasis. Symptoms include headache, epilepsy, paralysis, and behavioral changes.[1] Here, we present a case of a woman with a history of epilepsy who was found dead at home. Autopsy revealed cerebral involvement by *Paragonimus*.

CASE DESCRIPTION

A 58-year-old ethnically Korean woman with a history of epilepsy was discovered dead at home. Because of the unexpected nature of her death, she fell under the jurisdiction of the medical examiner. Per the medical examiner's investigative report, she had been described as "depressed" but without formal psychiatric evaluation, and carried a diagnosis of epilepsy due to remote "scarring" of her brain from "childhood meningitis."

On further medical record review, she was born in Korea but lived in the United States for decades. She had her first seizure at 7 years of age, and then did not have another seizure until age 46. She subsequently suffered generalized, tonic–clonic seizures approximately once per month. She was prescribed phenytoin with questionable compliance. Because of seizures that occurred while she was boiling soup, she had suffered from multiple third-degree burns that required skin grafting. Six months before her death, she had presented to the emergency room (ER) with dizziness and memory loss. Although her physical exam and a chest X-ray were normal, a computed tomography (CT) of the head demonstrated a large area of hypoattenuation and dystrophic calcification involving the right lateral temporal lobe, right inferior parietal lobe, and right lateral occipital lobe (Figure 1). This was interpreted as most consistent with a remote infarct or vascular malformation. She was discharged from the ER with instructions to follow up with neurology; however, there is no record that this occurred.

General autopsy revealed a normally developed adult female without an anatomic cause of death. Notably, her lungs were grossly and microscopically unremarkable. Formal neuropathologic examination of her formalin-fixed brain revealed an irregular area of calcification nearly replacing her entire right temporal lobe (Figure 2). Histologically, this corresponded to extensive necrotic, partially calcified debris enveloped by dense collagenous rinds, surrounded by gliotic brain parenchyma. Focal osseous metaplasia, indicative of the long-standing nature of the lesion, was also identified. Numerous parasitic eggs with thick, refractile, yellow-brown walls, consistent with *Paragonimus* species were identified (Figure 3), which was confirmed by the DPDx Team at the Centers for Disease Control and Prevention. The eggs were operculate, broadest centrally, and birefringent when exposed to plane polarized light, characteristic of *Paragonimus.* Viable micracidia were not found within the eggs. Polymerase chain reaction (PCR) testing of DNA extracted from the formalin-fixed brain tissue with five different primer tests was nondiagnostic, likely secondary to the age of the lesion. Serum was not available for serologic testing. Her death was ultimately certified as a natural death due to epilepsy caused by cerebral paragonimiasis.

DISCUSSION

This case highlights a rare presentation of cerebral paragonimiasis resulting from aberrant migration of the larval fluke. Human infection with species of the trematode genus *Paragonimus* occurs most commonly as a subacute to chronic inflammatory disease in the lungs and pleura, causing findings similar to tuberculosis. Extrapulmonary disease occurs when the immature flukes migrate to other sites, including the brain, abdomen, and subcutaneous tissues. Cerebral paragonimiasis is the most common extrapulmonary manifestation.[1,2] However, brain involvement remains relatively rare, occurring in less than 1% of patients with symptomatic infection.[3] It occurs most frequently in younger patients, with > 90% of patients less than 30 years of age and is more common in men compared with women.[4,5]

Paragonimiasis occurs throughout the world, including east Asia, west Africa, and the Americas. Infection occurs via consumption of raw or undercooked freshwater crab or crayfish, or contamination while preparing crabs and crayfish. Infection has also occurred when crab and crayfish juice is used for traditional medicinal purposes in Korea and Japan. Our patient most likely acquired her infection while she lived in Korea during her youth. There are over 50 species of the genus *Paragonimus*, with nine species known to infect humans.

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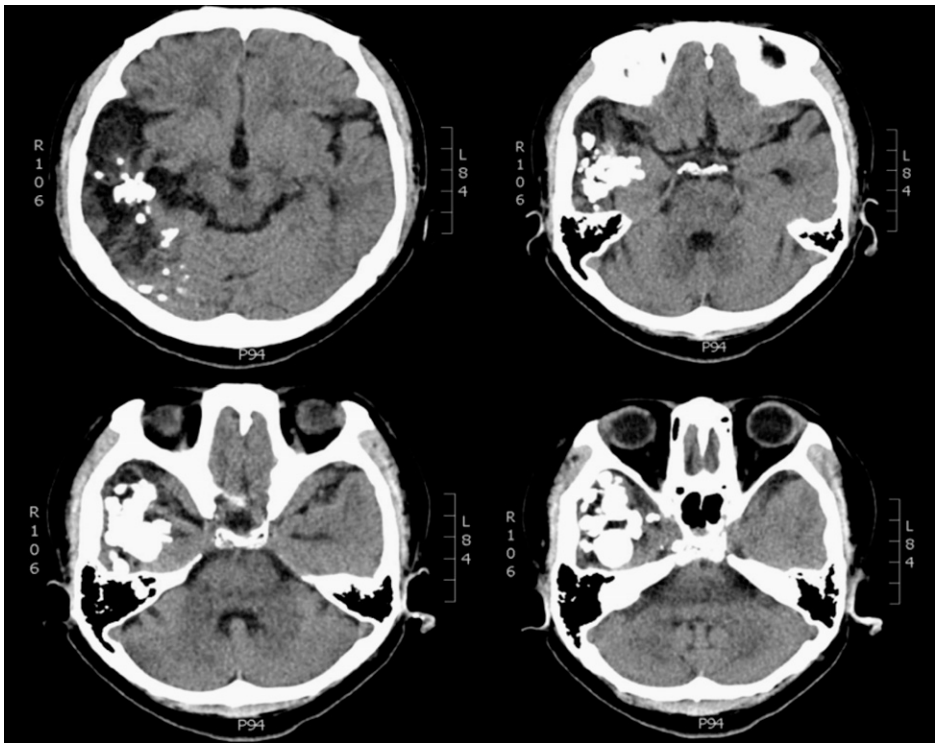

FIGURE 1. Axial images demonstrate a large area of hypoattenuation and dystrophic calcification involving the right lateral temporal lobe, right inferior parietal lobe, and right lateral occipital lobe.

The most common species is *Paragonimus westermani*, also known as the oriental lung fluke, which is found throughout China, Korea, Japan, the Philippines, Taiwan, and India. There have been cases of *Paragonimus kellicotti* infection reported in North America, which occurred after patients ingested undercooked crayfish from rivers in Missouri; however, infections more commonly occur in the United States in the immigrant population.[6]

After the immature flukes are ingested, they typically excyst in the duodenum, enter the peritoneal cavity, and migrate through the diaphragm into the lungs where they develop into adult flukes over the course of 6 weeks. The adults encapsulate in pairs within the parenchyma or on the pleural surface of the lungs and eggs are excreted in sputum and stool. The life cycle is continued when the eggs enter a fresh water source, where they hatch as miracidia and penetrate the soft tissues of a freshwater snail to develop into cercariae. The snail-borne cercariae subsequently invade the gills and soft tissues of crustaceans to become metacercariae.

The mechanism of *Paragonimus* fluke migration to the brain is not well characterized. One hypothesis is that immature larvae travel via the loose connective tissue that surrounds the jugular vein or the carotid arteries. This is consistent with the finding that the distribution of lesions tend to follow that of the middle and posterior cerebral arteries, with lesions most commonly occurring in the temporal, occipital, and parietal lobes.[3] The fluke penetrates the meninges and is able to invade the brain tissue.

Three histopathologic stages of cerebral paragonimiasis have been described.[3] The first stage is the exudative and infiltrative

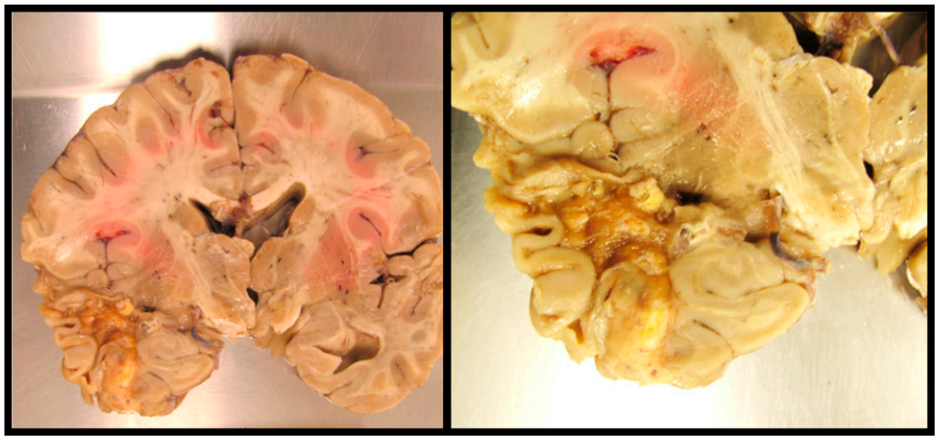

FIGURE 2. Coronal sections of formalin-fixed whole brain with yellow discoloration and induration of right temporal lobe.

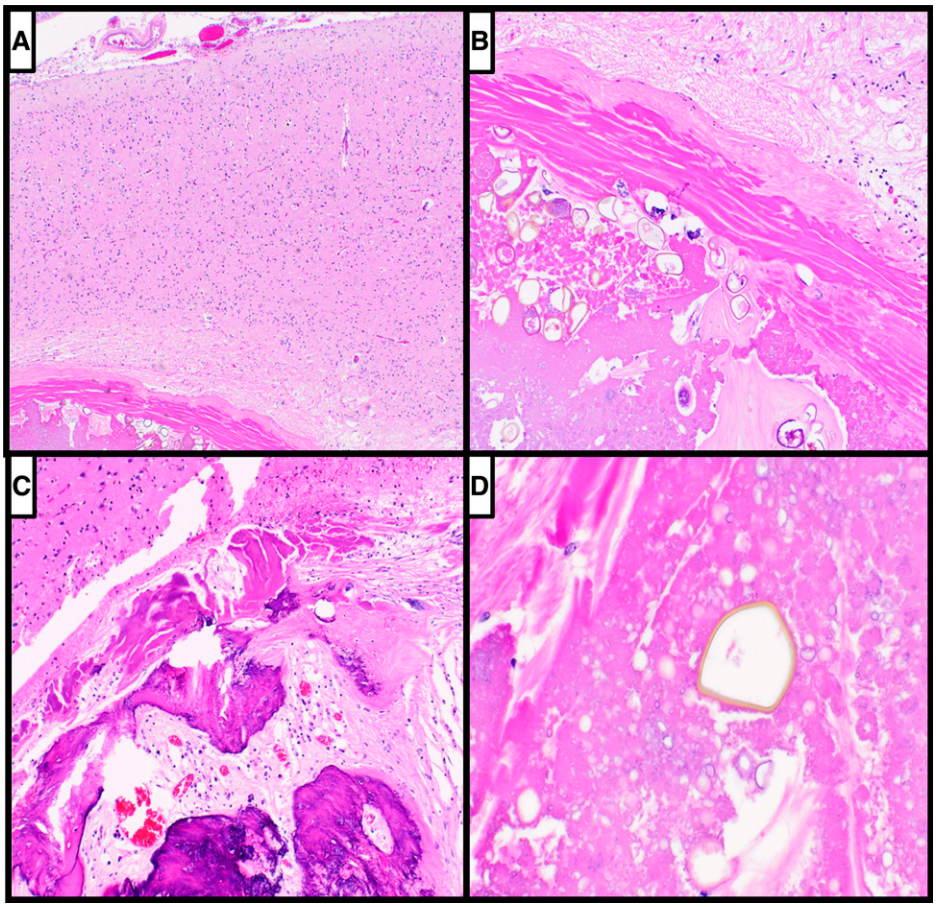

FIGURE 3. (**A**) Hematoxylin and eosin–stained sections of formalin-fixed brain tissue reveal a gliotic rim of temporal lobe around walled-off, necrotic, and partially calcified debris (×40). (**B**) Higher magnification reveals abundant necrotic debris and numerous intermingled eggs (×100). (**C**) Focally, osseous metaplasia, testament to the long-standing nature of the lesion, is identified (×100). (**D**) Careful scrutiny of the parasitic egg reveals a thick, golden-brown hue of the egg wall and lack of spine, consistent with *Paragonimus* (×400).

phase, which consists of an early, unencapsulated, necrotizing granuloma. The second stage consists of a localized, well-encapsulated granuloma. The final stage represents the chronic phase of infection and is characterized by an organized and calcified, well-encapsulated lesion, consistent with our patient's findings.

Early symptoms of cerebral paragonimiasis include fever, headache, vomiting, seizures, and neck stiffness. Examination of cerebrospinal fluid at this time can reveal eosinophilia and elevated protein. Chronic infection can lead to persistent neurologic deficits due to local tissue damage from the lesions. Symptoms include seizures, personality changes, visual changes, chronic headache, focal weakness, and sensory deficits. Epilepsy occurs in approximately 37% of patients and is caused by an intense inflammatory response triggered by a massive release of parasite proteins during the degeneration of the lesions.[1] Chronic lesions can calcify and subsequently be detectable on plain radiographs as "soap-bubble" calcifications. CT or magnetic resonance imaging can demonstrate multiple, cystic, ring-enhancing lesions that have been described as having a "grape-cluster" appearance. Findings may be mistaken for tumors or sequelae of hemorrhagic stroke.

Because of nonspecific symptoms, the diagnosis of cerebral paragonimiasis is often delayed. Clinical diagnosis of paragonimiasis is reliant on identification of eggs in sputum or on tissue biopsy. *Paragonimus* eggs are operculated, birefringent when exposed to plane polarized light, enveloped by a double shell, lack a spine, and are relatively large at approximately 100 × 50 μm. In sputum samples, the fresh eggs can be detected with Ziehl–Neelsen staining, which appears to be superior to wet mount.[7] In tissue specimens (after formalin fixation), the eggs have a characteristic yellow-brown, refractile wall. Serologic tests, including complement fixation, counter-current immunoelectrophoresis, and enzyme-linked immunosorbent assay, are available for identification of *P. westermani*, and are more useful for extrapulmonary disease when eggs may not be shed in the sputum. Antigen from the eggs can cause persistent elevation of antibodies even up to 34 months after appropriate treatment.[8] PCR tests are under development for the diagnosis of *P. westermani* infection, but are not currently commercially available.[9]

Successful treatment of cerebral paragonimiasis relies on early clinical suspicion or neurosurgical intervention in some cases. The treatment of choice for cerebral paragonimiasis is a 3-day course of praziquantel, with triclabendazole as an alternative agent. A course of steroids and mannitol are often warranted during the time of treatment if the cerebral lesions have significant surrounding edema. Single superficial lesions may be amenable to surgical removal. At the time of surgery, a clear distinction is seen between the lesions and surrounding brain tissue.[1] Correlation between histologic stage of cerebral paragonimiasis and treatment outcomes is not well

known; however, even chronic infection may be amenable to surgical resection if recognized in time.[10]

Received December 14, 2015. Accepted for publication September 8, 2016.

Published online October 17, 2016.

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