Pulmonary Paragonimiasis Diagnosed by Fine Needle Aspiration Biopsy

Running title: Paragonimiasis

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Abstract

We report a case of paragonimiasis involving a 12-year-old Latin-American boy. The diagnosis was made by fine needle aspiration biopsy of a pulmonary nodule. Identification to species by morphometric analysis of the eggs indicated that the infection was caused by Paragonimus mexicanus.

Case Report

A 12-year-old boy with a two-year history of seizures, headaches and intermittent hemoptysis presented to the Ben Taub General Hospital emergency room (ER) after a cluster of five seizure attacks. The boy was from El Salvador, had been in the United States for 14 months and had been treated with phenytoin for his seizures. On presentation his head CT scan showed a calcified cystic lesion in the left anterior frontal area. The EEG was abnormal with recurrent spica slow waves in the left temporal lobe and frontal spike of slow wave. He was diagnosed with symptomatic localized epilepsy with secondary generalized tonic/clonic seizures. He was started on tegretol and followed monthly by the Neurology service. He had been seizure free for nine months when he presented to the ER for a second time with two episodes of self-limited tonic-clonic seizure at school, each lasting less than one minute. There was no loss of bladder or bowel control. The patient reported a one-year-history of intermittent hemoptysis. His sputum was reported to be blood-streaked with no gross blood. He had an occasional productive cough, but no hematemesis, nasal congestion, chest pain or shortness of breath. He occasionally had fever but no chills, or night sweats. The patient’s mother reported he has had a 20-pound weight loss in the past year. No diarrhea was reported. His physical activity was normal and he did
not complain of fatigue. Headaches had been worse over the past few months; therefore, he had missed several days of school. The headaches were frontal, throbbing and associated with photophobia. He was also complained of problems with visual acuity. He denied any syncope, vomiting or persistent poor vision. His headaches were relieved with Tylenol.

His physical examination was unremarkable. His laboratory investigation documented a normal complete blood count with no eosinophilia. His metabolic panel was also normal. His cerebrospinal fluid (CSF) had 4 white cells and no red cells; CSF culture was negative for bacteria, fungus and viruses. Abdominal and pelvic CT scans were normal. His chest x-ray & CT scan showed multiple lung nodules measuring up to 2.2 cm, but no lymphadenopathy (figure 1). Pulmonary angiography showed no evidence of hypervascular tumor, or arteriovenous malformation. A head CT scan revealed a focus of encephalomalacia in the left superior frontal gyrus involving the underlying white matter and a 2-3 mm focal calcification. A CT-guided lung fine needle aspiration biopsy (FNAB) showed abundant necrotic cellular debris surrounding numerous thick-walled parasite eggs morphologically consistent with those of the trematode or lung fluke Paragonimus mexicanus (figure 2). The specimen was sent to CDC where the identification to species was confirmed. The patient was treated with six doses of 1200 mg of Praziquantel. He was discharged on Tegretol.

The patient has been followed for 5 years. He was admitted recently because of an increased frequency of seizures. His head CT showed no change in the size of the cyst and no enhancing brain lesion.
Discussion

Paragonimiasis is a zoonotic disease caused by the trematodes *Paragonimus* spp. Other names of this disease are oriental lung fluke, endemic hemoptysis, Mason hemoptysis, pulmonary distomiasism, and parasitic hemoptysis (11). An estimated 20 million people are currently infected in Africa, Asia and the Americas (17). About 48 species of *Paragonimus* have been described, but only 16 of these infect humans (2, 16), including *Paragonimus westermani* in the Far East and Southeast Asia, *Paragonimus africanus* in West Africa, *Paragonimus mexicanus* in Central and South America, and *Paragonimus kellicotti* in North America (3). Adult flukes reside mainly in the lung, but ectopic localizations such as lymph nodes, heart, mediastinum, adrenal glands and kidneys have also been reported (11). *P. westermani* is the most common species infecting humans causing pulmonary, pleuropulmonary and cerebral paragonimiasis (2, 16). *P. kellicotti* is the second most common cause of diagnosed human cases and the endemic species in the United States.

The life cycle of *P. spp* is complex, involving two intermediate and one definitive host (11). The early developmental stages are carried through the snails of Pleuroceridae and Thiaridae families. Over a period of 10-12 weeks they transform through sporocyst and rediae stages, and eventually become cercariae. The cercariae leave the snail and through water reach the second intermediate host, a crustacean like a fresh-water crab or crayfish (2, 16). Here they develop into encysted forms (metacercariae) and human infection occurs where these contaminated crustacea are eaten poorly cooked or raw (18). Metacercariae
excyst in duodenum and within 1 hour pass through the intestinal wall into the peritoneal cavity (15). After 3 to 6 hours they migrate into the abdominal wall and then through the diaphragm into the pleura and lung tissue (15, 18), where they become encapsulated, usually in pairs or triplets. It takes 65 to 90 days for the flukes to develop fully, although the symptoms may begin earlier. Eggs are shed around the worm and with rupture of the contents of the encapsulated cyst into bronchioles are excreted in the sputum or swallowed and excreted in the feces.

Disease is caused by inflammation and fibrosis elicited by worms in the lung or ectopic locations. Manifestations depend on the duration of infection and probably the intensity of infection. Flukes and eggs initially elicit an acute inflammatory response, consisting predominantly of eosinophils, which is followed by the formation of a fibrous capsule (15). The cysts are 1.5 cm in diameter, and these may rupture into the bronchioles, extruding blood, eggs, and inflammatory exudate. Several excretory-secretory (ES) and somatic products from tissue-invading helminths have been related to the modulation of host’s immune response, e.g. through the induction/inhibition of different host immune mediators such as nitric oxide (NO) (7). NO plays an important role in many infectious diseases due to both its direct effector function and its potent immunoregulatory properties (6). It has been shown that ES products from P. mexicanus adult worms trigger NO production from alveolar macrophages (1). Further studies are needed to reveal the exact effect of NO production on the host immune system. Histologically, a fibrous and granulomatous reaction may be seen in association with the eggs. Secondary bronchopneumonia is common. Pleural involvement is common (15) and can cause an eosinophilic empyema that can be confused clinically with tuberculosis. Long standing lesions exhibit fibrosis and
decreased inflammatory response which may eventually calcify. Common ectopic locations  
of flukes are the pleura, abdominal wall, viscera and brain. Brain involvement is  
particularly a serious complication (15). The adult fluke is thick, ovoid, red-brown, and  
with a rounded anterior aspect and a tapered posterior. It measures 7.5 to 12 mm in length  
and 4 to 6 mm in thickness. It may live for 20 years (18).

The initial illness is characterized by diarrhea, abdominal pain, urticaria, fever, malaise and  
eosinophilia that last from days to weeks when the immature flukes are migrating. As  
larvae penetrate the diaphragm and migrate within the pleural cavity, pleuritic chest pain  
may develop occasionally associated with pleural effusion and pneumothorax. Pulmonary  
manifestations include dyspnea, cough, and hemoptysis. Leukocytosis with prominent  
eosinophilia and transient pulmonary infiltrate occurs during this time. Signs and  
symptoms due to involvement of ectopic locations can also be seen at this stage.

Later in the chronic stage when the adult worms reside in the lungs and produce eggs, the  
patient may develop chronic cough, expectoration of rusty or pigmented sputum and  
hemoptysis, as in our case. Dyspnea, chest pain, fever and constitutional symptoms are  
found less frequently. Chest x-ray findings are variable, non-diagnostic. Localized or  
multisegmental infiltrates, usually poorly defined, are most common, but nodular (as in our  

case), cystic, cavitary, and ring shadow patterns are also found. Pleural effusion, empyema,  
pleural thickening and calcification of lesion can also be seen. In contrast to tuberculosis,  
apical lesions are not predominant, cavities are smooth and regular, and infiltrates are less  
well defined. Although lung involvement alone appears to cause little mortality, morbidity  
and mortality are significant with ectopic lesions. Acute involvement of the brain is  
associated with sudden onset of neurologic symptoms, usually in the presence of
pulmonary disease, as in our case. Chronic brain involvement occurs in up to 10% of patients and is associated with seizure and long-term deficits (15, 18). Most lesions of cerebral paragonimiasis are located in the posterior loci of the cerebral hemispheres (parietal, occipital, and/or posterior temporal area), but, frontal lobe involvement is not uncommon as it presented in this case. The brain stem, the cerebellum, and the spinal cord are rarely involved. The radiological findings of cerebral paragonimiasis are variable, depending on the evolutorial stage of the cerebral infection. Diagnosis of cerebral paragonimiasis, in the early stage is important because curative chemotherapy with Praziquantel is possible. Today, CT and MRI are the imaging methods of choice in the evaluation of the nature and extent of cerebral infection, as well as virtually all other intracranial abnormalities (4, 5). In the chronic stage of cerebral paragonimiasis, the granulomas may become calcified. The classical pattern of calcification is seen as congregated multiple round nodular or cystic lesions (so-called soap-bubble or egg-shell appearance) on plain skull radiographs (10, 13).

The pulmonary lesions are most commonly mistaken for tuberculosis (in some series in about half the patients). Indeed, tuberculosis is common in countries where paragonimiasis is endemic. The lesions of paragonimiasis are more peripherally located and much more common in the mid and lower lung zones as opposed to the predominant apical location of tuberculous cavities. In the chronic inactive stage of cerebral paragonimiasis, the calcified lesions may be mistaken for cysticercosis, tuberculosis, or other chronic inflammations, unless the characteristic conglomerate and soap-bubble appearances are identified on plain film radiography, CT or MR imaging (5, 9).
The eggs of Paragonimus spp may be mistaken for those of other operculate trematodes including Clonorchis sinensis, which are much smaller (26-35 micron) and those of Fasciola hepatica and Fasciolopsis buski, which are considerably larger (130-140 micron). The eggs of Schistosoma japonicum are about the same size and shape, but schistosome eggs lack an operculum, have thinner shells and are not birefringent (2, 15). Diagnosis is established by detection of the characteristic ova in stool or sputum. The eggs of Paragonimus spp are yellow to brown with a flattened operculum at one end. In addition, as a result of their thick shell, the eggs are birefringent with polarized light (figure 2). Over time, the eggs may undergo calcification (18). The eggs of P. mexicanus measure on average 80 x 40 microns. The intact eggs from our patient measured on average 79 x 48 microns. Egg size and geographic location of our index case are helpful in establishing the species of Paragonimus involved in our patient’s infection (Table 1) (12).

Concentration techniques may be needed for detection of eggs in lightly infected patients or those with suspected ectopic lesions. In acute disease, eggs may not be detected until 2 to 3 months after exposure (15). Serologic testing for anti-paragonimus IgG by ELISA has a sensitivity of 100% and specificity of 91% to 100% (12). This test is mainly available at Center for Disease Control and Prevention (CDC).

The intradermal test has been widely used, mainly for screening of patients in endemic areas. A positive reaction does not always mean active infection and a test can remain positive as long as 20 years after complete recovery. Praziquantel is the treatment of choice at 25 mg/kg/day for 2 days; and it is usually given three times a day. The overall cure rate is more than 90% (8, 14). In cases of cerebral lesions higher doses must be given but only
under the protection of steroids to prevent epilepsy secondary to perilesional edema. Older
drugs like bithionol and niclofolan are also effective but more toxic (14).

In summary, *P. mexicanus* is an uncommon cause of paragonimiasis in North America.
Infected patients are usually from South American countries or have travel history to South
America. The most common presentation is pulmonary involvement. Brain involvement
usually occurs in the presence of pulmonary lesions, and can cause a hemorrhagic lesion
and even death. Recognition of brain involvement in early stages is critical since it can be
treated with medication. In the late stages, brain lesions calcify and can cause seizures and
long-term deficit. Our patient displayed both pulmonary and cerebral lesions, and we were
able to establish the diagnosis via FNAB of one of the pulmonary nodules.

References

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Figure Legends

Figure 1. CT scan of chest illustrating well defined lung nodules

Figure 2. *Paragonimus* egg, composite photograph. The left panel shows an egg from the aspiration biopsy where we see the characteristic thickened shell and slightly flattened end. (Papanicolaou stain, x 400). The right side illustrates the birefringent *Paragonimus* egg; this characteristic helps differentiate this parasitic egg from *Schistosoma japonicum* (Papanicolaou stain, x 400).

Table 1. Comparison of the egg sizes and endemic locations of different *Paragonimus* species (*)

<table>
<thead>
<tr>
<th>Species</th>
<th>Geographic location</th>
<th>Egg size (Microns)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>P. mexicanus</em></td>
<td>Mexico, Central and South America</td>
<td>79 x 48</td>
</tr>
<tr>
<td><em>P. ecuadoriensis</em></td>
<td>Ecuador</td>
<td>91 x 51</td>
</tr>
<tr>
<td><em>P. westermani</em></td>
<td>Asia</td>
<td>100 x 56</td>
</tr>
<tr>
<td><em>P. kellicotti</em></td>
<td>North America</td>
<td>42-67 x 75-118</td>
</tr>
</tbody>
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(*) Adapted from reference 12.