Paragonimiasis: a common cause of persistent pleural effusion in Lao PDR

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Summary Southeast Asia is the major endemic area for paragonimiasis. Diagnosis relies on identification of ova in the sputum, pleural fluid or tissue specimen, or serology. Low awareness, however, frequently results in the disease being overlooked. We report nine cases presenting as primary, massive and protracted pleural effusions. All patients had evidence of Paragonimus spp. in the pleural fluid; one discharged an adult worm through a chest tube during treatment with praziquantel. In three cases, resolution of symptoms and pleural effusions could not be achieved, despite repeated fluid evacuation procedures and courses of praziquantel, which contradicts the widely accepted statement of paragonimiasis being self-limited and easy to cure. The disease should be considered in any case of elusive pleural effusion occurring in endemic areas.

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1. Introduction

Paragonimiasis is a food-borne zoonosis caused by trematode worms of the genus Paragonimus and predominantly affects the lung. Infection results from ingestion of metacercariae (larval stage of the parasite) harboured in the intermediate host, freshwater crab or crayfish, when consumed under-cooked or pickled. Once ingested, the larvae excyst in the duodenum of the definitive host (humans or other mammals) and migrate through the intestinal wall, the peritoneum, the diaphragm and the pleura to finally reach the lung parenchyma, which is the usual final target organ. There, the larvae mature into adult worms, forming cysts and laying eggs, which may be expectorated or swallowed and passed with stools, thus initiating a new cycle.

The usual clinical symptoms of paragonimiasis include chronic cough and protracted haemoptysis that last for months to years, and less frequently chest pain. The general status is usually preserved, and fever is reported in...
less than 10% of the cases. The pleura may be involved at various stages, at a frequency ranging from 22 to 70%, resulting in inflammatory effusion, pneumothorax or pleural thickening.1–3

Radiographic abnormalities are found in around 80–90% of cases; these include effusions, air space consolidation and linear opacities in the initial stage of the disease, then thin-walled cysts, mass-like opacities, nodules and finally pleural thickening in the more advanced stages.1–3 The clinical and radiological picture may often be confused with other lung diseases, especially tuberculosis (TB)1–3,4 and cancer.3 Diagnosis is made by identifying Paragonimus ova in the sputum or pleural fluid, or in lung or bronchial tissue specimens obtained by biopsy, but the sensitivity of these methods may be as low as 50%.1,2 Serology (ELISA), although not widely available, is actually the best diagnostic method, reaching a sensitivity and specificity of between 96 and 100%.4

Ninety percent of the estimated 22 million people infected with paragonimiasis worldwide reside in Southeast and East Asia; the remaining 10% live in Africa and Central and South America.1 Formerly, the disease was endemic in Japan, Korea and Thailand, where it has nearly disappeared because of improved food hygiene and socio-economic standards.4 Notwithstanding, the disease continues to be present in the impoverished areas of southern China and northeastern India.6,7,11 Cases have also been reported in Asian immigrants to Australia and the United States.12 In Lao PDR, several foci have been described, some of them very recently, and the species identified so far in the intermediate hosts (not patients) are P. heterotremus, P. westermani, P. harinasutai and P. bangkokensis.11,13

2. Patients and methods

Here, we report nine cases of paragonimiasis seen at Vientiane tertiary hospitals with massive, apparently idiopathic and recalcitrant pleural effusions, between 2003 and 2005. Informed consent was obtained from all nine patients. Cases 1 to 3 are briefly described. Table 1 summarizes the clinical data and outcome. Baseline data were collected retrospectively and follow-up data prospectively. All patients had a minimum of three sputum examinations for acid-fast bacilli (AFB) and Paragonimus ova. Diagnosis was made based on a microscopic finding of Paragonimus in the pleural fluid. The serology for paragonimiasis and mycobacterium culture were not performed because they are not readily available in Lao PDR. A computed tomography (CT) scan, although available, was not performed because the cost was prohibitive for the patients.

3. Results

All nine patients (five males and four females) were young adults between 13 and 45 years of age (mean, 28 years) and most were rural poor (7/9). All had chest pain and a clear pleuritic syndrome of unclear origin. The mean duration of symptoms was 8.8 months (range 1 to 36). Chronic cough and protracted blood-tainted sputum was present in five and six patients, respectively. Two patients had substantial weight loss and one reported undocumented fever. All patients gave
a dietary history of raw/undercooked freshwater crustacean consumption. Elevated eosinophil count was found in the blood of 5/8 patients (>10% of total leukocyte count), and in the pleural fluid of 4/7 patients (>10 eosinophils/ml fluid). No other agents and no AFB were found in repeated sputum and pleural fluid specimens.

On standard chest films, pleural effusion was consistent, covering and masking >33% of one total lung surface, and was bilateral in 4/9 patients. The visible part of the lung parenchyma did not show any abnormal parenchymal lesion. Five patients could be followed-up for 2 years after treatment. Despite parasitic clearance in all cases, clinical and radiological improvement did not occur as a rule, as 2/5 patients had persistent clinical symptoms, including chest pain, cough or haemoptysis, and 3/5 had persistent radiological abnormalities, which occasionally worsened in the second year (see Case 1, below).

3.1. Case 1

A 14-year-old boy living in a rural area 120 km north of the capital city complained of chest pain and a dry cough, with slight but recurrent haemoptysis that had lasted for 1 year. He also had anorexia, fatigue and episodic fever not relieved by antibiotics. Clinical examination revealed bilateral pleural effusion. There was no family history of TB.

The patient was referred to Mahosot Hospital in March 2003. He had no fever, was severely stunted (height 1.42 cm, weight 31 kg), had a respiratory rate of 24/min, dullness in both lung bases and pleural friction rub on the left side. Blood eosinophils were 1190/mm³. Chest radiograph revealed significant bilateral pleural effusion, but more on the left side. Aspiration revealed a thick, chylous-like fluid containing 16% eosinophils and 20 typical trematode operculated eggs/ml. *Paragonimus* eggs were found in the sputum. Stool examination disclosed *Paragonimus* eggs together with hookworm eggs, and a large number of motile *Strongyloides stercoralis* larvae. On retrospective interview, the boy acknowledged the frequent eating of raw river crabs.

He was given oral praziquantel 75 mg/kg/d for 3 consecutive days, and albendazole (400 mg/d for 3 d). Within 2 weeks, the symptoms improved, although fluid evacuation was far from satisfactory: three subsequent thoracocenteses resulted in only 660 ml fluid subtraction. He became sputum-negative for *Paragonimus* at the 2 month follow-up and remained so. On the last follow-up, 2 years later, he was well (152 cm, 39 kg), was sputum-negative, had no more parasites in the stools and had a normal range of blood eosinophils (450 cells/mm³); however, his chest radiograph showed a persistent bilateral pleural effusion that had even increased in size on the right side compared with baseline. The patient and family declined any further thoracocentesis or other procedure.

3.2. Case 2

A 33-year-old urban woman from Vientiane was seen in April 2004 at a city district hospital with a 1 month history of chest pain, dyspnoea, cough, rusty sputum and a 5 kg weight loss. A chest film was performed that showed a massive right pleural effusion. Three consecutive sputum specimens were negative for AFB. Despite this, a diagnosis of smear-negative pleuro-pulmonary TB was made, and the patient was started on the directly observed treatment, short-course (DOTS) regimen. As she did not improve after 3 weeks, she decided to go to Mahosot Hospital.

The medical history was significant for raw crayfish consumption and hyperthyroidism. There was no history of TB among household members. Clinical examination disclosed no fever but an obvious pleuritic syndrome, and also a goitre with exophthalmia. Blood count showed 1500 eosinophils/mm³. Neither *Paragonimus* eggs nor AFB were found in three consecutive daily sputum specimens; however, the pleural fluid aspirate yielded *Paragonimus* eggs and a 5% eosinophil rate. Stool examination revealed *Opisthorchis viverrini* eggs. The anti-TB treatment was stopped and a standard course of praziquantel given. Three thoracocenteses were performed during the subsequent month, allowing a total subtraction of 3700 ml thick fluid; however, complete pleural evacuation could not be achieved.

At the 12 month follow-up, the patient was almost symptom-free, although a residual right basal pleural effusion was noted with ill-defined patchy nodular and multiple small cystic lesions at the right lung base.

3.3. Case 3

A 33-year-old male farmer from Bolikhamsai Province complained of chest pain with progressive dyspnoea that had lasted 3 months. Fever was absent. He received several courses of antibiotics to no effect. Chest film showed complete left-side pleural effusion. Two thoracocenteses, 2 d apart, withdrew a total of 1000 ml thick brownish fluid that rapidly refilled the pleura within days. Eosinophils were within normal ranges in the blood and absent in the pleural fluid: the latter was predominantly lymphocytic. Ova were not found in either the sputum or pleural fluid. TB, paragonimiasis or a tumoral cause were considered. A pleural tube was placed in the left cavity and praziquantel was started the same day. On the second day, a motile worm passed through the tube. This had the typically curved, leaf-shaped, brown fleshy aspect of an adult trematode worm, measuring 11 × 6 mm, with morphologic characteristics of *Paragonimus* spp.

4. Discussion

In our experience, paragonimiasis is a relatively common and under-recognized cause of pleural effusion in Lao PDR; grossly, as common as pleural TB. All nine patients described here presented as a typical, apparently primary pleuritic syndrome. In settings where TB is highly prevalent in poor, young or middle-aged people, this picture inevitably suggests pleural TB (Cases 2 and 3), which is, however, more likely to be acute, unilateral and of relatively moderate volume.^

Misdiagnosis between paragonimiasis and TB seems common throughout the world (e.g. in India, where some 60% of paragonimiasis cases may be confused with smear-negative TB). Only two of our nine patients had concurrent general symptoms of wasting or low-grade fever, which might have
suggested TB but were later attributed to co-morbidities, i.e. massive intestinal strongyloidiasis (Case 1) and hyperthyroidism (Case 2). Remarkably, six of our nine patients reported protracted blood-tainted sputum, which is the hallmark symptom of paragonimiasis. In none of our cases did pleural fluid have a clear sero-fibrinous appearance, but rather appeared yellow-brown, odourless and pus-like, and had to be differentiated from thoracic empyema or chylothorax.

An eosinophilic pleural fluid was an inconsistent finding (3/7 cases), and despite suggesting paragonimiasis in endemic areas, it lacks specificity and has been described in many different diseases including parasitic diseases such as fascioliasis, sparganosis, strongyloidiasis or metagonimiasis, or non-parasitic diseases such as TB, lymphoma and cancer. To our knowledge, the discharge of a vivid adult Paragonimus worm through a chest tube (Case 3) is unprecedented. Eosinophilia (in blood or pleural fluid) may be prominent in acute phase but not in the chronic stage. Finding Paragonimus ova (in sputum, pleural fluid or stools) is actually the basic and most easily available diagnostic tool despite suboptimal sensitivity rates, ranging from 37 to 88% for sputum ova; for this reason we think that paragonimiasis is largely under-diagnosed. ELISA serologic tests may increase sensitivity to 99–100%; unfortunately, they are unavailable in most endemic areas.

Regarding the outcome of paragonimiasis, most reference papers and textbooks mention cure rates of around 90%. Thus, we expected a much higher rate of pleural effusion resolution, as a result of repeated thoracocenteses and praziquantel courses. In fact, in six of our nine cases, the fluid was difficult to evacuate, owing to its thickness, or to pleural thickening or loculation, which may occur in the late course of the disease.

Clinical mid- or long-term outcomes and possible sequelae of paragonimiasis are not well documented, and most statements are inferred from the high parasitic clearance rates. The disease was once referred to as ‘benign epidemic haemoptysis’ because of its usually self-limited course. However, several well-documented case reports of massive and recalcitrant pleural effusion that required surgery Patients with unsatisfactory outcome, like some of those described here, may be late-presenting or heavily-infested with definitive tissue damage like lung and pleural fibrosis or bronchiectasies. In a previous study from Cameroon, 86% of the patients had persistent radiographic changes 6 months to 4 years after praziquantel, and one case had worsening images, similar to our Case 1. In another study from Japan, careful endoscopic, CT-scan assessment and follow-up of 13 patients showed 69% with persistent pleural lesions, 78% with bronchial stenosis and 25% with atelectasia, some of these changes persisting well after praziquantel in five patients, and requiring thoracotomy and decortication in one. A few case reports from Japan also documented recurrent pleural effusion and one case of chronic pleuritis due to P. westermani that showed resistance to standard chemotherapy but was finally cured with three additional courses of praziquantel.

The mechanisms by which pleural effusion forms and persists remains unclear. Parasitic antigens and cytokines released in the pleural space may induce inflammatory, vascular and fibrotic changes that may persist or even worsen after anti-parasitic drugs have killed the adult worms. In addition, co-infection with TB should be ruled out, which is not easy in settings lacking technical facilities for pleural biopsy and PCR. Further investigations are needed to assess the best management options, including the risk of bacterial infection from drainage in unsafe environments, and possible lung and pleural sequelae. Finally, paragonimiasis should be considered in any pleural effusion, especially when it occurs in endemic areas, in association with discrete haemoptysis, and a protracted course.

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