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Diagnosis and surgical management of pericardial effusion due to paragonimiasis

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ABSTRACT

Objectives: The pericardial effusion (PE) caused by paragonimiasis is rarely reported. This study aims to present experience in the diagnosis and surgical management of PE due to paragonimiasis.
Methods: Medical records of 57 children who were diagnosed with PE due to paragonimiasis and underwent surgery at Children's Hospital of Chongqing Medical University between January 2012 and August 2018 were retrospectively reviewed.
Results: The average age of this group was 7.6 ± 3.0 years. Patients were mainly from Chongqing and Sichuan areas. ELISA for *Paragonimus skrjabini* in all 57 patients showed positive results. Moderate or large PE were identified in 12 and 45 patients, respectively. All patients underwent surgery either by pericardectomy or thoracoscopic surgery. Pathological exams indicated massive eosinophil infiltration in all 57 specimens. After 3–4 courses of praziquantel therapy, the clinical outcomes were satisfactory.
Conclusions: Typical endemic history, eosinophilia and multiple serous effusion raise suspicions of paragonimiasis. Once moderate to large PE is identified in patients with paragonimiasis, surgical treatment is necessary.

Introduction

Paragonimiasis is a parasitic infection caused by trematodes of the *Paragonimus* genus. Consumption of raw or undercooked crustaceans (ie, crab or crayfish) containing *Paragonimus* metacercariae leads to Paragonimiasis. It is an important food-borne zoonosis that is endemic in Asia, America and Africa (Devi et al., 2007). It is believed that at least 195 million people in China are at risk of infection with *Paragonimus*parasites (Liu et al., 2008). In southwest China, *P. skrjabini* is predominantly prevalent and it is also the main causative agent of extra-pulmonary paragonimiasis (Peng et al., 2017; Procop, 2009). In the literature, surgical management of pericardial effusion (PE) due to paragonimiasis is rarely reported. In our institution, a large number of patients need to undergo surgery due to moderate to large PE. Therefore, in this study, we aim to present our experience in the diagnosis and surgical management of PE due to paragonimiasis in 57 children.

Methods

Patient demographics and definition

A review of the medical database at Children's Hospital of Chongqing Medical University between January 2012 and August 2018 identified 57 consecutive patients with paragonimiasis who underwent surgery due to PE. It is difficult to find eggs in *P. skrjabini* infected humans, as humans are not the normal definitive host. Typical endemic history, eosinophilia and multiple serous effusion raised suspicions of paragonimiasis. And the confirmed diagnosis of paragonimiasis was based on serologic tests for paragonimiasis and biopsy. Inclusive criteria were: patients with paragonimiasis underwent surgery due to moderate or large PE. Exclusive criteria were: (1) patients with paragonimiasis were diagnosed with minimal PE and did not undergo surgery; (2) patients with paragonimiasis underwent surgery due to other causes such as cerebral hemorrhage.

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The time to diagnosis was defined as the time period from initial symptoms to confirmed diagnosis. High protein level (>30 g/L) of the PE indicated exudative fluid. Cardiac tamponade was considered in PE patients with low blood pressure and jugular vein distension, and urgent surgery would be performed in such cases.

Diagnosis

Once the cardiac ultrasonography revealed PE in patients who have been living in or have travelled to the endemic region and who have consumed raw crustaceans or drank unboiled stream water, the diagnosis of paragonimiasis was considered. Routine blood test (RBT) was obtained to count leukocytes and eosinophils. Leukocyte counts over 12000/mm^3 and eosinophils percentage over 5% of leukocytes were considered abnormal. A specific serologic test for *P. skrjabini* by using enzyme linked immunosorbent assay (ELISA) was performed in suspected patients. *P. skrjabini* adults antigens were used in the ELISA with 95.5% sensitivity and 100% specificity (Yu et al., 2017). Cardiac ultrasonography was performed in every patient to detect PE. The amount of PE was graded according to depth of the maximal diastolic separation between epicardium and pericardium, and was categorized as minimal (<9 mm), moderate(10–19 mm) or large (>20 mm).

A review of chest X-ray, chest computed tomography (CT), abdominal CT, and abdominal ultrasonography were performed to evaluate combined serous effusion, pulmonary and abdominal lesions. Magnetic resonance imaging (MRI) or CT of the brain was conducted in patients who complained of neurological symptoms. To exclude tuberculosis (TB) in particular patients, the smears obtained from sputum or effusion were stained with Ziehl–Neelsen stain and cultured for acid-fast bacilli. Furthermore, purified protein derivative test and interferon-γ release assays were also performed to exclude suspected TB. Effusion specimens were tested with routine and biochemical examinations.

Surgical method

The indication for surgery was moderate or large PE. Patients were placed in supine position with left chest elevated 30 degrees. A left parasternal incision through the 4th or 5th intercostal space was performed. The parasternal incision was horizontal and 4–5 cm width. Then a 3–4 cm width of rib was resected with periosteum reserved to expose the mediastinum. Parietal pericardium then was opened and effusion was aspirated for laboratory examinations. On the left side, the partial resection of pericardium was limited to anterior of left phrenic nerves. On the right side, the pericardium was extracted and resected as much as possible. A 4×4 cm pericardial specimen was sent for pathological examination. The parietal pleura was opened to connect the pericardial window with the pleural cavity. Due to the viscous and mucopurulent nature of pleural effusion in paragonimiasis patients, pleural debridement and chest drainage were necessary in most of our patients.

In recent years (after 2015), thoracoscopic surgery was performed for PE. The approach was carried out via a left posterolateral position. A thoracoscope was introduced through the sixth intercostal space in the middle axillary line. Two additional trocars were placed along the anterior and posterior axillary line. After identification of the right phrenic nerve, a partial resection of the pericardium was performed. An exploration and clearance of ipsilateral pleural effusion was also performed as necessary. However, in patients with severe pleural adhesion and unsatisfactory exposure, the thoracoscopic surgery would be converted to thoracotomy. No operation was needed to drain the ascites.

Post-operative management

Chest CT scan and cardiac ultrasonography were conducted in every patient before discharge to evaluate the serous effusion. Praziquantel therapy was conducted when the diagnosis of paragonimiasis was considered. A dose of 25 mg/kg, 3 times a day were ordered. A complete course was defined as 7 days treatment when oral praziquantel was taken consecutively in the first 3 days and no praziquantel consumption in the latter 4 days. Patients would be discharged if no or only minimal PE was found after first course of praziquantel therapy.

Follow-up

All of the 57 patients were required to take one course of praziquantel weekly and return for outpatient follow-up after discharge. Weekly praziquantel therapy was required until chest CT scan or ultrasonography showed minimal pericardial and pleural effusion.

Results

Patient demographics and clinical manifestations

During a time period of 6 years, a total of 57 patients with paragonimiasis who underwent surgery due to PE were included. Due to the involvement of pericardium, all 57 cases were categorized into ectopic paragonimiasis. This group consisted of 40 males and 17 females, with an average age of 7.6 ± 3.0 years (range 2.8–13.7 years).

23 patients (40.4%) were from the Chongqing area, 30 patients (52.6%) were from the Sichuan area, 2 patients (3.5%) were from the Guizhou area and 2 patients (3.5%) were from the Yunnan area (Figure 1). 54 patients (94.7%) were from a rural area, while 3 patients (5.3%) were from an urban area. All three patients who lived in the urban area reported a history of traveling to a rural area. 29 patients (50.9%) presented with a history of consuming raw or undercooked crabs or crayfish. 12 patients (21.5%) presented with a history of drinking unboiled stream water, however, declined a history of raw or undercooked crustaceans consumption. 17 patients (29.8%) reported no history of raw crustaceans or stream water consumption.

The initial symptoms are summarized in Table 1. The most frequent symptom was GI symptoms. 2 patients were asymptomatic and were admitted to our institution due to PE which was discovered by physical exams. Neurological symptoms were seen in 5 patients, and 3 of them complained of syncope once. One patient was admitted to our institution due to cerebral paragonimiasis primarily. However, after one course of praziquantel therapy, the cardiac and chest ultrasonography revealed moderate pericardial and pleural effusion. Two patients were diagnosed with paragonimiasis at the pulmonary department, and neither of them presented with PE during the hospitalization. Therefore, they were discharged after one course of praziquantel therapy. However, they were re-admitted to our institution due to large PE after overall 2 courses of praziquantel.

Laboratory findings

RBT was performed in all 57 patients (100%). The leukocytes level was elevated in 31 patients (>12000/mm^3) with average leukocyte counts of $17.7 \pm 5.9 \times 10^3$/mm^3, while the RBT of the other 26 patients indicated a normal leukocyte level. RBT of 53

Figure 1. Distribution of our included patients and location of the Three Gorges Dam.

patients (93.0%) indicated eosinophilia with elevated eosinophils level (>5% of leukocytes). The mean eosinophils percentages and counts were 28.4 ± 17.1% and 4.7 ± 4.4 × 10^3/mm^3, respectively. The TB relevant examinations were performed in 15 patients, and none of them established a diagnosis of TB. ELISA for paragonimiasis was performed in 57 patients, and all of them showed positive serologic results for *Paragonimus* infection.

The examinations of PE of 46 patients were available. In 36 patients, the PE was viscous, yellowish and turbid. In the other 10 patients, the PE was hemorrhagic and turbid. All 46 patients showed an elevated level of protein (>30 g/L) and eosinophil counts.

Table 1
Summary of the initial symptoms of included patients.

Symptoms	Number of patients (n)	Percentage (%)
GI symptoms[a]	43	75.4%
Dyspnea	17	29.8%
Cough	12	21.5%
Fatigue	12	21.5%
Fever	11	19.3%
Edema	10	17.5%
Chest pain	6	10.5%
Migratory subcutaneous mass	6	10.5%
Neurological symptoms[b]	5	8.8%
Palpitation	3	5.3%
Asymptomatic	2	3.5%
Rash	1	1.8%
Weight loss	1	1.8%

GI Gastrointestinal.
[a] GI symptoms included abdominal distension, abdominal pain, diarrhea, vomiting and poor appetite.
[b] Neurological symptoms included headache, dizzy and syncope.

Imaging findings

Cardiac ultrasonography was performed in all 57 patients, chest CT scan was performed in 52 patients (91.2%), abdominal CT scan was performed in 21 patients (36.8%), cerebral CT scan was performed in 5 patients (8.8%), chest ultrasonography was performed in 41 patients (71.9%), and abdominal ultrasonography was performed in 41 patients (71.5%).

Moderate or large PE was identified in 12 (21.1%) and 45 (78.9%) patients, respectively. Unilateral pleural effusion was identified in 8 patients (14.0%), bilateral pleural effusion was identified in 47 patients (82.5%) and ascites was identified in 38 patients (66.7%). Multiple serous effusion was identified in all 57 patients (Figure 2).

According to the imaging findings, pulmonary consolidation was identified in 34 patients (59.6%), and it is the most frequent imaging finding among our patients (Table 2). Pulmonary cavity lesion, which was the typical sign for paragonimiasis, was only identified in 7 patients (Figure 3).

Surgical outcomes

Pericardectomy was performed in 32 patients (56.1%). Thoracoscopic surgery was performed in the other 25 patients, however, 3 of them were converted to open surgery due to severe

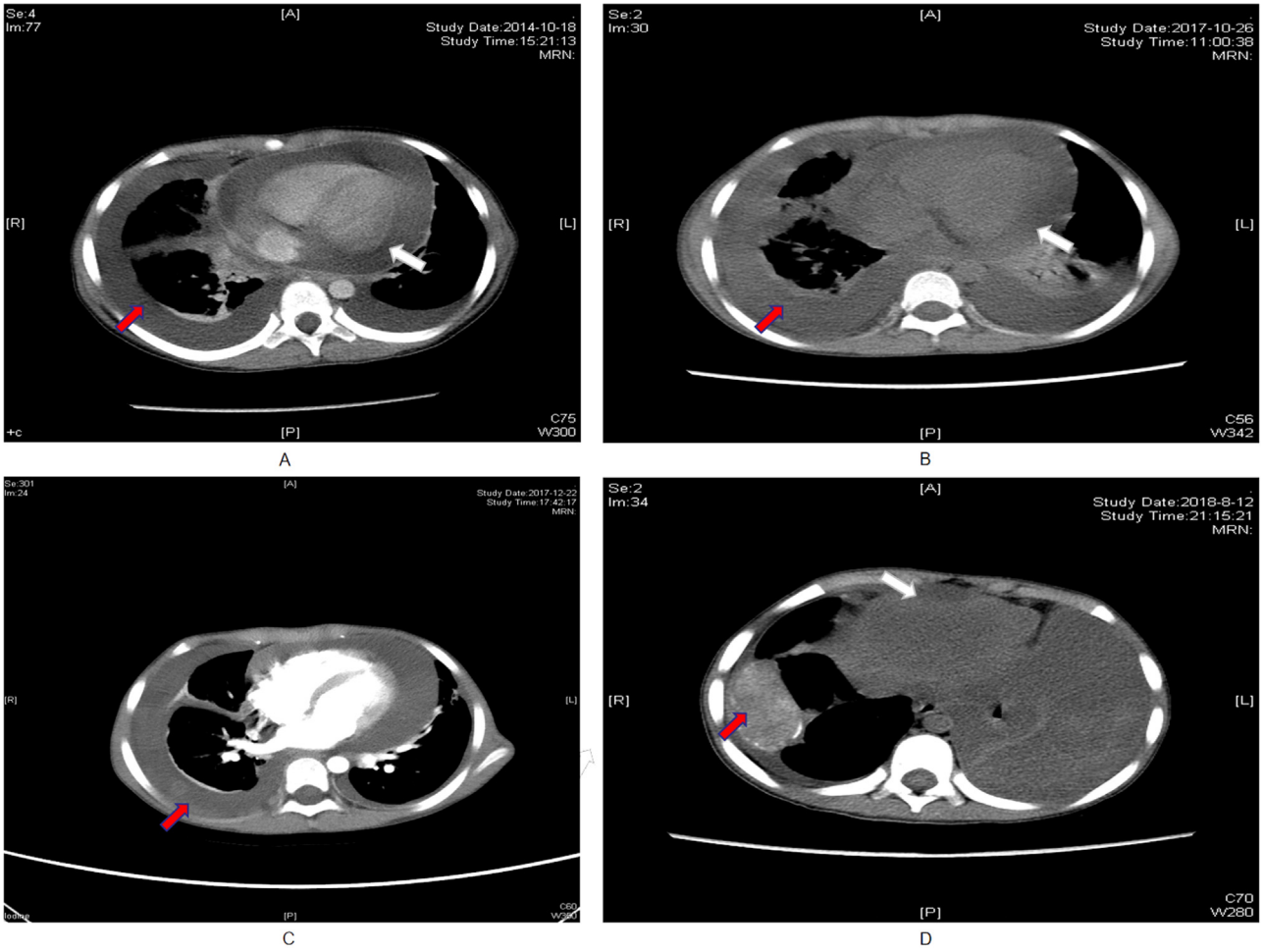

Figure 2. Chest and abdominal CT scan of four patients with paragonimiasis.
A. 12-year-old female. (A) shows the large pericardial effusion and bilateral pleural effusion. *Red arrow* indicates pleural effusion and *white arrow* indicates large pericardial effusion.
B. 9-year-old male. (B) shows the large pericardial effusion and bilateral pleural effusion. *Red arrow* indicates pleural effusion and *white arrow* indicates large pericardial effusion.
C. 8-year-old female. (C) shows large pericardial effusion and bilateral pleural effusion. *Red arrow* indicates fibrous exudation in the effusion with elevated density.
D. 6-year-old male. (D) shows encapsulated effusion, pleural calcification (*red arrow*) and moderate pericardial effusion (*white arrow*).

adhesion and unsatisfactory exposure. Urgent surgery was performed in 36 patients due to cardiac tamponade. In addition, 8 patients underwent unilateral chest drainage and 47 patients underwent bilateral chest drainage. Additionally, 11 patients underwent pleural decortication due to encapsulated effusion or chronic purulent effusion.

Table 2
The imaging findings of included patients.

Imaging findings[a]	Number of patients (n)	Percentage (%)
Pulmonary consolidation	34	59.6%
Hepatomegaly	32	56.1%
Pleural thickening	27	47.4%
Hilar/mediastinal lymphadenopathy	14	24.6%
Atelectasis	10	17.5%
Splenomegaly	8	14.0%
Pulmonary cavity lesion	7	12.3%
Hepatic nodule	5	8.8%
Pulmonary nodule	4	7.0%
Hepatic/splenic calcification	2	3.5%
Pleural calcification	2	3.5%
Cerebral haematoma[b]	1	1.8%

[a] Pericardial effusion was identified in every patient in this group, so it is not presented in this table.
[b] This patient was admitted due to cerebral paragonimiasis, but the cardiac ultrasonography revealed moderate pericardial after one course of praziquantel therapy.

Pathological examination

All 57 pericardial specimens were sent for biopsy. Procop (2009) reported that residual necrosis and inflammatory response instead of worms are usually observed in the biopsy of ectopic paragonimiasis. Similarly, due to ectopic infection of *P. skrjabini*, all specimens showed massive eosinophils infiltration (Figure 4).

Diagnosis and post-operative management

Typical endemic history, eosinophilia and multiple serous effusion increased suspicions of paragonimiasis. The diagnosis of paragonimiasis was mainly established by the serologic test and pathological examination. The mean time to diagnosis was 16.5 ± 13.5 days.

All patients underwent praziquantel therapy after diagnosis of paragonimiasis was confirmed, and all of them responded well to praziquantel therapy. The chest CT scan and cardiac ultrasonography of all 57 patients showed absorption of pericardial and pleural effusion after one course of praziquantel therapy.

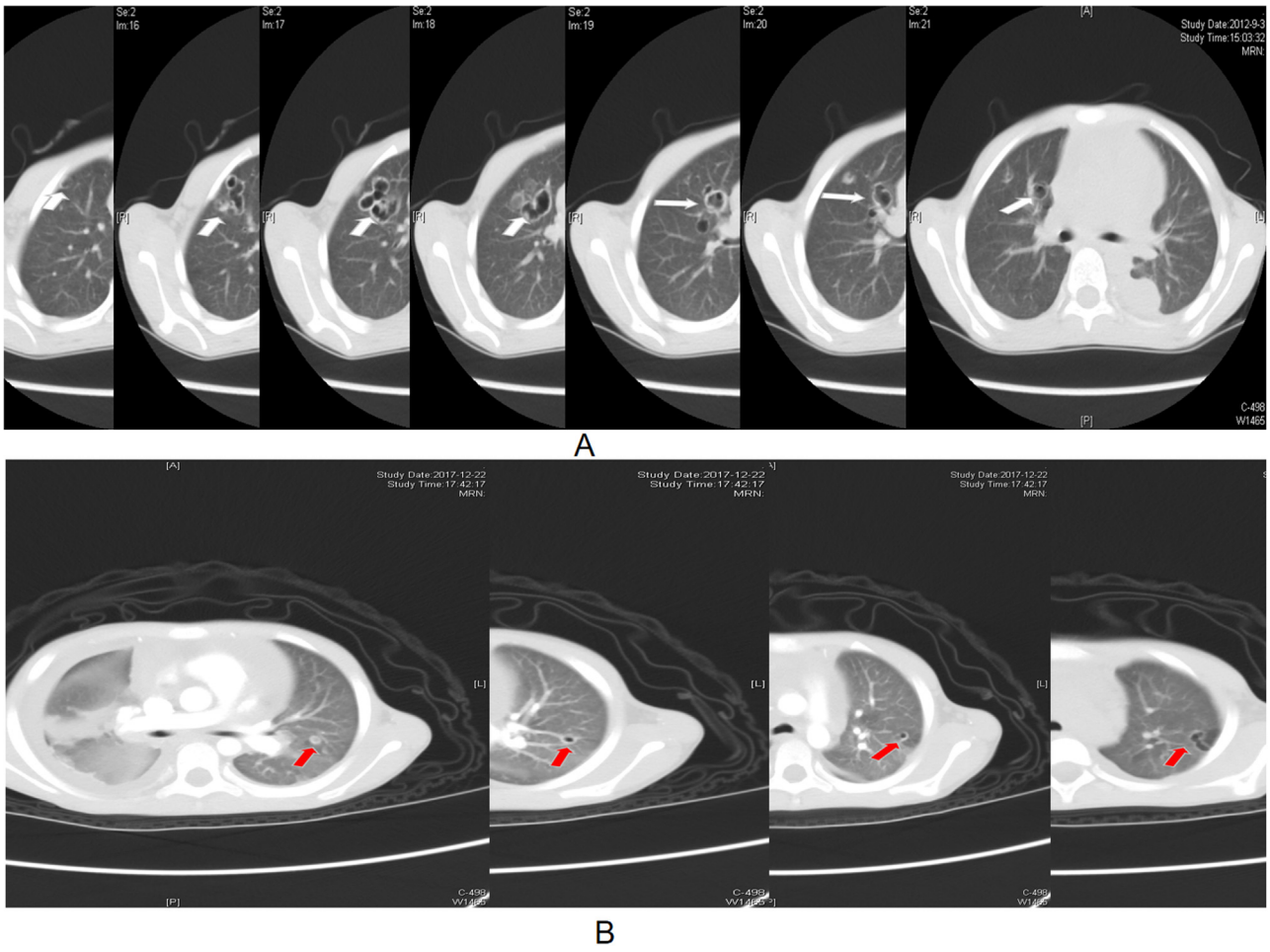

Figure 3. Pulmonary cavity lesions and 'tunnel sign' which is a tubular structure on CT scan and indicative for migratory worms.
(A) shows cavity lesions in the right lower lobe in a 11-year-old male. (B) shows cavity lesions in the left lower lobe in a 8-year-old female.

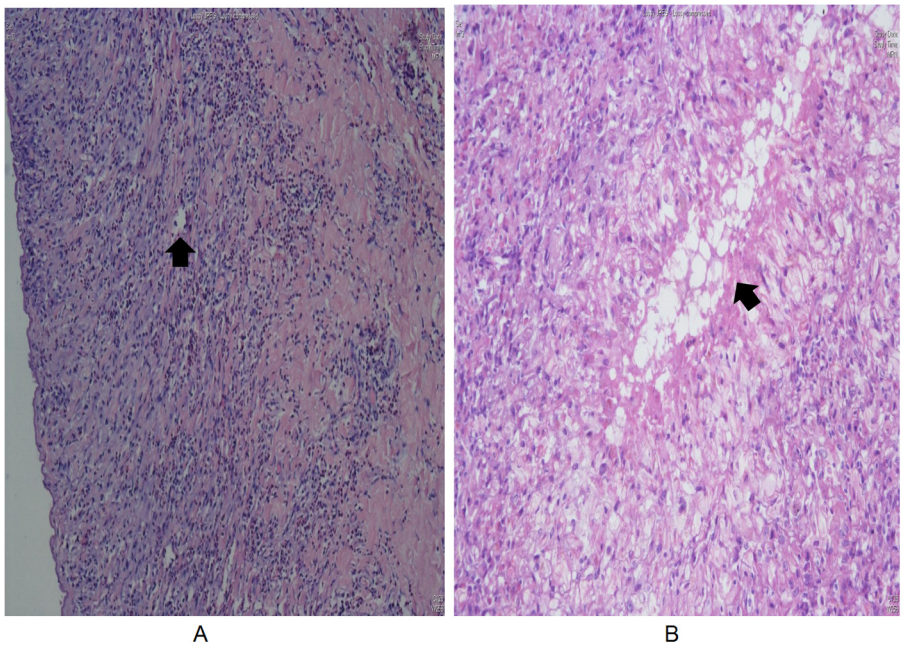

Figure 4. The pathological examinations of pericardial specimens after surgery (HE staining).
A and B shows massive eosinophils infiltration and areas of relative hypocellularity that may be consistent with previous passage of a migratory worm (*black arrow*).

Follow-up

All 57 patients were required to return for outpatient follow-up, however, 3 of them were lost to follow-up. The mean follow-up time was 34.7 ± 23.5 months. All 54 patients needed an additional course of praziquantel therapy after overall two courses of praziquantel therapy due to incomplete absorption of pulmonary lesions and pleural effusion. Eventually, 33 patients finished overall 3 courses of praziquantel therapy, while 21 patients finished overall 4 courses of praziquantel therapy. At the last follow-up, minimal pleural or pericardial effusions (Figure 5) were found in 5 and 2 patients, respectively. None of them needed further treatment. In 47 patients, neither pleural nor pericardial effusion was detected.

Comment

Paragonimus genus has a complex life cycle that includes snails and crustaceans as their intermediate hosts and mammals as the definitive hosts (Procop, 2009). After consumption of raw snails or crustaceans, the juvenile stage of *Paragonimus* genus penetrates through the small intestine and enters the peritoneal cavity (Lane et al., 2009). In the next stage, migration through the diaphragm into the pleural cavity occurs. In most *Paragonimus* species, the metacercariae migrates to human's lung and matures into adult worms that produce eggs (Vélez et al., 1937). However, *P. skrjabini*, which is predominantly prevalent in the Sichuan and Chongqing areas, cannot mature into adults in humans (Zhang et al., 2012; Xia et al., 2015). Therefore, *P. skrjabini* migrates into different organs and leads to severe complications.

The diagnosis of paragonimiasis could be challenging due to variable and non-specific presentations. The most frequent symptoms of this group are gastrointestinal symptoms, which is consistent with previous studies (Yatera et al., 2015; Nagayasu et al., 2015; Gong et al., 2017), and this possibly could be explained by the penetration of the small intestine after infection (Procop, 2009). Other symptoms, such as syncope, dyspnea, fatigue, edema and palpitation, are mainly due to the PE and obstruction of venous blood inflow. Migratory subcutaneous mass, which raises strong suspicions of paragonimiasis, was only identified in 6 patients (10.5%). Traditionally, the confirmed diagnosis of paragonimiasis is based on the presence of eggs in stool or sputum, or of flukes in pathological specimens (Nagayasu et al., 2015). Unlike the other *Paragonimus* species (ie. *P. westermani*), it is difficult to find eggs in *P. skrjabini* infected humans, as humans are not the normal definitive host (Yu et al., 2017; Wang et al., 2014). Furthermore, the immature worm is not usually found in biopsy from patients with larva migrans of *P. skrjabini*. Instead, residual necrosis and inflammatory response are observed (Procop, 2009). Therefore, the diagnosis in our group is highly suspected by the serologic test and confirmed by pathological examination. Although the ELISA for *P. skrjabini* in our group (Yu et al., 2017) tested against *Schistosoma, Echinococcus,* and *Trichinella* etc, no other species of *Paragonimus* genus such as *P. westermani* was tested. So the

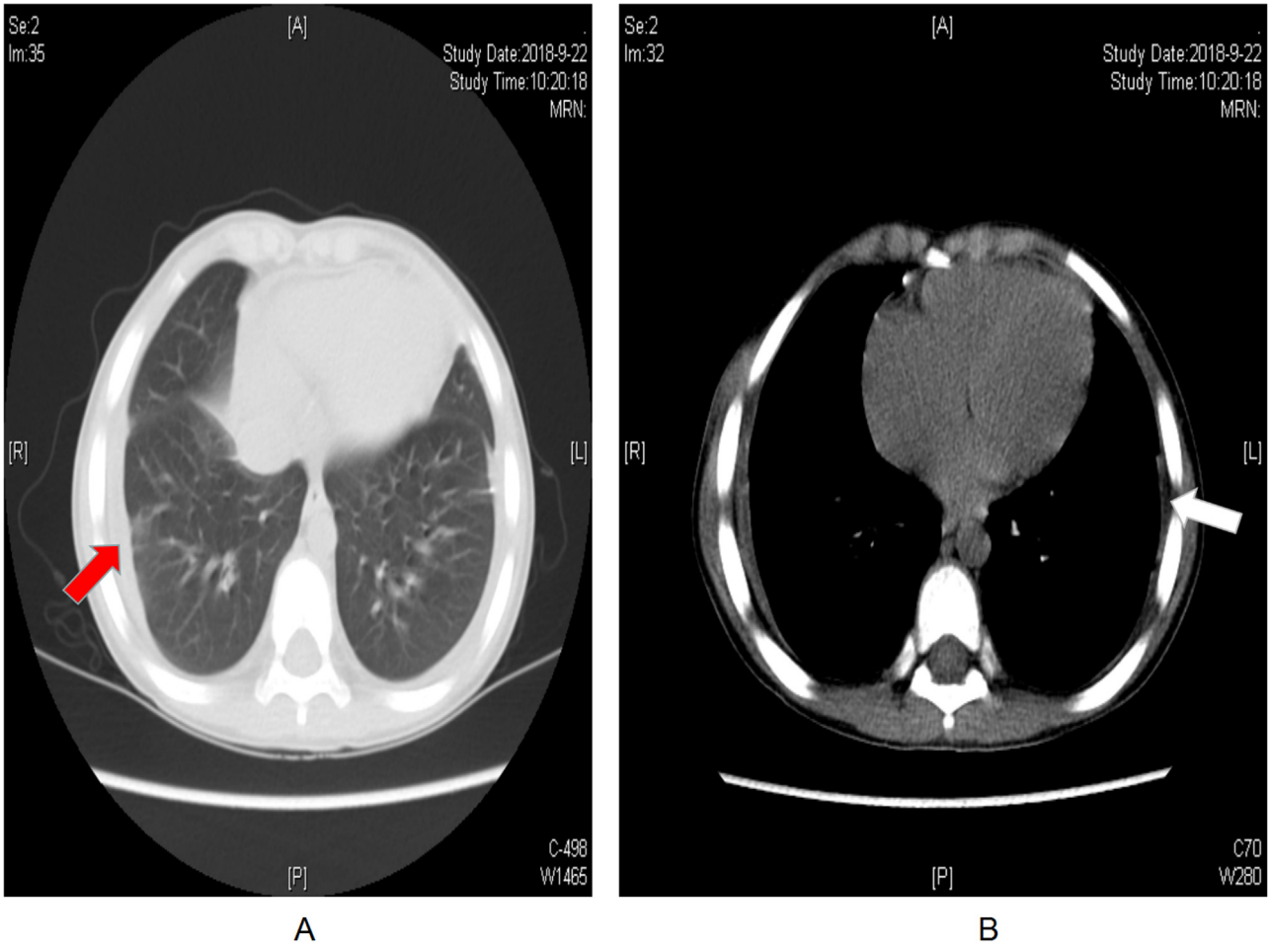

Figure 5. The chest CT scan after overall three courses of praziquantel therapy in a 6-year-old male. (A) shows mild pleural effusion(*red arrow*). (B) shows thickening pleura (*white arrow*).

causative agent in our group is most suggestive of *P. skrjabini*, however, further investigation is required to confirm the exact species.

Paragonimiasis is a severe public health issue in southwest China. The water level of the Yangtze River rose significantly after the construction of Three Gorges Dam (Figure 1), resulting in more streams that are suitable for crab reproduction (Zhang et al., 2002). A previous investigation (Zhang et al., 2012) result showed that the rate of crab infection with *P. skrjabini* metacercariae was about 40% in the Sichuan and Chongqing areas. Therefore, knowing the endemic history is very essential in the diagnosis of paragonimiasis. However, not every child presented a clear endemic history. A total of 17 patients declined a history of raw crustaceans or stream water consumption. Therefore, even in the endemic area, paragonimiasis could not be excluded completely when there is no history of raw crustacean consumption, especially in pediatric patients who may not be able to describe their dietary history clearly.

Generally, patients with minimal PE could be manipulated with medication, and no constrictive pericarditis was observed in our institution. The indication of surgery is moderate to large effusion. In the late 1990s and early 2000s, patients with paragonimiasis and moderate PE who simply underwent pericardiocentesis in our institution suffered from constrictive pericarditis in the follow-up, and pericardial stripping could not be avoided. The effusion in patients with paragonimiasis is generally viscous and contains massive fibrous exudation. To potentially lessen the likelihood of subsequent constrictive pericarditis, surgical drainage should be considered. On the other hand, due to the unavailability of egg identification, surgery also offers us pericardial specimens for biopsy. Surgery also guarantees pleural debridement and drainage as encapsulated effusion is found in many of our cases. Traditionally, the pericardium covering the left ventricle and right ventricular outflow tract could be excised to prohibit formation of constrictive pericarditis with partial pericardectomy. Thoracoscopic resection was not performed in our institution until 2015. And it could excise the pericardium covering the vena cava and right atrium. In that case, the lowest part of the pericardial sac could be opened to guarantee sufficient drainage of effusion. However, no conclusion could be made regarding the superiority of one approach over the other in the current study. The approach is mainly determined by the preference of surgeons and adhesions of the pleural cavity.

The outcomes in the follow-up are overall satisfactory. 54 patients needed an additional course of praziquantel therapy after overall two courses of praziquantel therapy due to incomplete absorption of pulmonary lesions and pleural effusion. However, in the literature, cure rate is about 100% after one course of praziquantel therapy (Liu et al., 2008). In our previous practice (Li et al., 2011; Li and Liu, 2013) (two Chinese studies published before 2011), one course of praziquantel therapy was not sufficient in patients with PE. There were also similar reports from two English studies (Gong et al., 2017; Oh et al., 2011). In our group, accumulation of pericardial effusion occurred pre-operatively in three patients after one or two courses of praziquantel therapy. Therefore, we recommend longer courses of praziquantel therapy in the management of paragonimiasis with moderate or large PE. This may be related to a different drug susceptibility of *P. skrjabini* versus other *Paragonimus* genus.

In conclusion, typical endemic history, eosinophilia and multiple serous effusions indicate the likelihood of paragonimiasis. ELISA for *Paragonimus* species should be performed to provide a rapid diagnosis. Cardiac ultrasonography and CT scan are crucial in the diagnosis and evaluation for multiple serous effusions. Once moderate or large PE is identified, surgical treatment is necessary. Longer courses of praziquantel therapy should be required in the treatment for patients with paragonimiasis and moderate or large PE.

Conflict of interest

None declared.

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Ethical approval

Due to the retrospective nature of this work, ethical approval is not required.

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