Case Report

Paragonimiasis diagnosed by CT-guided transthoracic lung biopsy: Literature review and case report

Cung-Van Cong, MD, PhD, Tran-Thi Tuan Anh, MD, Tran-Thi Ly, MD, Nguyen Minh Duc, MD

ABSTRACT

More than 40 different species of the parasitic flatworm Paragonimus have been identified worldwide, including in Vietnam, but only 10 species are known to cause disease in humans, particularly Paragonimus westermani. Paragonimus are transmitted through the ingestion of raw foods, especially freshwater shrimp, and crab. Paragonimiasis causes pneumonia, which can present as acute or chronic, with symptoms including prolonged cough, chest pain, shortness of breath, and hemoptyis. Hematologic changes include eosinophilia and the presence of specific antibodies for Paragonimus in the blood. Diagnosis is confirmed when Paragonimus specimens or eggs are found in the sputum or pleural fluid. The specificity of imaging is not high, but imaging can be used to guide the diagnosis. After the failure of microbiological diagnostic methods, lung biopsy can be used to confirm a diagnosis of paragonimiasis. We present a paragonimiasis case associated with unique features, including epidemiologic factors, atypical clinical signs, no increases in blood eosinophils, and negative microbiological tests. Although the patient was suspected of tuberculosis or lung cancer, imaging studies were consistent with the presence of lung flukes. Three transthoracic lung biopsies were performed, and pathology revealed a cystic structure containing Paragonimus on the third biopsy.

© 2022 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)
Introduction

The parasitic flatworm genus *Paragonimus* contains more than 40 different species, but only 10 species cause disease in humans, particularly *Paragonimus westermani*. In Vietnam, the primary species associated with this disease is *Paragonimus heterotremus* [1,2,3]. Although paragonimiasis occurs globally, 90% of cases have been reported in Asia [1]. Once they reach the lungs, *Paragonimus* lay eggs that can be found in sputum, entering the environment when sputum is expectorated. When sputum is swallowed into the digestive tract, the eggs can survive, and be released in feces. In an aquatic environment, the eggs hatch into hairy larvae (miracidium), which infects snails and develops into tailed larva ( cercaria). The caudal larva leaves the snail to penetrate shrimp and freshwater crabs, forming cysts in the viscera of these organisms (metacercaria). When humans or animals eat shrimp or crabs containing *Paragonimus* larvae, the larvae escape the cyst in the duodenum, pass through the wall of the digestive tract into the abdominal cavity, and then pass through the diaphragm into the pleural cavity and nest in the lung parenchyma, which restarting the cycle. *Paragonimus* lesions in the lungs are visible on chest X-ray and chest computed tomography (CT), and these parasites can also reside in the heart, peritoneum, liver, kidneys, subcutaneous tissues, intestines, and brain [1,4,5,6].

Clinically, paragonimiasis belongs to a group of diseases caused by pulmonary parasites, characterized by eosinophilia and the appearance of specific antibodies in the blood. Diagnosis is confirmed when *Paragonimus* specimens or eggs are found in the sputum [1,2,3,4,7,8]. Chest radiographs have low specificity but are very useful in guiding the diagnosis. When microbiological diagnostic methods were negative, a definitive diagnosis can be obtained through pathology (transthoracic lung biopsy specimens, postoperative specimens) [1]. Intervventional diagnostic measures are often used as a last resort due to the potential for complications, but in medical facilities, transthoracic biopsy techniques have improved, and this technique should be encouraged for the early diagnosis of patients [1].

We report a case of a middle-aged woman with an extremely difficult diagnostic process who received medical examinations and treatment at many medical levels. Due to our expertise in chest CT imaging, combined with our perseverance, the case was finally diagnosed, and the patient is currently receiving treatment with good initial results. We hope that describing this case will contribute to the knowledge bases for rare disease cases, assisting our colleagues in determining an optimal approach when encountering similar cases.

Case report

A female patient, 54 years old, who lives in a mountainous area and has a habit of eating grilled shrimp and crab (stone crab caught in freshwater streams), she visited, and was treated at the National Lung Hospital (NLH) 3 times over a period of 3 months.

Fig. 1 - Chest X-ray images from the first time of the patient to our hospital appears many diffuse opacities with different sizes, distributed throughout both lung.

Two months before the first admission, the patient had a severe cough without hemoptysis, chest pain, and mild dyspnea. The patient was examined at the provincial lung hospital, where a chest X-ray showed many round nodules in both lungs. The patient was diagnosed lung metastasis and was transferred to the NLH.

Examination of the patient at the first time of admission. BMI was in the average range. The patient has mild dyspnea. Routine chest x-ray of the patient was performed; The details of the images are presented in Figure 1.

The patient had a chest CT scan with a 64-slice machine, before, and immediately after intravenous contrast injection. Contrast: Xenetic 350 x 100 mL, speed: 4 mL/sec. Capture formula: 130 kV, Xtube 115 mA, slice thickness 3 mm. WW WL: 1200/ -800 (lung parenchymal window); WW WL: 350/50 (mediastinal window). After reconstruction of 0.75 mm thin slices. Images and detailed radiograph reading results are shown in Figure 2.

The patient was tested for tuberculosis (TB) in sputum and bronchial lavage (BAL) samples, with the following results: acid-fast bacillus (AFB) negative; Gene Xpert MTB/RIF was negative; and culture negative for MTB. The white blood cell (WBC) count was not elevated (9400 G/L), and eosinophils were within normal limits (0.22%). Blood biochemical tests were within normal limits. The presence of *Paragonimus* antibodies was assessed using enzyme-linked immunosorbent assay (ELISA), which revealed a positive outcome, but the antibody titer was only slightly elevated (optical density of 0.185 compared with the normal value of < .147).

The patient had a transthoracic biopsy under computed tomography guidance. Detailed images of which are presented
Fig. 2 – CT image of chest, lung window (A-C) and mediastinal window (D) Before contrast injection; (E-F) After contrast injection. (A-C) 3 lower slices of carina showing multiple nodules, 1-3 mm in size, round, smooth, few nodules involving pulmonary vessels (red arrow). (D) Before contrast injection, mediastinal window, many nodules, irregular size, heterogeneous density, with calcified components (yellow arrow). (E-F) Chest CT after contrast injection shows strongly contoured nodule, with no enhancement in the nodule (yellow arrow). The radiologist thinks highly of the possibility of malignancy spreading to the lungs (metastasis), but does not rule out the presence of inflammatory nodules due to parasites. (Color version of the figure is available online.)

Fig. 3 – First transthoracic lung biopsy images. (A) In the prone position of the patient, determine the nodule will be biopsied (yellow arrow). (B) Image of a 20 G coaxial core biopsy needle inserted into the node (yellow arrow). Three pieces of node have been cut. (C) After the needle is removed, there is light bleeding in the cut area, no pneumothorax (red arrow). (Color version of the figure is available online.)

In Figure 3 and microscopic pathology results are presented in Figure 4.

The patient was diagnosed with pneumonia and treated with specific antibiotics for 2 weeks (15 days), resulting in clinical improvement. Based on the chest CT image, we still have not ruled out the possibility of pulmonary parasites, so the patient was transferred to a hospital specializing in parasitology for the specific diagnose, and treatment of *Paragonimus*.

Examination upon admission to the NLH for the second treatment. After receiving specific treatment for fascioliasis at the Parasitology Institute for 12 days (Trial treatment even though there is no evidence of parasites), the radiologist found an increase in the density of nodules on chest X ray, suggesting the possibility of progressive pulmonary TB, and the patient returned to the NLH.

We take back this patient and performed chest X-ray for her. The images of which are presented in Figure 5.

The patient underwent multiple tests to obtain diagnostic evidence and exclude potential differential diagnoses. All TB tests (sputum and BAL) were negative, and all tests for *Parag-
results
morphology
Representative
image
Fig. 4 – Microscopic pathology results for the first lung biopsy specimens. Hematoxylin and eosin (HE) stain (× 40; Code 0282 – B18) revealed the biopsy fragments consisted of alveolar tissue, fibrous connective tissue, polymorphonuclear leukocytes, mononuclear inflammatory cells, and macrophages (red arrow), indicative of chronic inflammatory lesions. (Color version of the figure is available online.)

onimus (sputum and BAL) were also negative. Blood counts revealed no increase in WBCs and a normal eosinophil ratio. The D-dimer test, which evaluates the likelihood of thrombosis, was within the normal range. The second ELISA test for Paragonimus was negative. Expert consultation remained oriented toward suspicion of parasitic lung disease, and a second lung biopsy was ordered. Detailed transthoracic biopsy images are shown in Figure 7, and the results of microscopic pathology are shown in Figure 8, which indicated a diagnosis of chronic inflammatory lesions.

The patient continued to be diagnosed with pneumonia and was treated with a combination of 2 antibiotics within 10 days. Treatment results were not satisfactory. Dissatisfied with the diagnosis, the panel of expert doctors ordered a third biopsy (10 days after the second biopsy). Images from the transthoracic biopsy are presented in Figure 9. This time, a deep lesion was targeted. The results of microscopic pathology are shown in Figure 10.

The final confirmed diagnosis: Paragonimiasis. After reaching a confirmed diagnosis, the patient was treated with 1 course of the specific anti-parasitic drug praziquantel at a dose of 25 mg/kg/time (administered in 600-mg tablets), 3 times/day, for 2 days; prednisolone was administered at 30 mg/day (6 tablets divided into 2 times) for 10 days. Clin-

Fig. 5 – Chest X-ray, PA of the patient at the second examination. Compared with the radiograph in Figure 1, we see that the density of opacities increases significantly. The patient had a second chest CT scan, detailed images are shown in Figure 6.

Fig. 6 – CT images of the patient from the second examination at the NLH. The results were compared with previous images. (A) cross section representing the parenchymal window shows many nodules with similar morphology to the previous image but with higher density. The nodules have a well-defined border, but some fused nodules appear morphologically. B: Representative view of mediastinal window after intravenous contrast injection: Multiple nodules have similar contrast morphology to the first scan. The radiologist concluded that lung injury could be caused by parasitic diseases, but these results need to be differentiated to rule out pulmonary tuberculosis.
Second transthoracic lung biopsy. (A) and (B) The patient was supine, and an 18 G core biopsy needle was used to pierce the lung wall from the front targeting a 3-mm nodule near the chest wall (white arrow), which obtained 3 pieces of the specimen. (C) After the biopsy needle was removed, no complications were observed at the injection site (red arrow). (Color version of the figure is available online.)

Fig. 8 – Microscopic pathology of the second lung biopsy specimens. Hematoxylin and eosin (HE) stained slide (x20), Code 1791 - B18 shows the biopsy specimen, revealing the alveolar wall (blue arrow), fibrous connective tissue, infiltrating lymphocytes, and macrophages. The lung tissue appeared benign, with no evidence of tuberculosis or tumor lesions.

Fig. 9 – Third transthoracic lung biopsy. (A) and (B) In the prone position of the patient, and an 18G coaxial needle was inserted from the back to target a 5-mm nodule deep in the parenchyma of the left lower lobe (red arrow) obtaining 3 specimens. (C) After the biopsy needle was removed, no complications were observed at the insertion site (yellow arrow). (Color version of the figure is available online.)

Fig. 7 – Second transthoracic lung biopsy. (A) and (B) The patient was supine, and an 18 G core biopsy needle was used to pierce the lung wall from the front targeting a 3-mm nodule near the chest wall (white arrow), which obtained 3 pieces of the specimen. (C) After the biopsy needle was removed, no complications were observed at the injection site (red arrow). (Color version of the figure is available online.)

Paragonimiasis belongs to a group of diseases caused by parasites. The adult Paragonimus is approximately the size of a coffee bean, measuring 7-13 mm long and 4-6 mm wide, with a red or light pink color. The Paragonimus species primarily parasitize the lungs, creating cysts in the bronchioles that each typically contain 2 individual specimens in a red purulent fluid, with new blood vessels surrounding the cyst. The eggs are dark brown, oval, 80-120 μm long, and 4-8 μm wide, with a thick shell containing an embryo [2,3].

Paragonimiasis is caused by the flatworm genus Paragonimus, and the species most commonly associated with human diseases is Paragonimus westermani. Paragonimiasis is most commonly reported in Southeast Asia, particularly the Philippines, and is less common in South and Central America or Africa [9]. In North America, the disease is more common.
Fig. 10 - Microscopic pathology of the lung third biopsy specimen. (A) Hematoxylin and eosin (HE)-stained slide (× 40) show clear alveolar structures that were within normal morphologic limits (red arrow). (B) In the stromal area, fibrous proliferation was observed, and a section of Paragonimus was observed in the vascular lumen (blue arrow); no malignant lesions were observed. The histopathological images were consistent with paragonimiasis (Color version of the figure is available online.)

among immigrants, and the common causative organism in North America is *Paragonimus kellicotti* [1].

Lesions are caused by the parasite during the larval stage, which migrate into the lungs. Typically, clinical diagnosis depends on the patient's history, particularly if they live in endemic areas and might eat undercooked fish, shrimp, or crab. Therefore, the disease often has regional epidemiologic factors that depend on dietary habits. The first case was discovered in 1981, and fascioliasis is recognized as a significant foodborne parasitic disease in India. The fluke data collected in this country have made significant scientific contributions to understanding the epidemiology, life cycle, pathology, and characteristics of fascioliasis [5].

Patients with *Paragonimus* infections often cough up rust-colored, sporadic blood, which is also a common occurrence associated with pulmonary TB, which is a common misdiagnosis for paragonimiasis [4-6,8,10-15]. Chest radiographs and CT may show no specific lesions. Chest radiographs in patients with fascioliasis may show small, thin-walled cysts, and ring-shaped lesions may also be observed, with consolidation of areas with indistinct borders due to the aggregation of solid nodules. The cysts are usually smaller than 1 cm in diameter but can be as large as 5 cm. On CT, thick-walled cysts may appear, representing parasite lesion foci [1,9]. Lung parenchymal lesions can become chronically calcified, often in combination with nodular lesions, pleural effusion, interstitial thickening, cavitation, and bronchiectasis-like ring-shaped coconos. Pleural effusion occurs in more than half of all patients [3].

The disease often causes eosinophilia, and diagnosis is often confirmed when eggs are found in the sputum or feces. The ELISA test can be positive for antibodies against lung flukes, with high sensitivity, and specificity [5].

Ahn et al., analyzed 22 years of data, including 49,012 serologic samples diagnosed with parasitic diseases, including 685 cases diagnosed with lung fluke, among which 665 of 685 samples were positive for anti-*Paragonimus* antibodies on ELISA. The characteristics of routine X-ray and chest CT images showed that the timing of patients’ symptoms typically correlated with the appearance of chest X-ray signs. Among the 665 patients with positive ELISA results, 359 cases showed evidence of pleural lesions, 33 cases showed evidence of both parenchymal and pleural lesions, and 264 cases showed evidence of parenchymal lesions only (these differences were significantly different *P* < .001), whereas only 29 patients presented with normal chest radiographs. Eosinophilia was reported in 304 cases (primarily in the group presenting with lung and parenchymal-pleural lesions). Chest pain and dyspnea were associated with the group with pleural lesions. Patients with parenchymal lesions coughed up malodorous sputum containing blood. Among these cases, 119 cases were misdiagnosed with lung TB misdiagnosed, and an average of 25 weeks was necessary to reach the correct diagnosis of lung fluke invasion. The study concluded that the symptoms and radiographic signs detected in the pleural body depend on the stage of infection. Suspected TB, malignancy, and chronic obstructive pulmonary disease are the primary causes of delayed diagnosis [11].

Ogata et al., reported the clinical case of a 47-year-old woman who was admitted to the hospital with pleural effusion and parenchymal infiltration, with elevated blood eosinophils, and eosinophils in the pleural fluid. Thoracoscopy showed many pleural nodules, and pathology showed lung flukes. Patient history revealed that 1 month before hospitalization, the patient had eaten wild boar and raw deer meat [10]. Rodríguez et al. reported a similar clinical case in a 7-year-old pediatric patient. Kunitomo et al. reported the clinical case of a 46-year-old Chinese woman living in Japan with a cough lasting more than 20 days. She reported traveling to Cambodia 50 days before hospitalization, where she ate grilled freshwater crab. A chest CT scan showed a large, cavernous nodule, and opacity around the left upper lobe of the lung. Blood eosinophils were increased (5%). Subsequent sputum examination demonstrated a case of lung fluke [9].

A review of the literature and reported clinical cases revealed that our case was both consistent and inconsistent with a lung fluke diagnosis. Our patient had epidemiologic factors (eating shrimp and grilled crab) and a persistent cough but no hemoptysis. A sputum examination found no evidence
of bacteria. Blood counts showed no evidence of increased eosinophils. The first ELISA for lung flukes was only weakly positive, and the second ELISA was negative. The patient was initially treated specifically for lung flukes, but the clinical signs did not decrease, and the lesions observed on X-ray increased. The chest CT scan for this patient revealed fairly typical cystic lesions.

On the mediastinal window, many round nodules are visible with clear borderlines, uneven contrast enhancement, with a core area that is mostly non-enhanced (hypodense and/or hypotensive), similar to the images described in the literature, and consistent with a clear image of fluke cysts in the lungs. This image led the clinical imaging team to seek diagnostic pathology evidence of lung fluke invasion, even after other tests repeatedly returned negative results. During the diagnostic process, the patient was diagnosed and monitored for both pulmonary TB and metastasis to the lungs, and similar misdiagnoses are commonly observed in many other reported cases. Misdiagnoses of TB or lung cancer increase the burden on patients, requiring multiple visits and long-term treatment. Clinicians should always consider the possibility of fascioliasis in typical cases of lung injury with eosinophilia and elevated serum IgE [8]. In atypical cases, such as the case reported here, imaging features observed on chest CT can be extremely important in guiding the diagnosis.

Conclusion

Compared with cases reported in the literature, our case was a difficult case, with atypical clinical presentation (no hemoptysis, no eosinophilia, no gold standard for diagnosis from specimens, positive ELISA with low titer), and multiple differential diagnoses (secondary pulmonary disease, TB, PE). Imaging was consistent with lung fluke but in a rare group. The time required to reach a definite diagnosis was long (nearly 3 months), diagnostic imaging, interventional imaging, and pathology were important contributors to the definitive diagnosis. This case description can provide our colleagues with a multidimensional view of lung fluke disease, which may improve the diagnostic approach when encountering a similar case.

Authors’ contributions

Cung-Van C and Nguyen MD contributed equally to this article as co-first authors. All authors read and approved final version of this manuscript.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of patient information in this article.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Funding

No funding was received.

References

[1] Richard Webb W, Higgins Charles B. Thoracic imaging: pulmonary and cardiovascular radiology. Wolters Kluwer 2017:3:400–55.
[2] De Nguyen Van et Al. Paragonimiasis. Hanoi Medical Publisher. 2004:1–129.
[3] De Nguyen Van. Epidemiology pathology and treatment of paragonimiasis in Vietnam. Southeast Asian J Trop Med Public Health 2004;35(Supplement 1):331–6.
[4] Yoshida A, Doanh PN, Maruyama H. Paragonimus and paragonimiasis in Asia: an update. Acta Trop 2019;199:105074. doi: 10.1016/j.actatropica.2019.105074.
[5] Singh TS, Sugiyama H, Rangiriji A. Paragonimus & paragonimiasis in India. Indian J Med Res 2012;136(2):192–204.
[6] Strobel M, Veasna D, Saykham M, Wei Z, Tran DS, Valy K, et al. Pleuro-pulmonary paragonimiasis. Med Mal Infect 2005;35(10):476–81. doi: 10.1016/j.medmal.2005.08.002.
[7] Aka NA, Adoubryn K, Rondelaud D, Dreyfuss G. Human paragonimiasis in Africa. Ann Afr Med 2008;7(4):153–62. doi: 10.4103/1596-3519.55660.
[8] Nakamura-Uchiyama F, Mukae H, Nawa Y. Paragonimiasis: a Japanese perspective. Clin Chest Med 2002;23(2):409–20. doi: 10.1016/s0272-5231(01)00006-5.
[9] Kunitomo K, Yumoto S, Tsuji T. A case of paragonimiasis in a patient with wet cough. Am J Trop Med Hyg 2020;103(9):939–42. doi: 10.4269/ajtmh.20-0395.
[10] Ogata H, Harada E, Moriya S, Fukuyama S, Suzuki K, Shiraiishi Y, et al. Pleuropulmonary paragonimiasis with multiple nodules in the pleura. Intern Med 2020;59(15):1879–81. doi: 10.2169/internalmedicine.4457-20.
[11] Ahn CS, Shin JW, Kim JG, Lee WY, Kang I, Im JG, et al. Spectrum of pleuropulmonary paragonimiasis: an analysis of 685 cases diagnosed over 22 years. J Infect 2021;82(1):150–8. doi: 10.1016/j.jinf.2020.09.037.
[12] Belloso Rodriguez JA. Pulmonary paragonimiasis pediatric case report. Arch Argent Pediatr 2019;117(6):e659–63. doi: 10.5546/arp.2019.e659.
[13] Strobel M, Veasna D, Saykham M, Wei Z, Tran DS, Valy K, et al. Pleuro-pulmonary paragonimiasis. Med Mal Infect 2005;35(10):476–81. doi: 10.1016/j.medmal.2005.08.002.
[14] Gómez-Seco J, Rodríguez-Guzmán MJ, Rodríguez-Nieto MJ, Gómez-Escolar PF, Presa-Abos T, Fortes-Alen J. Pulmonary paragonimiasis. Arch Bronconeumol 2011;47(12):610–12. doi: 10.1016/j.arbres.2011.01.005.
[15] Maticorena Agramont VE, Ormeño Julca AJ, Coveñas Coronado CDP, Polar Córdova V, Bellosor Rodríguez JA. Pulmonary paragonimiasis pediatric case report. Arch Argent Pediatr 2019;117(6):e659–63. doi: 10.5546/arp.2019.e659.