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One delayed diagnosis of paragonimiasis case and literature review

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Abstract

Human paragonimiasis has been appearing all over the world due to increased human migration, international travel, and worldwide food trading. However, delayed and missed diagnosis rates are also increasing due to atypical clinical manifestations and the lack of disease understanding by clinical workers. We describe the case of a 43-year-old man, who was hospitalized with cough and chest pain for two months. Chest computed tomography (CT) revealed bilateral emphysema, left pleural effusion, and bilateral atelectasis. The hypereosinophilia gave us a clue; ultimately, the diagnosis of paragonimiasis was made through a diet history and a positive result of serum *Paragonimus* sp. immunoglobulin (Ig) G antibody. Moreover, 27 misdiagnosed paragonimiasis cases in the past decade have been reported. We draw conclusions by summarizing their characteristics for suspicious eosinophilic paragonimiasis patients; we should inquire diet history carefully, test serum IgG antibodies, and try to detect eggs. Once diagnosed, praziquantel is preferred for treatment.

Introduction

Paragonimiasis is a food-borne parasitic disease caused by trematodes belonging to *Paragonimus* spp. that is endemic in Asian, African, and South American countries such as China, Japan, Liberia, Nigeria, and Viet Nam [1], where people have the habit of ingesting the raw or undercooked crustaceans that harbour the infectious stages of the parasites (i.e. metacercariae). Nowadays, human paragonimiasis has been appearing all over the world due to the increase of human migration, international travel, and worldwide food trading. It has been estimated that 22.8 million people worldwide are at risk of paragonimiasis [2].

A typical migration route of *Paragonimus* in human is as follows: when metacercariae are ingested by the final host, they exist in the small intestine wall, penetrate the abdominal cavity, and then pass through the peritoneum, diaphragm, and pleura into the lung, where they mature into adult flukes. In a few cases, the metacercariae may migrate to some other tissues, such as the liver, neck, brain, kidney, peritoneum, and spinal cord, resulting in an ectopic infestation, which is named extrapulmonary paragonimiasis [3].

We herein present a patient with a delayed diagnosis of paragonimiasis admitted at our hospital in 2018. We also include a bibliographic search that we conducted to identify the relevant misdiagnosed case reports in database (including PubMed, Web of Science, and Embase) in the past decade by 31 December 2019 using the key words: "parogonimiasis" or "*Paragonimus*." Non-English writing and incomplete descriptions articles were excluded. Twenty-seven misdiagnosed paragonimiasis cases were collected to provide some reference for future clinical practice.

Case Report

A 43-year-old man lived in Enshi, a remote mountainous area with many small streams in China, for decades. He presented to the local hospital with the chief complaint of cough and chest pain for half a month, accompanied by small amount of white sputum, intermittent low fever, and

fatigue, sometimes out of breath after exercise. Two hundred millilitres of yellow turbid pleural effusion was extracted from the left side and the number of nucleated cells in the pleural fluid was 1540×10^6/L, with 73% lymphocytes, 22% neutrophils, and few eosinophils. Lactate dehydrogenase (LDH) was 1866 U/L, c(glucose) 0.12 mmol/L, and protein was 56.95 g/L. Rivalta test, also known as qualitative mucinous protein test, was positive but acid-fast bacilli negative. Then, he received only antibiotics for pneumonia, and visited our hospital after 1.5 months, because of no obvious improvement and weight loss of 4 kg. He had no history of allergies and smoked 20 cigarettes every day for 20 years.

On admission, physical examination showed temperature (T) of 36.5°C, pulse (P) 84/cent, respiration (R) 21 times/min, and blood pressure (BP) of 14.26/7.46 KPa; the breath sounds in both lungs were soft and the pleural friction sounds existed without obvious rhonchi or moist rale. Serum white blood cell (WBC) level was elevated at 11.89×10^9/L with 43.9% neutrophils and 24.5% eosinophils. Total immunoglobulin (Ig) E was 91.39 IU/mL. The sputum smear for tuberculosis and fungi was negative, t-SPOT was non-reactive, and there were no obvious abnormalities in serum tumour markers, liver, and kidney function. Chest X-ray showed small amount of pneumothorax with compression of about 10% on the right side and a small quantity of pleural effusion on the left side (Fig. 1A). Thoracic colour ultrasound revealed that the maximum anteroposterior diameter of the left and right pleural effusions was only 3.0 and 3.2 cm, respectively, and it was not suitable for positioning due to the float of the lung tissue inside.

Given the patient's mountain living history and high eosinophils, we asked repeatedly about his diet history and discovered that he had a history of eating raw freshwater crabs seven months earlier. Ultimately, positive serum *Paragonimus* sp. IgG antibody test confirmed the paragonimiasis diagnosis. Chest CT revealed bilateral pulmonary emphysema and left pleural effusion with left lower lobe segmental atelectasis (Fig. 1B–E).

From 8 November 2018, he received praziquantel therapy (25 mg/kg/day, three times a day for three days) combined with dexamethasone 5 mg/dose. After a treatment course, his symptoms improved significantly. Only a little left effusion on the chest X-ray, smaller than before (Fig. 1F), remained after 10 days of medication. The eosinophils decreased from 24.5% to 7.5% at 10 days, ultimately to 3.7% at four months following the treatment.

Discussion

Paragonimiasis is a rare parasitic disease due to consumption of raw or undercooked freshwater crabs, crayfish, and other aquatic products that are contaminated with metacercariae. Because of the atypical clinical manifestations of patients with paragonimiasis, delayed diagnosis, misdiagnosis, and missed diagnosis occur frequently.

For the patient admitted in our hospital, atypical symptoms delayed the diagnosis. Fortunately, three key clinical evidences were captured: first, his living in mountainous areas with streams for decades. An epidemiological study conducted by Dong et al. reported that the serological positive rate of Enshi population to paragonimiasis was 4.67%

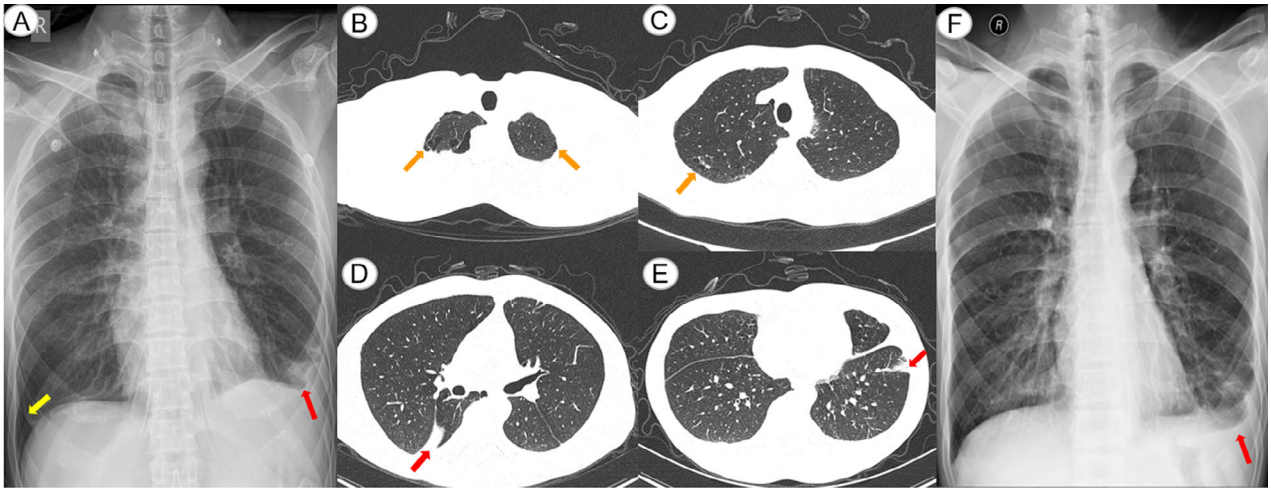

Figure 1. Radiological changes of the patient. On 3 November 2018 (at admission), chest X-ray showed small amount of pneumothorax with compression of about 10% on the right side and a small quantity of pleural effusion on the left side (A); on 8 November 2018 (the first day of treatment), the computed tomography (CT) showed bilateral pulmonary emphysema (B, C) and left pleural effusion with left lower lobe segmental atelectasis (D, E). On 20 November (10 days after treatment), there was only a little effusion on the left side, less than before (F).

and the positive rate of intermediate host (freshwater crab) was 15.00% [4]. Second, peripheral blood eosinophils of our patient were significantly increased. Third, his dietary history of consuming a raw fresh crab seven months earlier. Therefore, the possibility of parasitic disease was considered and a serum *Paragonimus* sp. IgG test was performed.

A review of the 28 previously reported misdiagnosed paragonimiasis cases including the present case is summarized in Table 1. The average age of 28 patients was 38.68 ± 15.63 years, with males (71.43%) being more frequently infected by *Paragonimus* spp. than females (28.57%). The primary cause of infection was consumption of fresh crabs (60.71%), followed by crayfish (7.14%) and slugs (3.57%).

As shown in Table 1, 67.86% of patients had lung involvement, two cases each had skin or cerebral involvement, while one case each had involvement in the pancreas, heart, bladder, ovary, liver, or colon. The factors contributing to aberrant migration are heavy infection, host immune status, and the adaptability of parasite species in the host [32].

Because of eosinophilia in our patient, peripheral blood eosinophilia is a main clue of paragonimiasis diagnosis. It has been previously reported that the proportion of eosinophilia in paragonimiasis patients can be 75.5% [33]. Of the 15 patients who mentioned eosinophils in Table 1, 10 had eosinophils greater than 8%. Although pleural effusion with eosinophils ≥10% (normal ≤3%) is typical for paragonimiasis patients [3], this characteristic is absent in some patients and two cases described in Table 1 were dominated by lymphocytes in pleural effusion. Therefore, without ≥10% eosinophils in pleural effusion, we also need to consider the possibility of paragonimiasis after excluding other lung diseases. The pulmonary imaging findings were determined by the trajectory of the *Paragonimus* after they entered the lungs. According to a 12-year study in Japan, pleural effusion, pneumothorax, nodular opacity, infiltrative shadow, and mass shadow accounted for 47%, 16.9%, 11.5%, 8.8%, and 6.5%, respectively [33]. Similarly, in the 19 patients with lung involvement in Table 1, 57.89% (11/19) of patients presented pleural effusion. Other chest radiological abnormalities included consolidation (six patients), nodular opacity (five patients), cavitation (five patients), pneumothorax (four patients), ground-glass opacity (two patients), and cystic lesion (one patient).

Serum *Paragonimus* sp. IgG–serology (enzyme-linked immunosorbent assay (ELISA)), an immunodiagnostic method that can detect and measure antibodies in the blood, although not widely available, is actually the best diagnostic method, reaching a sensitivity of 92% and specificity of 97% [34]. As previously reported, ELISA with urine samples is much more easy, safe, and non-invasive [35]. Despite the fact that 13 cases in our data were serum *Paragonimus* sp. IgG-positive, a positive IgG test does not always imply active infection, as it needs four to 18 months for the antibody level to return to normal level [26].

To date, the best diagnostic approach for paragonimiasis is eggs detection, and eggs detecting rate here is 71.43%, including eight detected in sputum, seven in tissue biopsy, one in pleural effusion, two in bronchoalveolar lavage (BAL), and two in stool. However, paragonimiasis is so rare that laboratory workers are less able to recognize eggs. Besides, as Kim et al. [8] demonstrated, eggs are not present in the sputum until two to three months after an infection.

The time between ingestion of raw crab and onset of symptoms is uncertain due to the uncertain dietary history or long-term raw food history of many patients; the incubation period in this case was as long as five months. The median interval between the onset of symptoms and paragonimiasis diagnosis was 12 months (range one day to seven years), and the most common misdiagnosis is tuberculosis (n = 12), including seven pulmonary tuberculosis, two tubercular meningitis, and three tuberculous pleurisy. Therefore, identification of the two diseases is important through acid-fast staining, GeneXpert MTB/RIF, tuberculosis culture, etc. Furthermore, pneumonia, bronchiectasis, lung cancer, and other visceral tumours are also common misdiagnosed diseases.

With regard to treatment, praziquantel is the mainstay at 25 mg/kg thrice daily for two to three days, which has the advantages of high efficacy, low toxicity, and short course [36]. Previous study reported the cure rate is up to 80–90% [37]. Allergic reactions to praziquantel, such as itching, febrile sensation, wheal, and painful swellings on the lip and eyelids, may rarely occur. Besides, triclabendazole is also effective against paragonimiasis, the recommended regimen is 10 mg/kg body weight in a single dose, which may be repeated after 12–24 h in heavy infections [38]. Adding steroids in the early stage of treatment helps to suppress inflammatory response [39] and prevents drug allergic reaction. For cerebral paragonimiasis, a course of mannitol is often warranted if the cerebral lesions have significant surrounding oedema [40]. Surgical excision and drainage are also feasible when it is necessary, as both procedures not only help in diagnosis but also achieve the aim of treating ectopic disease. As a simple, economical, and reproducible therapeutic procedure, radiofrequency ablation could be one of the means used in treating patients with hepatic paragonimiasis [41].

In conclusion, due to the non-specific symptoms of patients with pulmonary paragonimiasis, it is often difficult to make a definite diagnosis. Therefore, if eosinophilia appeared, clinicians should consider the possibility of

Table 1. Description of misdiagnosed cases of paragonimiasis reported over the past decade.

Authors, years	Age/sex	Diet history	Involved organs	Misdiagnosed disease	Blood eosinophils	Chest imaging findings	Methods of diagnosis	Time to diagnosis	Treatment
Sim, 2010 [5]	39/F	Crabs	Derma Lung	Tuberculosis		Pleural effusion (lymphocyte-dominant)	Biopsy observed Charcot–Leyden crystals, one larva of *Paragonimus westermani*, and both IgM and IgG were positive for *P. westermani*	Three months	Praziquantel (75 mg/kg/day for two days)
Wright, 2011 [6]	54/M	Crabs	Lung	Asthma	7.4%	Pleural effusion	Pleural effusion observed eggs of *P. westermani* and IgG was positive for *P. westermani*	Two weeks	Praziquantel (9000 mg/day for two days), retreated two weeks later
Singh, 2011 [7]	8/M	Crabs	Lung	Tubercular meningitis	17%		Sputum samples were positive for *Paragonimus* sp. eggs, and IgG was positive for *P. westermani*	One month	Praziquantel (75 mg/kg/day for five days)
Kim, 2011 [8]	27/F		Lung	Pulmonary tumour		Nodular opacity Ground-glass opacity	IgG was positive for *P. westermani*	Four months	Praziquantel (75 mg/kg/day for two days), surgery
Wu, 2013 [9]	30/M	Crabs	Cerebra	Cerebral infarction			CSF analysis showed positive *Paragonimiasis* antibody reaction	39 months	Praziquantel, 2 g
Lall, 2013 [10]	34/M	Crabs	Lung	Tuberculosis		Pleural effusion Consolidation	Sputum samples were positive for *Paragonimus* sp. eggs	One year	Praziquantel (75 mg/kg/day for two days)
Tantipalakorn, 2014 [11]	47/F		Ovary	Ovarian carcinoma			A frozen section revealed *Paragonimus* eggs in the enlarged ovarian mass	Five months	Praziquantel, surgery
Yue, 2014 [12]	61/M	Crabs, crayfish	Bladder	Bladder tumour			Surgical specimens observed multiple sinus tracts caused by the fluke migration into the tissues and a fluke body	One month	Praziquantel (for three days), surgery

Kodama, 2014 [13]	39/F	Crabs	Derma	Lipoma			Surgical specimens observed a number of parasite ova, a parasite body with a presumed oral sucker, and reproductive organ; serum was positive for *P. westermani* antigen	One year	Surgery
Song, 2014 [14]	38/M		Lung	Tuberculous pleurisy	5.2%	Pleural effusion (67% lymphocytes) Pneumothorax	Pathological examination observed parasitic eggs, IgG was positive for *P. westermani*	One year	Praziquantel (two days), surgery
Yang, 2015 [15]	21/F		Pancreas	Pancreatic cystic-solid tumour	22.9%		Surgical specimens observed Charcot–Leyden crystal	One week	Praziquantel, surgery
Kohli, 2015 [16]	10/F		Cerebra	Tuberculous meningitis	10%		Lung biopsy revealed Charcot–Leyden crystals. Stool showed ova	Five years	Praziquantel
Prasad, 2015 [17]	34/M	Crabs	Lung	Eosinophilic pneumonia	46%	Pleural effusion (34% eosinophils) Consolidation Cavitation	Sputum revealed operculated, oval, yellowish-coloured eggs of *Paragonimus* spp.	18 months	Praziquantel (for two days)
Kalhan, 2015 [18]	26/M	Crabs	Lung	Tuberculous pleurisy	12%	Pleural effusion (eosinophil-dominant)	Sputum showed operculated eggs of *P. westermani*	One year	Praziquantel (1800 mg/day for three days)
Sahni, 2015 [19]	49/M		Lung	Tuberculosis		Pleural effusion Cavitation Ground-glass opacity	BAL showed oval eggs with an operculum	One year	Praziquantel
Yatera, 2015 [20]	45/M	Crabs	Lung	Eosinophilic pneumonia	2.01%	Pneumothorax Cystic lesion Nodular opacity	BAL showed eggs	Seven years	Praziquantel (75 mg/kg/day for three days)
Singh, 2015 [21]	50/F	Crabs	Lung	Tuberculosis	16%	Nodular opacity Cavitation	Sputum sample was positive for *Paragonimus* sp. eggs	Two years	Praziquantel (75 mg/kg/day for three days)

Table 1. Continued

Authors, years	Age/sex	Diet history	Involved organs	Misdiagnosed disease	Blood eosinophils	Chest imaging findings	Methods of diagnosis	Time to diagnosis	Treatment
Roy, 2016 [22]	8/M		Lung	Pneumonitis	17%	Consolidation Nodular opacity	Sputum and stool sample were positive for *Paragonimus* sp. eggs	Two years	Praziquantel (75 mg/kg/day for two days), albendazole
Horn, 2016 [23]	46/M	Crayfish	Lung	Pneumonitis		Consolidation	Intraoperative frozen section revealed "numerous apparent parasitic ova"	Six months	Praziquantel (four days)
Itoh, 2016 [24]	66/M		Lung	Pulmonary tumour	13.6%	Pleural effusion (eosinophil-dominant)	Sputum sample was positive for *Paragonimus* sp. eggs, IgG was positive for *P. westermani*	10 months	Praziquantel (75 mg/kg/d for three days)
Luo, 2016 [25]	43/M		Lung	Tuberculous pleurisy	3.1%	Pleural effusion Consolidation	Charcot–Leyden crystals were found in the pleural necrosis and IgG was positive for *P. westermani*	1.5 months	Praziquantel (75 mg/kg/day for three days)
Kim, 2017 [26]	45/M	Crabs	Colon	Recurrent diverticulitis	3.3%		Specimen showed multiple parasite eggs, antibodies for *P. westermani* were positive	Three years	Praziquantel (75 mg/kg/day for two days), surgery
Calvopina, 2017 [27]	30/M		Lung	Tuberculosis		Pleural effusion Nodular opacity	Eggs of *Paragonimus* spp. were observed in sputum smears	Five years	Praziquantel (75 mg/kg/day for three days)
Lin, 2018 [28]	54/M		Liver	Hepatocellular carcinoma			Pathological examination showed oval-shaped eggs and Charcot–Leyden crystals. Serology was positive for *P. westermani* IgG antibody	Two weeks	Praziquantel (75 mg/kg/day for three days)
Sah, 2019 [29]	45/F	Slugs	Heart	Pericardial tamponade	41%		Sputum detected *Paragonimus* spp. eggs, IgG was positive for *P. westermani*	One month	Praziquantel (75 mg/kg/day for three days)

Griffin, 2019 [30]	26/M	Crabs	Lung	Tuberculosis		Consolidation Cavitation	Sputum microscopy revealed the presence of *Paragonimus* sp. eggs	63 months		Praziquantel (75 mg/kg/ day for three days)
Kwon, 2019 [31]	65/M	Crabs	Lung	Tuberculosis		Pneumothorax Cavitation	Biopsy showed parasite eggs, IgG was positive for *P. westermani*	One year		Praziquantel, surgery
Present case	43/M	Crabs	Lung	Pneumonitis	24.5%	Pleural effusion (73% lymphocytes) Pneumothorax	IgG was positive for *P. westermani*	Two months		Praziquantel (75 mg/kg/ three 3 days)

BAL, bronchoalveolar lavage; CSF, cerebrospinal fluid; Ig, immunoglobulin.

paragonimiasis, inquire diet history carefully, test serum *Paragonimus* sp. IgG antibodies, and try to detect *Paragonimus* eggs. Once diagnosed, praziquantel is preferred for treatment. In addition, we need to educate patients, especially those in rural areas near streams, not to encourage raw or undercooked freshwater crabs and crayfish consumption.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

Author Contribution Statement

Luxia Kong drafted the manuscript. Data collection and screening were performed by Qian Liu and Lijuan Hua. Chen Bao and Jiannan Hu interpreted the data and revised the manuscript. Supervision and mentorship were performed by Shuyun Xu. All authors critically reviewed the manuscript and approved the final version.

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