Occupational exposure to freshwater crustaceans as a route of paragonimiasis presenting with eosinophilic pleural effusion misdiagnosed as tuberculous pleurisy: A case report and literature review

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Abstract. Paragonimiasis, a foodborne parasitic disease caused by *Paragonimus*, typically presents with pleural effusion and is often misdiagnosed as tuberculous pleurisy, especially in endemic regions. The present study aimed to investigate the causes of misdiagnosis of pleural effusion (PE) caused by paragonimiasis as tuberculous pleurisy and to propose preventive strategies. The clinical diagnostic and treatment course of one patient with paragonimiasis misdiagnosed as tuberculous PE (TPE) was analyzed. A literature review of English-language case reports and series on paragonimiasis with PE misdiagnosed as TPE was performed using PubMed, Google Scholar, and Web of Science databases up to January 1, 2026. A 41-year-old male patient presented to Gucheng County People's Hospital (Shiyan, China) in October 2024 with a 10-day history of cough, sputum production, fever and shortness of breath. with cough, sputum, fever and dyspnea. Chest computed tomography (CT) showed left-sided PE. Tuberculosis antibody detection was positive and erythrocyte sedimentation rate was elevated. The patient was misdiagnosed with TPE and showed poor response to antituberculosis treatment. At 8 months later, readmission revealed markedly elevated eosinophils in peripheral blood (18%; normal range: 0.4-8.0%, absolute count, 2.61x10^9/l; normal range: 0.02-0.5x10^9/l), pleural fluid and pleural biopsy tissue. The patient had longterm occupational exposure to freshwater aquatic products without a history of raw seafood ingestion. Intradermal test for *Paragonimus*-specific antigen (IDTPA) and serum *Paragonimus* IgG antibody were both positive. Following four courses of praziquantel (25 mg/kg three times daily; 3 days/course), the patient achieved clinical cure with resolution of PE and normalization of eosinophil count (0.46x10^9/l). The correct diagnosis of paragonimiasis was established by peripheral and pleural eosinophilia, positive IDTPA and serology and response to praziquantel. A literature review of 16 English language publications (51 cases) showed that 92.2% of patients had a history of raw or undercooked freshwater product ingestion, 94.1% had peripheral blood eosinophilia and 93.8% were seropositive by ELISA. By contrast, the present case involved long-term occupational exposure to freshwater aquatic products without raw seafood ingestion, an unusual but important route of infection. All reported patients responded to praziquantel. Elevated eosinophil levels in peripheral blood and pleural fluid and biopsy tissue are valuable clues for the diagnosis of paragonimiasis. Detailed inquiry into occupational and environmental exposure in addition to dietary history is essential. IDTPA and/or serum *Paragonimus* IgG antibody testing enables early diagnosis. Praziquantel remains the standard effective treatment.

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Introduction

Paragonimiasis, also known as lung fluke disease, is a foodborne parasitic zoonosis caused by trematodes of the genus *Paragonimus* (1,2). Infection in humans typically results from the consumption of raw or undercooked freshwater crabs, crayfish, shrimp or snails contaminated with

metacercariae (2,3). According to estimates from the World Health Organization and multiple epidemiological studies, ~20 million people are infected worldwide (1,4). The disease is mainly distributed in specific regions of Asia, Africa and the Americas where raw or undercooked freshwater products are consumed (1,4). In China, the prevalence of paragonimiasis is 1.7%, and the general population has no innate immunity, meaning that anyone exposed to the infectious metacercariae is susceptible to infection (5). Pleural effusion may occur as the sole or predominant manifestation of paragonimiasis, and the true incidence is likely underestimated due to frequent misdiagnosis (6,7).

While many patients present with cough, chest pain, fever, and hemoptysis, a significant subset develops pleural effusion (PE) when the parasites remain in the pleural cavity or enter the pleura after failing to migrate to the lungs (6). The clinical and radiological manifestations of paragonimiasis induced PE are nonspecific and mimic those of tuberculous pleurisy, especially in tuberculosis-endemic regions, leading to frequent misdiagnosis (8-23); patients may also be misdiagnosed with malignant PE (24,25). The consequences of misdiagnosis include unnecessary anti-tuberculosis therapy (which exposes patients to drug toxicity without clinical benefit), disease progression (from isolated effusion to parenchymal cavitation or extrapulmonary dissemination), and prolonged impairment of quality of life.

Conventional diagnostic methods for paragonimiasis have low sensitivity: sputum smear, culture, and even metagenomic next-generation sequencing (mNGS) often fail to detect the parasite, particularly in early-stage disease or when the infection is limited to the pleural space (7,26). Therefore, serological tests, including ELISA for Paragonimus-specific IgG antibody and the IDTPA test for Paragonimus-specific antigen, play a crucial role in diagnosis (27-29).

The standard treatment for paragonimiasis is praziquantel, administered at 25 mg/kg three times daily for 3 consecutive days. One to two courses are usually sufficient, but more courses may be needed in severe or complicated cases (5,7,30). An alternative agent is triclabendazole, which has shown comparable efficacy and better tolerability in clinical trials (31,32). Early diagnosis and prompt antiparasitic treatment are essential to prevent chronic disease and irreversible organ damage.

The present study reports a patient with no definite history of raw freshwater crab, shrimp or snail ingestion but with long-term occupational exposure to freshwater aquatic products, who was misdiagnosed with TB pleurisy for 8 months. The present study also aimed to review the relevant literature to provide a reference for the clinical diagnosis and management of paragonimiasis.

Case report

A 41yearold male patient living in a rural area presented to the Department of Respiratory and Critical Care Medicine at Gucheng County People's Hospital (Xiangyang, China) in October 2024, with a 10 day history of cough, sputum production, fever and shortness of breath. The patient reported no night sweats, chills, chest pain or hemoptysis, had no known history of TB, no contact with patients with TB and no family members with similar respiratory symptoms. Physical examination revealed clear percussion notes bilaterally, coarse breath sounds in the left lung and a few fine crackles in the left lower lobe. Chest CT showed an infectious lesion in the left lower lobe (Fig. 1A). Laboratory findings on admission were as follows: Highsensitivity Creactive protein (hs-CRP), 1 μg/ml (normal range: 0-10 mg/l); CRP, <5.0 μg/ml (normal range: 0-10 μg/ml); procalcitonin, 0.05 ng/ml (normal range: 0-0.5 ng/ml); erythrocyte sedimentation rate (ESR), 23 mm/h (normal range: 0-15 mm/h); negative respiratory virus antibody detection; positive TB antibody (TBAb) detection; and normal carcinoembryonic antigen (CEA) (normal range: 0-5 μg/l). Routine urinalysis was unremarkable. Complete blood count showed the following results: White blood cells, $12.5x10^9$/l (normal range: 3.5-$9.5x10^9$/l); neutrophils, 50.3%; lymphocytes, 33.6%; monocytes, 5.2%; eosinophils, 15.2% (absolute count, $1.9x10^9$/l) and basophils, 0.7%. Liver and kidney function, electrolytes and lipids were normal. Based on these findings, the patient was diagnosed with left lung infection and treated with ceftezole (antibiotic), doxofylline (bronchodilator) and nebulized inhalation.

At 9 days later, repeat chest CT revealed new leftsided, small PE (Fig. 1B). Ultrasoundguided thoracentesis was attempted but yielded little fluid. Given the clinical course, imaging findings, laboratory results (positive TBAb, elevated ESR) and poor response to 1 week of antibiotics, the patient consented to diagnostic antiTB therapy with isoniazid, rifampin, pyrazinamide and ethambutol. The patient took these medications at home for 7 months, but his clinical symptoms did not improve. The patient did not attend follow-up during the 8 month anti-TB therapy.

At 8 months after the initial presentation, the patient was admitted to the Department of Respiratory and Critical Care Medicine at Taihe Hospital, Shiyan, China, in June 2025, with persistent cough, sputum production, dyspnea on exertion and intermittent fever. Physical examination was unremarkable except for dullness to percussion and diminished breath sounds in the left lower lobe, along with a few crackles in the same area. No peripheral edema was noted. The patient had lost 5 kg since initial presentation. Chest CT showed progression of the left lower lobe lesion with increased left PE (Fig. 1C). Laboratory tests revealed the following results: ESR, 34 mm/h; hs-CRP, 15.7 mg/l; and peripheral blood eosinophil count, $2.61x10^9$/l (18.0%). Pleural fluid analysis showed yellow, turbid fluid with a positive Rivalta test (indicating an exudative effusion). The total nucleated cell count was $91,763x10^6$/l, with 10% mononuclear and 90% polymorphonuclear cells. Biochemical analysis revealed total protein, 55.22 g/l; glucose, 2.07 mmol/l; total cholesterol, 3.44 mmol/l; lactate dehydrogenase, 1,111.8 U/l; adenosine deaminase, 38.7 U/l; and CEA, 1.17 μg/l. No bacteria, fungi or acidfast bacilli were detected on smear or culture after 7 days. Pleural fluid cytology showed numerous eosinophils, with no malignant cells (Fig. 2). Pleural fluid cytology was performed using liquidbased cytology (LBC) with hematoxylin and eosin staining. For specimen preparation, the pleural fluid was fixed in 95% ethanol at room temperature for 10 min. For hematoxylin staining, the slides were immersed in Harris hematoxylin solution for 5 min at room temperature, then briefly differentiated with 1-2 dips in 0.3% acid alcohol, followed by bluing in tap water (or

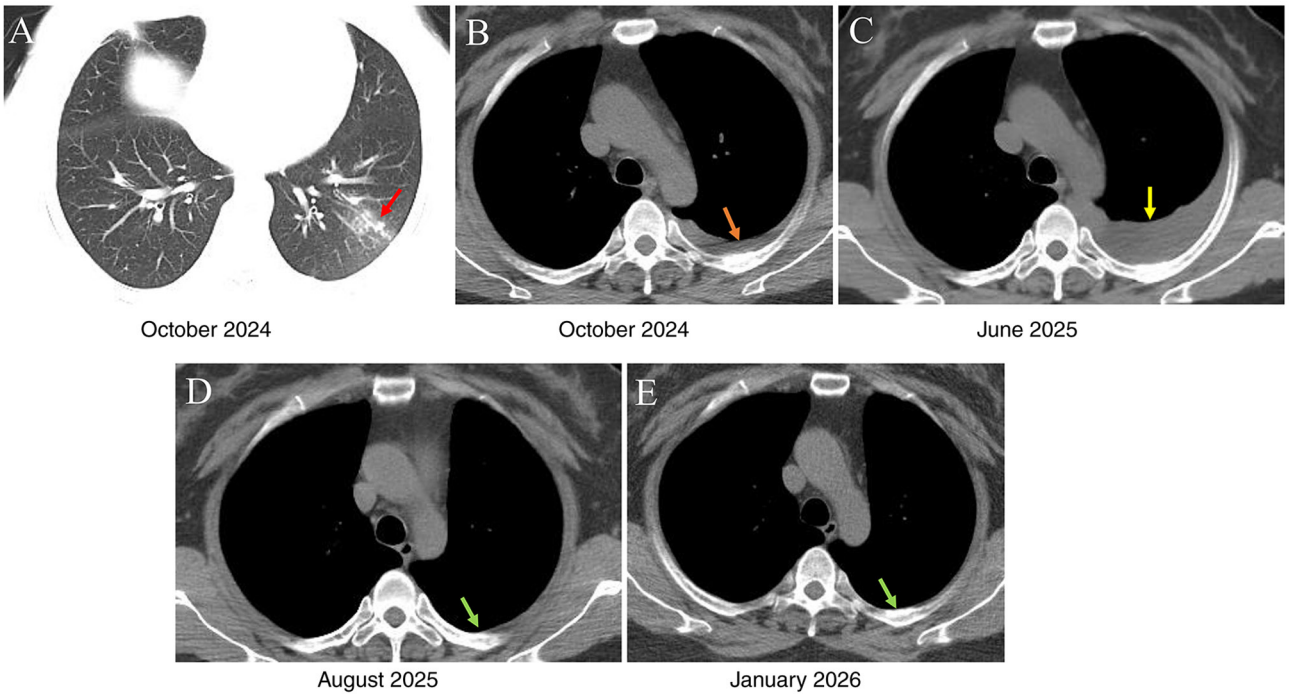

Figure 1. CT changes during the disease course of a patient with paragonimiasis misdiagnosed as TPE. Chest CT showing (A) infectious lesion in the left lower lobe (red arrow), (B) new, small left-sided pleural effusion (orange arrow), (C) progression of the left lower lobe lesion with increased left pleural effusion (yellow arrow), (D) normal lungs with resolution of pleural effusion at 2 months following praziquantel treatment (green arrow) and (E) normal lungs with no pleural effusion or other abnormalities at 7 months following praziquantel treatment (green arrow).

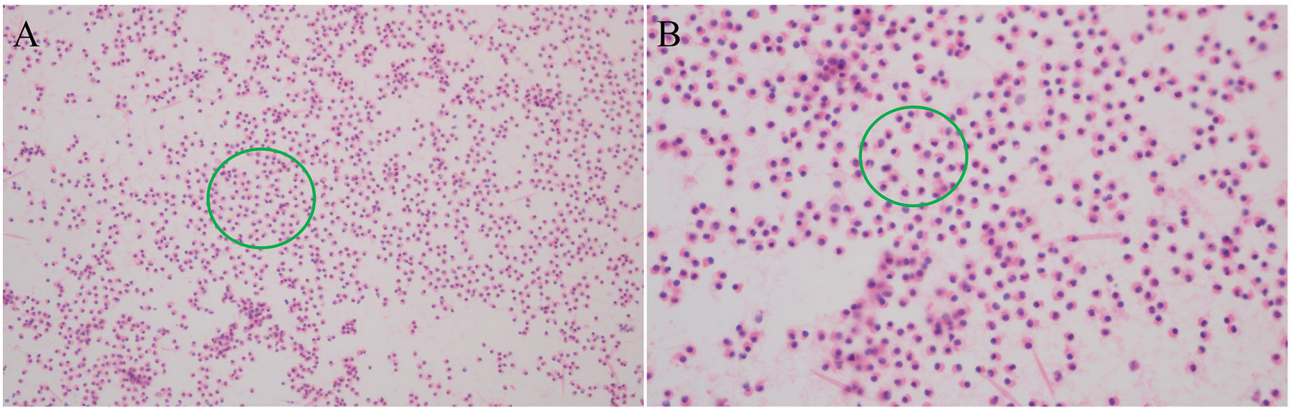

Figure 2. Cytological examination results of the pleural effusion obtained through thoracentesis. Pleural fluid cytology showing many eosinophils (green circles), with no malignant cells (hematoxylin and eosin staining). Magnification, (A) x200 and (B) x400.

Scott's tap water substitute) for 5 min. Counterstaining was performed using 1% eosin Y solution for 1-2 min at room temperature. The slides were then dehydrated through graded alcohols (70, 95, and 100%), cleared in xylene, and mounted with coverslips. Finally, the stained slides were examined under a standard light microscope (Olympus BX43) with brightfield illumination at x200 and x400 magnifications, and representative images were captured using a digital camera. Bronchoscopy was normal and bronchoalveolar lavage fluid (BALF) culture and smear were negative. Metagenomic nextgeneration sequencing (mNGS) of BALF also failed to identify any pathogen; quality control parameters of mNGS of BALF are shown in Table SI. For mNGS of the BALF, nucleic acid extraction and library preparation were performed using the PMseq® workflow. For the DNA workflow, the MGIEasy Fast FS Library Prep Set V2.0 (MGI Tech Co., Ltd., cat. No. 1000006987 for 16 reactions, and Cat. No. 1000006988 for 96 reactions) was used, while the RNA workflow employed the MGIEasy Microorganism Fast RNA Library Prep Set (MGI Tech Co., Ltd.; Cat. No. 940-000107-00 for 16 reactions, and Cat. No. 940-000108-00 for 96 reactions). The library concentration was measured using a Qubit™ 4.0 fluorometer (Thermo Fisher Scientific, MA, USA) with the Qubit dsDNA HS Assay Kit (Cat. No. Q32854), and the acceptable concentration after purification was set at ≥5 ng/μl. The size distribution of the libraries was assessed using an Agilent 2100 Bioanalyzer (Agilent Technologies, CA, USA) with the High Sensitivity DNA Kit (Cat. No. 5067-4626). The quality acceptance

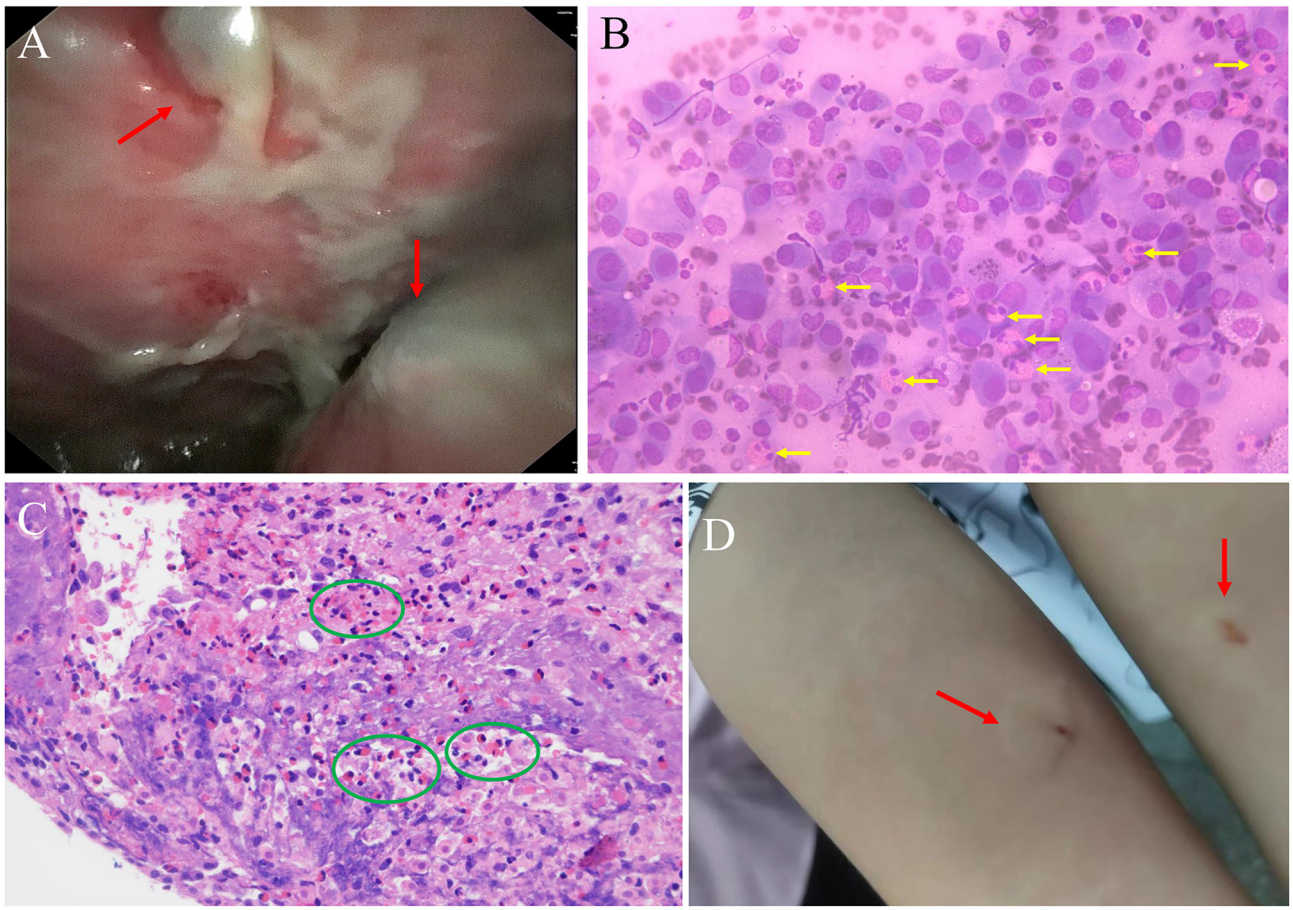

Figure 3. Thoracoscopic, ROSE, histopathological and IDTPA findings of a patient with paragonimiasis misdiagnosed as tuberculous pleural effusion. (A) Thoracoscopy showing necrotic material attached to the parietal and diaphragmatic pleura (red arrows). (B) ROSE of pleural tissue smears revealing numerous eosinophils (yellow arrows). (C) Histopathological examination of pleural biopsy specimens showing fibroadipose tissue with areas of exudation and necrosis, mesothelial cell hyperplasia, histiocytic proliferation and dense infiltration of lymphocytes and eosinophils (green circles; hematoxylin and eosin staining; magnification, x400). (D) Positive IDTPA reaction (red arrow). ROSE, rapid on-site evaluation; IPTPA, intradermal test for *Paragonimus*-specific antigen.

criteria were defined as a DNA Integrity Number (DIN) ≥6 for DNA samples, an RNA Integrity Number (RIN) ≥6 for RNA samples, and a minimum concentration of ≥1 ng/μl for both. Sequencing was performed on the DNBSEQ G99 platform (MGI Tech Co., Ltd.) using a single-end 50-bp (SE50) read length. For the RNA workflow, the DNBSEQ G99S High-throughput Sequencing Set (G99 SM FCL SE100/PE50; Cat. No. 940-000409-00; MGI Tech Co., Ltd.) was used. For the DNA workflow, the MGISEQ 200RS High-throughput (Rapid) Sequencing Reagent kit (cat. no. 1000019846; MGI Tech Co., Ltd.) was used. The loading concentration of the final pooled library was determined by Qubit 4.0 fluorometer. The actual loading concentration was 1.8 pM, as measured by the Qubit 4.0 fluorometer and further verified with the KAPA Library Quantification Kit. Primary base-calling analysis was performed using the built-in sequencing instrument software provided by MGI Tech Co., Ltd. Subsequent bioinformatics analysis was conducted using the HALOS PMseq Gene Data Analysis Workstation (Version V3.0, Shenzhen Huada Gene Technology Co., Ltd., China), which aligned the sequencing reads against the PMDB clinical-grade microbial database and the NCBI NT database (v2024.03; ftp.ncbi.nlm.nih.gov/blast/db/) (33). The analytical workflow comprised quality filtering, removal of host reads by alignment to the human reference genome (hg38), and taxonomic classification using a k-mer-based algorithm with a minimum confidence threshold of 50 RPhK (normalized reads per 100,000 total sequencing reads) for parasite detection. Quality assessment of the raw data was performed using FastQC v0.11.9 (bioinformatics.babraham.ac.uk/projects/fastqc/;), and multi-QC reports were automatically generated within the HALOS system.

As the cause of PE and systemic symptoms remained undiagnosed despite comprehensive investigations, medical thoracoscopy was performed, revealing ~1,000 ml yellow pleural fluid. The parietal and diaphragmatic pleura were congested and thickened, with white patchy material adherent (Fig. 3A). Multiple biopsies were taken from the parietal pleura. Rapid onsite evaluation showed numerous mesothelial cells and eosinophils (Fig. 3B). Histopathological examination of the pleural biopsy specimens revealed fibroadipose tissue with areas of exudation and necrosis, mesothelial cell hyperplasia, histiocytic proliferation and dense infiltration of lymphocytes, eosinophils and neutrophils (Fig. 3C). Stains, including periodic acid-Schiff (PAS), acid-fast and Gomori methenamine silver, were negative for specific microorganisms. Immunohistochemistry was positive for CK(P) (cytokeratin,

pan-specific; a marker of mesothelial cells), CD68 (histiocytes) and WT1/calretinin (Wilms tumor 1, markers of mesothelial cells) and negative for SOX10, S100, TTF1 (Thyroid Transcription Factor-1; a marker of lung adenocarcinoma and thyroid origin), napsin A, langerin, CD1a and P40. Special stains including periodic acid-Schiff, acidfast and silver stain were negative. PCR for *Mycobacterium tuberculosis* was negative. The pleural biopsy specimens were fixed in 10% neutral buffered formalin at room temperature for 24-48 h. Tissues were dehydrated through graded ethanol solutions (70, 80, 95, and 100%, each for 1 hour), cleared in xylene (two changes, each for 1 h), and embedded in paraffin. The resulting paraffin blocks were sectioned at a thickness of 4 μm. Sections were first deparaffinized in xylene (two changes, 5 min each) and rehydrated through graded ethanol solutions (100, 95, 80, and 70%, 3 min each). The sections were stained with Harris hematoxylin for 5 min at room temperature, rinsed in tap water for 5 min, differentiated with 1 to 2 dips in 0.3% acid alcohol, and blued in Scott's tap water for 2 min. Counterstaining was performed with 1% eosin Y solution for 2 min at room temperature. Finally, the sections were dehydrated, cleared, and mounted with coverslips using synthetic resin. The stained sections were examined under a standard light microscope.

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections at 4 μm thickness using a polymer peroxidase-based detection system (EnVision FLEX, Dako). Following deparaffinization and rehydration as aforementioned, heat-induced antigen retrieval was carried out using Target Retrieval Solution (at pH 6.0 or 9.0, depending on the primary antibody) in a pressure cooker at 120˚C for 3 min. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 10 min. The sections were then incubated with primary antibodies at 4˚C overnight (or at room temperature for 1 h). The panel of primary antibodies used included: CK(P) (clone AE1/AE3; Dako; 1:200), CD68 (clone KP1; Dako; 1:100), WT1 (clone 6F-H2; Dako; 1:50), calretinin (clone DAK-Calret1; Dako; 1:100), SOX10 (clone EP268; Zytomed; 1:100), S100 (polyclonal; Dako; 1:200), TTF-1 (clone 8G7G3/1; Dako; 1:100), napsin A (clone MRQ-60; Roche; ready-to-use), langerin (clone 12D6; Novocastra; 1:50), CD1a (clone O10; Dako; 1:50), and P40 (clone BC28; Zytomed; 1:100). After washing, the sections were incubated with a horseradish peroxidase-labeled polymer (EnVision FLEX, Dako) for 30 min at room temperature. Diaminobenzidine (DAB) was used as the chromogen for 5 min, followed by counterstaining with Harris hematoxylin. The sections were then dehydrated, cleared, and mounted. Positive and negative controls (by omission of the primary antibody) were run in parallel for each staining run. All sections were evaluated under bright-field light microscopy (Olympus BX43).

DNA was extracted from the pleural biopsy tissue using the QIAamp DNA Mini Kit (Qiagen GmbH; cat. No. 51304) strictly according to the manufacturer's protocol. Real-time PCR was performed using the TB PCR Kit (Da An Gene Co., Ltd., Guangzhou, China; cat. No. DA-TB-001). Amplification was carried out with an initial denaturation step at 95˚C for 5 min, followed by 40 cycles of denaturation at 95˚C for 15 sec and annealing/extension at 60˚C for 1 min. A FAM-labeled probe was used for specific detection. A positive control (genomic DNA from M. tuberculosis H37Rv) and a negative control (nuclease-free water) were included in each run. According to the manufacturer's instructions, Cq >38 was interpreted as negative. The amplification and detection were performed on the Applied Biosystems 7500 Real-Time PCR System (Thermo Fisher Scientific).

Given the marked eosinophilia in peripheral blood and pleural fluid and tissue, the patient was requestioned about his exposure history. The patient reported longterm occupational contact with freshwater aquatic products as a fish farmer, with no history of raw seafood ingestion. On day 6 of admission, he underwent intradermal test for *Paragonimus*-specific antigen (IDTPA) at the Department of Parasitology, Basic Medicine School, Hubei University of Medicine (Shiyan, China). The test was positive within 15 min (Fig. 3D). In accordance with standard clinical practice for IDTPA (7), the result was read at 15 min (immediate reaction); delayed readings at 24-48 h were not performed. Serum *Paragonimus*-specific IgG antibody was detected using a Paragonimus IgG ELISA kit (Eiger Diagnostics, Inc.; cat. number: EG-Par-G) according to the manufacturer's instructions, with a positive result defined as optical density >0.23. A positive result was obtained. This ELISA kit uses *Paragonimus* antigen-coated plates and anti-human IgG conjugate; it has been reported to show no or limited cross-reactivity with sera from patients with clonorchiasis or schistosomiasis (27). CT of the abdomen, and pelvis were normal, and brain magnetic resonance imaging were normal. A diagnosis of PE caused by paragonimiasis was made.

Because the patient had not been receiving antiTB medication for >2 weeks, empirical antiparasitic therapy with praziquantel was initiated at a dose of 25 mg/kg three times daily for 3 consecutive days. The course was repeated after a 1week interval. Given the prolonged diagnostic delay (8 months) and the presence of massive PE with marked peripheral eosinophilia (18.0%), a more extended regimen was adopted to ensure complete parasite eradication. The first course was administered during hospitalization and the subsequent three courses were completed in the outpatient setting. Following the first course, the patient reported partial improvement in cough and dyspnea, but peripheral blood eosinophils remained elevated (9.2%, absolute count $1.35x10^9$/l). After the second course, eosinophils decreased to 5.1% ($0.71x10^9$/l), and chest CT showed reduction but not complete resolution of PE. Therefore, two additional courses were administered. After four courses, the patient achieved clinical cure with no adverse effects. At 1 month later (August 2025), chest CT showed normal lungs (Fig. 1D), and peripheral blood eosinophil count decreased to $0.46x10^9$/l (6.2%). The patient remained well at followup in January 2026, with a normal chest CT and no PE (Fig. 1E), however follow-up serological testing (ELISA or IDTPA) was not performed because the patient was asymptomatic and declined further blood tests. The patient did not attend scheduled follow-ups after that time.

Literature review

A comprehensive search of the PubMed (pubmed.ncbi.nlm.nih.gov/), Google Scholar (scholar.nq69.top/) and Web of Science databases (ycfw.hbmu.edu.cn:9000/https/28jS5Bg4AKhLUpVG9oah1DPUUo1YgpmgrnPgYfOr2yqbl5IiX/wos/?Init=

Yes&SrcApp=CR&SID=USW2EC0F3EzPK3iv6njUeKoAZ4ePS) was conducted to identify relevant studies published from January 1, 2000 to January 1, 2026, using the following terms: (paragonimiasis OR lung fluke disease OR *Paragonimus*) AND (pleural effusion OR pleurisy OR pleuropulmonary) AND (misdiagnosis OR misdiagnosed OR diagnostic delay OR confusion) AND (tuberculosis OR tuberculous pleurisy OR tuberculous pleural effusion). Additionally, references from retrieved articles meeting the inclusion criteria [studies written in English; original case reports or case series or article (not reviews, systematic reviews, or meta-analyses); sufficient clinical or therapeutic details to allow data extraction; confirmed microbiological diagnosis of *Paragonimus* infection (including serology, IDTPA test, egg detection, mNGS, or histopathology); and pleural effusion as the primary or a major manifestation (i.e., not pericardial effusion as the primary presentation)] were manually searched. Exclusion criteria included studies not written in English, reviews without original case data, systematic reviews or metaanalyses, reports with insufficient clinical or therapeutic detail or cases with pericardial effusion as the primary manifestation. The extracted data included geographic region, age, sex, epidemiological history, diagnostic modalities, radiological findings, treatment details and clinical outcome.

In total, 53 published cases of pleuropulmonary paragonimiasis misdiagnosed as TB pleurisy or TPE were identified across 16 Englishlanguage publications (including 11 case reports and five case series; Table I). After excluding two cases with incomplete data, 51 unique published cases met the criteria for analysis. These cases were reported from 2001 to 2026 (8-23), with the following geographic distribution: China (n=14), Nepal (n=17), India (n=9), South Korea (n=5), Japan (n=4), Cambodia (n=1), Ecuador (n=1) and Peru (n=1). The patients included 32 males and 19 females. Age ranged from 6 to 68 years, with eight cases lacking age data. A total of 47 patients (92.2%) had a confirmed history of consuming raw or undercooked freshwater crabs, crayfish or other aquatic products (8-23). Among the 14 Chinese cases, the majority originated from paragonimiasisendemic provinces, including Yunnan, Sichuan, Chongqing, Zhejiang and Fujian (5,34).

The most common clinical manifestations included cough (88.2%) (8,10,12-15,17-23), chest pain (60.8%) (10,12, 14,15,17,19,22,23), fever (54.9%) (8,10-12,14,15,17,20,22,23), hemoptysis (47.1%) (8,10,12,14-16,20,22), expectoration (43.1%) (8,12,14,15,19,22) and dyspnea (31.4%) (10,14,15, 17-19,22). Radiologically, PE was the predominant finding (100%) (8-23), followed by pulmonary consolidation/nodules (64.7%) (8-10,12-15,17-20,22,23) and pneumothorax (7.8%) (14,22). Peripheral blood eosinophilia (eosinophils >5% or absolute count >$0.5x10^9$/l) was present in 48/51 patients (94.1%) (8-10,12-16,18-23). Pleural fluid analysis, available for 36 patients, revealed exudative effusion in all cases (100%) (8-10,12-15,17-20,22,23), with eosinophilic PE (EPE; eosinophils >10%) documented in 30/36 patients (83.3%) (8,12-15,17,18,20,22,23). The most common diagnostic method was serological testing (ELISA for *Paragonimus*-specific IgG antibody), which was positive in 45/48 tested patients (93.8%) (8-12,14-20,22,23). Direct visualization of *Paragonimus* eggs in sputum was achieved in 14 patients (27.5%) (8,10,12,14-16,22,23). Thoracoscopy with pleural biopsy was performed in 12 patients, revealing eosinophilic infiltration or parasite eggs in pleural tissue in 10 cases (83.3%) (12,14,15,18,20,22,23). mNGS of bronchoalveolar lavage fluid was employed in two cases, both with positive detection of *Paragonimus* sequences (8,23).

All patients received antiparasitic therapy, with praziquantel (standard regimen of 25 mg/kg three times daily for 3 consecutive days or equivalent dosing) as the primary treatment (8-23). Anti-TB treatment was discontinued following confirmation of paragonimiasis. Among the 51 patients, followup duration ranged from 1 to 24 months. Outcome analysis revealed clinical improvement or cure in all 51 patients (100%) (8-23), with resolution or marked decrease of PE and normalization of peripheral blood eosinophil counts. No deaths were reported.

Discussion

A systematic review and metaanalysis covering the period from 1954 to 2024 showed that in China, paragonimiasis is primarily caused by *Paragonimus westermani* and *Paragonimus skrjabini*, with cases predominantly distributed in provinces along the Yangtze River basin: Chongqing (20.85%), Zhejiang (18.39%), Hubei (17.08%), Sichuan (10.00%), and Hunan (4.88%), accounting for 71.21% of the national total (4,7,34). The present patient came from a rural mountainous area of Hubei Province, which is consistent with an endemic region for paragonimiasis. paragonimiasis affects all age groups, and the mean age of patients with paragonimiasis induced PE is 46.5±5.1 years, as reported by Wang *et al* (7). The clinical manifestations of paragonimiasis are predominantly respiratory, including cough, sputum production, chest pain and dyspnea, often accompanied by nonspecific symptoms such as lowgrade fever, night sweats, weight loss and fatigue (7,35). The present patient presented with cough, sputum and fever. Chest radiography or CT findings in paragonimiasis may include PE, hydropneumothorax, pulmonary nodules, cavities, and cystic opacities (15,30); among these, cavitary lesions are considered characteristic. In the present case, however, imaging only revealed PE without specific features.

Although the present patient had no history of ingesting raw freshwater crabs, shrimp or snails, he had longterm occupational exposure to freshwater crabs and crayfish. The present clinical course was characterized by cough, sputum, intermittent fever, poor response to initial antibiotics and empirical antiTB therapy. Peripheral blood eosinophil counts were markedly elevated on both admissions (1.9 and 2.61x10^9/l, respectively) and abundant eosinophils were observed in pleural fluid and biopsy tissue. IDTPA and serum *Paragonimus* IgG antibody were positive, and the patient responded well to praziquantel. Therefore, the diagnosis of paragonimiasisinduced PE was established.

Because PE as the sole imaging feature of paragonimiasis is nonspecific, misdiagnosis and diagnostic delay are common. A study by Ahn *et al* (36) analyzing 685 patients with pleuropulmonary paragonimiasis over 22 years found that 119 patients experienced diagnostic delays ≥25 weeks, mainly due to misdiagnosis as TB, malignancy or chronic obstructive pulmonary disease, with an odds ratio of 111.75 (95% CI: 43.25-288.74), indicating high risk of misdiagnosis.

Table I. Clinical data of previously reported cases of paragonimiasis with pleural effusion misdiagnosed as tuberculous pleurisy/pleural effusion (n=51).

First author/s, year	Country	No. of cases	Age, years	Sex	Raw consumption history	Clinical manifestations	Peripheral blood eosinophilia	Pleural fluid eosinophilia	Imaging findings	Diagnostic methods	Treatment	Outcome	(Refs.)
Li *et al*, 2026	China	1	18	F	Yes	Cough, sputum, hemoptysis for 4 years	Yes	NR	Pulmonary lesions	mNGS (+87 reads), ELISA (+), bronchial biopsy (-), GeneXpert (-), culture (-)	Praziquantel (1.2 g tid x 3 d)	Hemoptysis resolved in 15 d; CT lesion notably reduced at 2 months	(8)
Yang *et al*, 2024	China	1	NR	NR	NR	Isolated pleural effusion	NR	NR	Pleural effusion	Immunology, serology	Praziquantel	Cured	(9)
Villanueva-Villegas *et al*, 2023	Peru	1	29	M	Yes	Cough, chest pain, fever, hemoptysis for 3 years	NR	NR	Pulmonary lesions	Sputum smear positive for eggs, TB test (-)	Triclabendazole	Clinical and radiological improvement	(10)
Poudyal *et al*, 2022	Nepal	20	Median, 34	NR	100% (20/20)	Fever 80%, cough 90%, pleural effusion 100%	Mean absolute count 16,678/ml	100% (>10%)	GGO 65%	Sputum microscopy (5 cases), pleural fluid analysis	Praziquantel (19 effective)	95% effective	(22)
Calvopina *et al*, 2017	Ecuador	1	30	M	NR	Cough, rusty sputum, chest pain, dyspnea for 5 years	NR	NR	Multiple small bilateral lung nodules	Sputum smear positive for eggs (*P. mexicanus* by molecular ID), AFB (-)	Praziquantel	Cough and sputum resolved	(11)
Luo *et al*, 2016	China	1	43	M	NR	Cough, bloody sputum, chest pain	NR	NR	Patchy consolidation, pleural effusion	ELISA (+), thoracoscopy showing Charcot-Leyden crystals	NR	Cured	(12)
Sah *et al*, 2017	Nepal	3	NR	NR	100%	Cough, hemoptysis, dyspnea, chest pain, fever	Yes	NR	TB-like	Sputum smear positive for eggs, TB test (-)	Praziquantel	Improved	(17)
Singh *et al*, 2005	India	3	NR	NR	100%	TB-like	Markedly elevated	Markedly elevated	TB-like	Sputum smear positive for eggs	Praziquantel	Improved	(23)
Prasad *et al*, 2015	India	1	NR	NR	Yes	TB-like	NR	NR	NR	Failed anti-TB treatment	Antiparasitic	Improved	(13)

Table I. Continued.

First author/s, year	Country	No. of cases	Age, years	Sex	Raw consumption history	Clinical manifestations	Peripheral blood eosinophilia	Pleural fluid eosinophilia	Imaging findings	Diagnostic methods	Treatment	Outcome	(Refs.)
Lee *et al*, 2014	China	1	53	F	NR	Cough, foul-smelling sputum, bloody sputum	NR	NR	Subpleural cavitary consolidation, right upper lobe	VATS wedge resection pathology (+), bronchoscopy (-), cytology (-)	Anti-TB then recurrence, pathological confirmation	Cured	(15)
Song *et al*, 2014	South Korea	1	38	M	NR	Low-grade fever, pleuritic chest pain	NR	NR	Right pleural effusion, pleural thickening, subpleural consolidation	VATS pathology (+), ADA 85.3 U/l, TB test (-)	Anti-TB for 2 months ineffective	Cured	(14)
Nagakura *et al*, 2002	Japan	1	NR	NR	Yes	X-ray misdiagnosed as TB	Yes	NR	X-ray	Sputum smear: eggs, abundant eosinophils, Charcot-Leyden crystals	NR	NR	(16)
Sharma *et al*, 2024	Cambodia	1	62	M	Yes	Cough, dyspnea, recurrent hemoptysis	Yes	NR	Pleural thickening, subpleural nodules	ELISA (+)	Praziquantel	Improved	(19)
Yin *et al*, 2025	China	2	40 / 60	F	Case 1, NR; case 2, yes	Case 1: Cough, dyspnea for 1 week; Case 2: Cough, hemoptysis, chest pain, wheezing >1 month	NR	NR	Case 1: Right pleural effusion, lung lesion; Case 2: Cavitary lung lesion, pleural involvement	Case 1: ELISA (+). Case 2: ELISA (+), elevated serum IgG4	Antiparasitic (2 months for case 1, 1 week for case 2)	Case 1, improved; Case 2 improved, IgG normalized	(20)
Das *et al*, 2024	India	3	Children	NR	NR	TB-like	NR	NR	TB-like	NR	NR	NR	(21)
Hwang *et al*, 2015	South Korea	10	NR	NR	NR	Pleural fluid analysis	NR	Eosinophilic pleural effusion	NR	Pleural fluid analysis, ELISA	Praziquantel	Improved	(18)

F, female; M, male; mNGS, metagenomic next-generation sequencing; TB, tuberculosis; GGO, ground-glass opacity; ID, identification; AFB, acid-fast bacilli; VATS, video-assisted thoracoscopic surgery; ADA, adenosine deaminase; NR, not reported; tid, three times/day.

Paragonimiasis is often misdiagnosed as TPE (8-23), parapneumonic PE (7) or malignant PE (24,25). The present patient was misdiagnosed with TPE for 8 months. Misdiagnosis of paragonimiasis as tuberculous pleurisy carries clinical and economic consequences. In the 51 reviewed cases, the average duration of unnecessary anti-TB therapy before correct diagnosis was 4.2 months (range, 1-11 months), exposing patients to drug toxicity and financial burden without clinical benefit. Diagnostic delay also permits disease progression (from isolated effusion to parenchymal cavitation or extrapulmonary dissemination) and prolongs symptom-associated impairment of quality of life. Moreover, misclassification as TB may trigger unnecessary contact tracing, diverting public health resources from TB control efforts.

Paragonimiasis infection leads to increased absolute or relative eosinophil counts in peripheral blood or pleural biopsy tissue (3). However, eosinophilia is also common in allergic disease, parasitic infections, eosinophilic gastritis, hypereosinophilic syndrome and fungal infections, but is uncommon in TB (13). In addition, patients with TB pleurisy typically have a history of TB exposure and present with toxic symptoms such as prolonged lowgrade fever, fatigue and night sweats, and the tuberculin skin test (TST) is usually positive (8). Definitive diagnosis of paragonimiasis relies on the identification of parasite eggs, however, the sensitivity of detecting eggs in sputum, feces or pleural fluid is low (36). Thus, direct pathogen detection is difficult, and serological methods based on immunological tests are the most effective laboratory diagnostic approach (9). The primary immunological tests include IDTPA test, double agar gel diffusion test and immunoenzymatic assays (10,11). The IDTPA test has a positive rate of up to 95% (12,13). It has been reported that serum *Paragonimus* antibody ELISA has a sensitivity of 90.2% and specificity of 100.0% (26). However, ELISA is relatively complex and has a long turnaround time, whereas IDTPA is more convenient and rapid, yielding results within 15 min. Du *et al* (29) demonstrated that the IDTPA has good sensitivity in diagnosing cerebral paragonimiasis in 12 children. Xia *et al* (28) and Paranjape *et al* (29) also indicated that laboratory evaluation of cerebral paragonimiasis includes eosinophil count, IDTPA and ELISA. The present case showed a strong positive IDTPA reaction. These findings collectively underscore the importance of IDTPA in the diagnosis of paragonimiasis.

In recent years, molecular techniques such as mNGS and multiplex PCRbased targeted NGS (tNGS) have been widely used to directly detect target organisms in respiratory samples, with a detectable pathogen spectrum covering >95% of clinical infectious cases (37-39). To the best of our knowledge, however, reports on the use of these molecular techniques for diagnosing paragonimiasis are rare. Li *et al* (8) reported a case of paragonimiasis confirmed by mNGS and serological testing; thus, mNGS and tNGS serve as auxiliary diagnostic methods for paragonimiasis. Nevertheless, their clinical application has limitations, including high cost and long turnaround time (40). The positivity rate of NGS for detecting pathogens such as *Paragonimus* is low (41). Although mNGS theoretically detects all microorganisms, its sensitivity for parasite DNA in practice is generally poor. This is because, in the early stage of infection or under low parasite burden, the nucleic acid content is low and can be easily overwhelmed by host cell DNA or other microorganisms (42). Clinical studies (41,43,44) have shown that the detection rate of mNGS for thickwalled microorganisms (including certain parasites) is notably lower than that for bacteria, viruses and fungi. For example, in a study of 45 patients with pulmonary infection, the detection rates of mNGS for *Mycobacterium tuberculosis* and fungi were 70.6 and 100.0%, respectively, while the detection rate for parasites (such as *Paragonimus*) was typically <20.0% (41). Taken together, mNGS and tNGS are not allpowerful in the field of parasite detection (31,32,45). Their limitations stem from technical shortcomings (host background interference, lack of reference databases) and the biological characteristics of parasites (low abundance, difficulty in nucleic acid extraction). In the present case, several factors limited the sensitivity of mNGS for detecting *Paragonimus*. First, no host DNA depletion was performed and the human cell concentration was $4x10^6$ cells/ml, resulting in a high human background (>95% of total reads). Second, the patient presented with isolated eosinophilic PE without parenchymal lung lesions, indicating a very low parasite burden in the bronchoalveolar space. In the present literature review of 51 cases of paragonimiasis with PE, two (3.9%) had positive mNGS results from BALF. Third, the proportion of microbial reads was low (14,674 out of 29.7 million reads), illustrating the difficulty of detecting a low-abundance parasite without targeted enrichment. Therefore, a negative mNGS result does not rule out paragonimiasis. The present diagnosis was established on the basis of peripheral blood eosinophilia (18.0%, absolute count, $2.61x10^9$/l), EPE and pleural tissue infiltration, positive IDTPA and *Paragonimus* IgG ELISA and the excellent response to praziquantel. In clinical diagnosis, sequencing results should be considered as an important reference, but traditional methods such as serology and microscopy should be used in combination to improve diagnostic accuracy.

Although misdiagnosis of paragonimiasis as TB pleurisy is well documented (8,9,22,36), the present case possessed distinctive features. Unlike most previously reported cases in which patients had a definite history of ingesting raw or undercooked freshwater crabs or crayfish (92.2% of 51 reviewed cases) (8-23), the present patient had no dietary exposure but instead had long-term occupational contact with freshwater aquatic products as a fish farmer. The patient specifically reported wading in fish ponds, cleaning them and handling bycatch (freshwater crabs and crayfish) without gloves, sustaining minor hand injuries. This observation expands the spectrum of at-risk populations and emphasizes the importance of inquiring about occupational and environmental exposures in endemic regions. The diagnosis was rapidly established using the IDTPA, which yielded a positive result within 15 min; this bedside tool is particularly valuable in resource-limited settings where ELISA may be unavailable or delayed. Notably, mNGS of BALF failed to detect any pathogen, despite the high parasite burden suggested by extreme eosinophilia. Finally, despite an 8-month diagnostic delay and ineffective anti-TB treatment, the patient achieved complete clinical cure following four courses of praziquantel without any adverse effects, reinforcing the efficacy and safety profile of praziquantel, as consistently demonstrated in the reviewed literature (8-23). Apart from thoracentesis for PE drainage, the firstline treatment for paragonimiasis induced PE is oral praziquantel (2,5,6). Case series

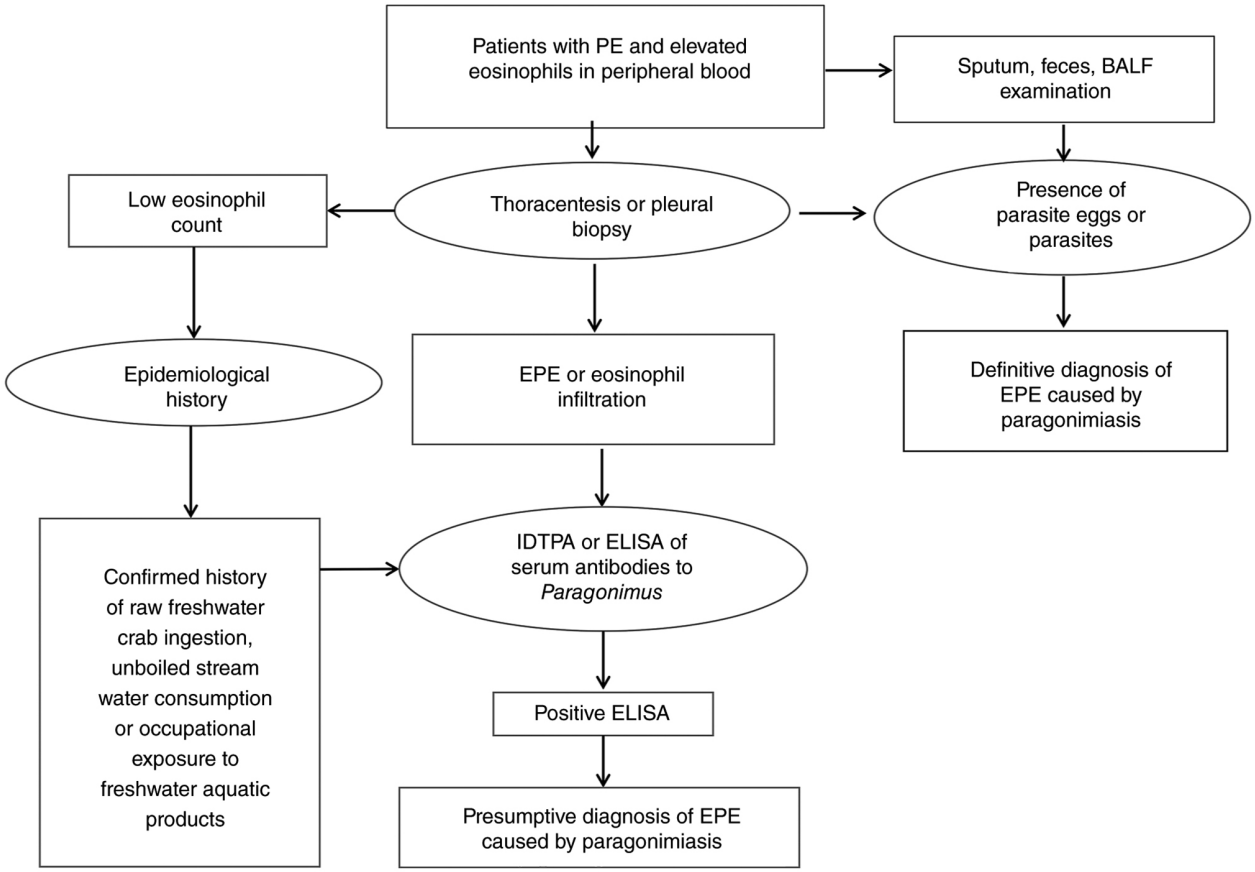

Figure 4. Proposed clinical diagnostic algorithm for EPE caused by paragonimiasis. EPE, eosinophilic pleural effusion; BALF, bronchoalveolar lavage fluid; IPTPA, intradermal test for *Paragonimus*-specific antigen.

and reports have demonstrated the effectiveness of praziquantel in achieving clinical cure, including cases complicated by PE (7,12,14,15,18,30,46). In China, praziquantel remains the standard antiparasitic therapy for paragonimiasis (5,30). In addition, triclabendazole is an alternative treatment option for paragonimiasis (47). Calvopiña *et al* (32) conducted a randomized clinical trial involving 62 patients with paragonimiasis and found that triclabendazole had comparable efficacy to praziquantel with better patient tolerance. A systematic review by Keiser *et al* (31): indicated that triclabendazole is a promising alternative to praziquantel. Furthermore, Hu *et al* (46) confirmed that triclabendazole is highly effective against *P. skrjabini* infection, with a favorable safety and tolerability profile.

The present case, together with the 51 previously reported cases (8-23), illustrates that paragonimiasis with PE is typically misdiagnosed as TB pleurisy, with an initial misdiagnosis rate approaching 100% and diagnostic delays ranging from weeks to years. Several factors contribute to this clinical pitfall. First, the clinical and radiological manifestations are highly nonspecific: Symptoms such as cough, sputum, fever, and dyspnea are indistinguishable from those of pulmonary TB and isolated PE without characteristic parenchymal lesions, present in all 51 reviewed cases, typically mimics tuberculous pleurisy, especially in TBendemic regions (8-23). Second, overreliance on positive TBassociated tests (TBAb, TST or IFNγ release assays) creates a cognitive bias toward TB (13,14,22), leading clinicians to overlook alternative diagnoses. TBAb test used has low sensitivity and specificity and is not recommended by the World Health Organization for the diagnosis of TB; nevertheless, its positive result contributed to the initial misdiagnosis in the present case. Third, the diagnostic value of eosinophilia is often ignored: Peripheral blood eosinophilia was present in 94.1% of reviewed cases, yet in the present case an initial eosinophil percentage of 15.2% was not followed up until the second admission 8 months later; similarly, EPE (observed in 83.3% of cases with available data) is typically overlooked. Fourth, inadequate epidemiological history taking is common: Although 92.2% of reviewed patients had a confirmed history of raw or undercooked freshwater product ingestion (8-23), the present longterm occupational exposure to freshwater crabs and crayfish was not elicited during the first admission, highlighting the need to inquire not only about dietary habits but also about occupational and environmental exposures in endemic areas (such as the Yangtze River basin provinces in China). Fifth, conventional pathogen detection methods have low sensitivity: Sputum smear, culture and mNGS failed to detect *Paragonimus* in the present case, and direct visualization of eggs in sputum was achieved in 27.5% of reviewed cases (8-23), underscoring the essential role of immunological tests (ELISA and IDTPA), which demonstrate high positivity rates (93.8 and 100.0%, respectively). Sixth, diagnostic delay and therapeutic inertia are pervasive: The median time to correct diagnosis ranged from 2 to 8 months, and the present patient received empirical antiTB therapy for 7 months without improvement. This pattern of 'diagnostic

momentum', continuing a treatment despite lack of response, is a common pitfall; clinicians should reassess the diagnosis if a patient with suspected TB shows no clinical or radiological improvement following 2 months of appropriate therapy, especially when eosinophilia or a relevant exposure history is present. Based on these observations, practical strategies to avoid misdiagnosis include maintaining a high index of suspicion for paragonimiasis in patients with unexplained exudative PE from endemic areas; routinely ordering a complete blood count with differential and, if available, pleural fluid eosinophil count; taking a detailed dietary and occupational history, including indirect exposure to freshwater crustaceans; when eosinophilia is present, performing serological testing (ELISA) and/or IDTPA without delay; not relying solely on mNGS to rule out paragonimiasis; and considering a therapeutic trial of praziquantel in suspicious cases after excluding TB and other contraindications.

Based on the findings of the present case and the 51 reviewed cases, a stepwise diagnostic approach may be proposed (Fig. 4). In any patient with unexplained EPE from an endemic area, *Paragonimus* serology (ELISA) or IDTPA should be performed regardless of raw seafood ingestion history; occupational exposure alone should be sufficient. Negative mNGS does not exclude paragonimiasis; traditional immunological tests (ELISA, IDTPA) are key. Lack of response to anti-TB therapy after 2 months warrants diagnostic reassessment; praziquantel is effective even after long diagnostic delays. As a single case report, the present findings may lack generalizability. However, the systematic review of 51 additional cases strengthens the evidence base. Other limitations include potential publication bias inherent to case series and the restriction to English-language publications, which may have excluded relevant cases reported in other journals, thereby introducing a languagebased selection bias. However, English is the most widely accepted language for international scientific communication; using Englishonly publications ensures that the reviewed data are accessible to the broadest possible readership, decreasing language barriers for global readers. Another limitation is the lack of interim follow-up data during the 8-month period of empirical anti-TB therapy. The present patient did not attend scheduled follow-ups during that time, which reflects real-world challenges in rural healthcare settings, but the eventual re-presentation with persistent symptoms supports the conclusion that no clinical improvement occurred. Additionally, follow-up duration was limited to 7 months and serological confirmation of cure (ELISA or IDTPA negativity) was not obtained. However, clinical and radiographic resolution together with normalization of peripheral eosinophil counts are widely accepted criteria for cure in paragonimiasis (9,11,12) and the patient remained asymptomatic with no evidence of relapse at the last follow-up. Clinicians should not rely on this test for clinical decisions, and a positive result alone does not confirm TB. Praziquantel is the treatment of choice; triclabendazole is an effective alternative. Heightened clinical awareness is key to reduce misdiagnosis and improve outcomes.

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Availability of data and materials

The data generated in the present study may be found in the National Center for Biotechnology Information Sequence Read Archive under accession number PRJNA1476379 or at the following URL: ncbi.nlm.nih.gov/bioproject/1476379.

Authors' contributions

XL and JL conceived and designed the study. XL and PW drafted the manuscript and analyzed and interpreted data. DC and XP interpreted data and revised the manuscript. LX, PW and JW interpreted data. XL and PW performed patient follow-up and the literature review. XL, JW and JL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present retrospective case report was reviewed and approved by the Institutional Review Board of Taihe Hospital, Hubei University of Medicine (Shiyan, China), which granted a waiver of formal ethical approval for single case reports. Written informed consent was obtained from the patient for participation in this study.

Patient consent for publication

Written informed consent was obtained from the patient for publication of the present cases report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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