



ORIGINAL ARTICLE

Hepatic paragonimiasis: a single-center retrospective analysis of 32 cases in Mainland China

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Abstract

Background: In paragonimiasis, the lungs and pleural cavity are the major target organs, and the central nervous system can also be affected. The liver is an organ in which ectopic paragonimiasis rarely occurs. Because the symptoms and examinations in hepatic paragonimiasis (HP) are not typical, the disease is often misdiagnosed in the clinic.

Methods: From February 2008 to March 2015, our department accepted 32 patients who presented with a liver mass upon ultrasound and computed tomography imaging and in whom the source of the mass could not be identified upon numerous further diagnostic tests. We ultimately obtained surgical biopsies of their lesions for pathological examination. We analysed the clinical data of these cases, along with their disease characteristics, the diagnostic strategies employed and their treatment experiences. Additionally, we performed patient follow-up for a period of 6–12 months.

Results: All patients underwent half/partial hepatectomy and were diagnosed with HP upon pathological examination. They recovered well after surgery and their original symptoms were markedly improved without recurrence. The liver functions of the patients reached normal levels before discharge and no additional liver lesions were found upon diagnostic imaging.

Conclusion: The diagnosis of HP based on clinical manifestations, laboratory tests or image examination is difficult and only pathologic analysis of biopsies could confirm HP. Surgical treatment not only removes lesions, but also allows for pathologic biopsy. This study encompasses the largest number of HP patients to date, but the surgical outcomes require further research and long-term follow-up.

Key words: hepatic paragonimiasis, parasitic disease, diagnostic strategies, hepatic resection

Introduction

Paragonimiasis is a food-borne zoonosis caused by eating raw or undercooked fresh-water crabs or crayfish infected with *Paragonimus metacercariae*. This parasite is endemic in Asian, African and South American countries, such as China, Japan, Liberia, Nigeria and Venezuela. The nationwide prevalence in China is estimated at 1.71% [1]. According to numerous studies, at least 293.8 million people are at risk of infection with *Paragonimus* parasites, with 195 million residing in China [2].

The lungs and tissues of the pleural cavity comprise the major target organs of paragonimiasis. Ectopic manifestations also occur in other sites. In cases of extrapulmonary paragonimiasis, the central nervous system (CNS) is the most common location, accounting for approximately 50% of extrathoracic diseases [3]. Paragonimiasis in the CNS can lead to serious complications, including headache, epilepsy, paralysis, behavioral changes and disturbed vision. However, ectopic paragonimiasis rarely occurs in the liver. As far as we know, only a few cases of hepatic paragonimiasis (HP) have been reported to date [4–7].

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As the symptoms, laboratory tests and imaging findings are atypical, HP is easily misdiagnosed in clinic. In this study, we summarize the clinical characteristics, diagnostic methods and treatment strategies of 32 patients diagnosed with HP by pathological samples.

Patients and methods

The study protocol was approved by the Institutional Review Board of our hospital. This study retrospectively evaluated 32 consecutive patients who underwent hepatic resection for HP at the Department of Surgery, West China Hospital of Sichuan University, from February 2008 to March 2015. Blood test, enzyme-linked immunosorbent assay, imaging examination and pathology were performed on all patients. Due to the small sample size, we do not perform statistical analysis and only report the results as individual values or mean \pm standard deviation (SD).

Results

Patients

The patient cohort was composed of 12 males and 20 females, with an average age of 41.6 ± 14.2 years. All patients reported that they had not been living in nor consumed food from an epidemic area. A majority of the patients (75%) presented with abdominal pain in the right or mid-upper abdomen that persisted for a period ranging from 15 days to 1 year. The nature of the pain was atypical. Pain intensity could always be tolerated, and some patients could find relief from their pain. Patients rarely presented with fever, cough, expectoration, jaundice, ascites or other related symptoms. Eight cases (25%) were asymptomatic and identified by chance.

Laboratory tests

Increased eosinophil levels were detected in 24 (75%) patients, with a mean level of $30.04 \pm 15.4\%$ (normal range 0.4–8%) and the highest level reaching 51.2%. The albumin globulin ratios (A/G) were found to be inverted in 16 patients (50%), with a mean ratio of 0.92 ± 0.14 (normal range 1.20–2.40). Additionally, alanine aminotransferase (ALT, normal range <50 IU/L) and aspartate aminotransferase (AST, normal range <40 IU/L) levels were elevated just in two samples (235/66 and 64/51 U/L, respectively). A single patient's hemoglobin was found to be decreased (89 g/L) and only one patient had slightly increased alpha-fetoprotein (AFP). A total of 20 patients underwent an enzyme-linked immunosorbent assay (ELISA) for paragonimiasis-specific antibodies in the serum, among which eight (40%) were found to be positive. The low prevalence of antibodies resulted in very low positive predictive values of ELISA test for HP.

Imaging examination (Table 1)

Ultrasound

Single or multiple masses were found, with sizes ranging from 1×1.5 to 8×4 cm. The echogenicity of the lesions were hypoechoic and their shapes were irregular. The borders of the masses were unclear or partially clear with a heterogeneous internal echotexture. Contrast-enhanced ultrasound images showed lesions with peripheral irregular hyper-enhancement with point- or line-enhanced echo inside the lesion (Figure 1).

Computed tomography (CT)

All patients underwent contrast-enhanced abdominal CT scans. In these images, the shapes of liver are almost normal. The

Table 1. Radiologic characteristics

Imaging findings	No. of cases	Percentage
Ultrasound scan	32	
Size (maximum diameter), cm	32	4.8 ± 3.9
Number of lesions		
Monofocal	28	87.5
Multifocal	4	12.5
Shape		
Regular	5	15.62
Irregular	27	84.38
Echogenicity		
Hypoechoic	32	100
Heterogeneous	28	87.5
Border of lesions		
Clear	6	18.75
Unclear	26	81.25
Contrast-enhanced ultrasound scan	15	46.88
Enhancement		
Peripheral hyper-enhancement	10	66.67
Heterogeneous enhancement	15	100
Computed tomography	32	100
Density		
Low	32	100
High	0	0
Location		
Right lobe	20	62.5
Left lobe	5	15.63
Both	7	21.87
Margins		
Clear	12	25
Obscure	24	75
Contrast-enhanced computed tomography	32	100
Enhancement		
Peripheral hyper-enhancement	26	81.25
Heterogeneous enhancement	29	90.63
Lobulated		
Yes	15	46.88
No	17	53.12
Nature of lesions		
Cystic	4	12.5
Cystic-firm mixed	28	87.5

lesions are low-density, ranging from 1 to 8 cm. The masses appeared to be relatively clustered. Among the 32 patients, 20 were found to have lesions in the right lobe, 5 in the left lobe and 7 in both lobes. The mass margins were found to be obscured in 24 cases. After the injection of a contrast agent, these lesions displayed mixed low-density shadows and two lesions showed multiple cysts with rim or circular enhancement. Furthermore, these masses became obvious on contrast-enhanced CT (Figure 2). We did not find any lesions in chest X-ray images.

Magnetic resonance imaging (MRI)

Only one patient had been examined by MRI and was not mentioned in this study.

Operation

After intraoperative ultrasonography to confirm lesion location, patients underwent open or laparoscopic surgery. Eleven patients underwent half hepatectomy, including eight right-half hepatectomy and three left-half hepatectomy. The remaining 21 patients underwent partial hepatectomy. Cholecystectomy was added in 16 cases. We summarized the surgical findings as

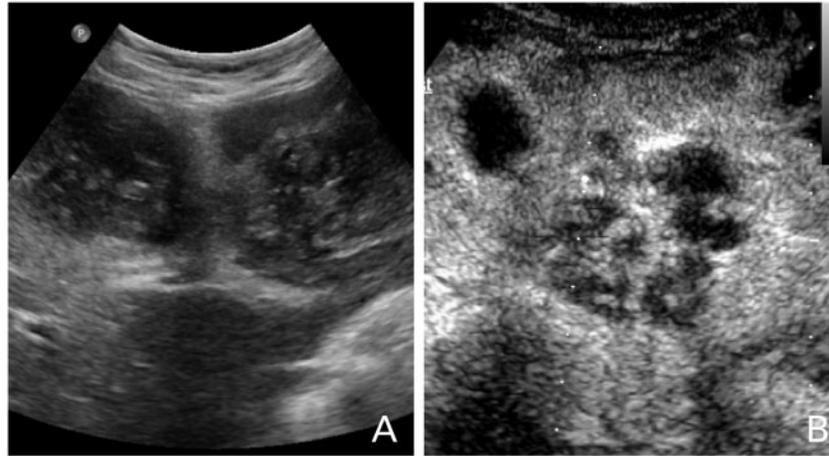


Figure 1. (A) Ultrasound scan shows hypoechoic lesions with irregular shape and unclear border. (B) After injecting contrast medium, there are some enhanced points in lesions, and internal echoes of lesions are asymmetric.

follows: no obvious change in the liver size and shape and soft liver texture without cirrhosis. In addition, the masses showed a variety of outgrowths, which were firm, cystic-firm mixed, irregular or lobulated. Upon dissection, a yellow, white or tawny fluid was expelled.

All patients underwent surgical treatment, with an average length of stay (LOS) of 13.9 days (6.76 days after operation) and an average cost of 34 852 RMB (5468 USD). The liver functions of the patients were abnormal from postoperative days 1 to 3, but they all recovered to normal ranges before discharge (Table 2). Eosinophil levels in 24 of 32 patients rapidly decreased after their lesions were removed. Only one patient developed an infection at the site of incision, which displayed swelling and discharge; this patient recovered rapidly after their dressings were changed.

Pathological results

All patients were diagnosed with HP by pathological examinations, which showed a high level of eosinophil infiltration, Charcot-Leyden crystals and paragonimiasis eggs. A total of 16 samples showed chronic cholecystitis (Figure 3).

Follow-up

All patients received follow-up care for a period of 6–12 months, with a mean follow-up time of 8.4 months. Patients returned to their normal work and routines after discharge. Their original symptoms were markedly improved, and their liver function and blood tests were normal. No patients were found to have any recurrent liver lesions upon follow-up ultrasound scans.

Discussion

In paragonimiasis, the lungs and pleural cavity are the major target organs, and the CNS can also be affected. Liver is an organ in which ectopic paragonimiasis rarely occurs. This study includes the largest known sample of HP patients for clinical research to assist doctors with the diagnosis and treatment of HP. Definitive diagnoses of paragonimiasis are always based on the finding of characteristic eggs in sputum or feces, but this method is challenging. For instance, our 32 hepatic paragonimiasis patients were negative according to this examination, likely because HP was confined to the liver and thus did not

appear in the lungs or intestine. The chest CT and clinical manifestations of these patients did not indicate any lesions in the lungs.

Infection occurs by ingesting raw or undercooked crustacean hosts (including those that are inadequately cured, dried, pickled or salted). The metacercariae reside in the small intestine (especially in the duodenum) and migrate through the intestinal wall to reach the abdominal cavity [8]. From here, they migrate through or around the diaphragm to the pleural cavity and lungs, finally arriving at the vicinity of the bronchioles, where they develop into adult worms [9]. Paragonimiasis may enter the liver during this process. The parasite penetrates the intestinal wall and migrates through the peritoneal cavity to the central liver parenchyma after perforating the Glisson sheath. Paragonimus can reach the sub-capsular space of the liver along the Glisson sheath [4,7,10]. Indeed, in this study, lesions were initially observed at sub-capsular regions (Figure 2) and this finding appears to be characteristic of HP [11]. Similarly, migration via the Glisson sheath route also causes diffuse lesions in the liver. In our study, we found that patients' CT images (Figure 2) were in accordance with these prior observations. In addition, because lesions are near the capsular space, they can cause obvious pain, which explains why the majority of our patients (24/32) presented with epigastric pain or discomfort as their first symptom.

A laboratory examination can also provide useful information relevant to the infection but comes with some limitations. Eosinophil levels were elevated in 24 patients, with the highest level reaching 51.2%. However, these results only imply the presence of a parasitic infection because there are many diseases that can cause elevated eosinophils, such as allergic diseases and hematopathy. Only two patients showed liver-function abnormality and had obvious acute abdominal pain, and their white blood cells were also elevated. We speculate that this acute stage of HP may cause obvious symptoms and abnormal examinations. ELISA is an important method with high sensitivity, specificity and reproducibility that has been widely applied to the serologic diagnosis of active paragonimiasis [12]. In our study, however, only eight patients showed a positive result for Paragonimus antibodies out of the 20 patients who were tested. Remarkably, these patients usually tested positive for other parasitic infections as a result of cross-reactions with other parasite antibodies (e.g. schistosome antibody

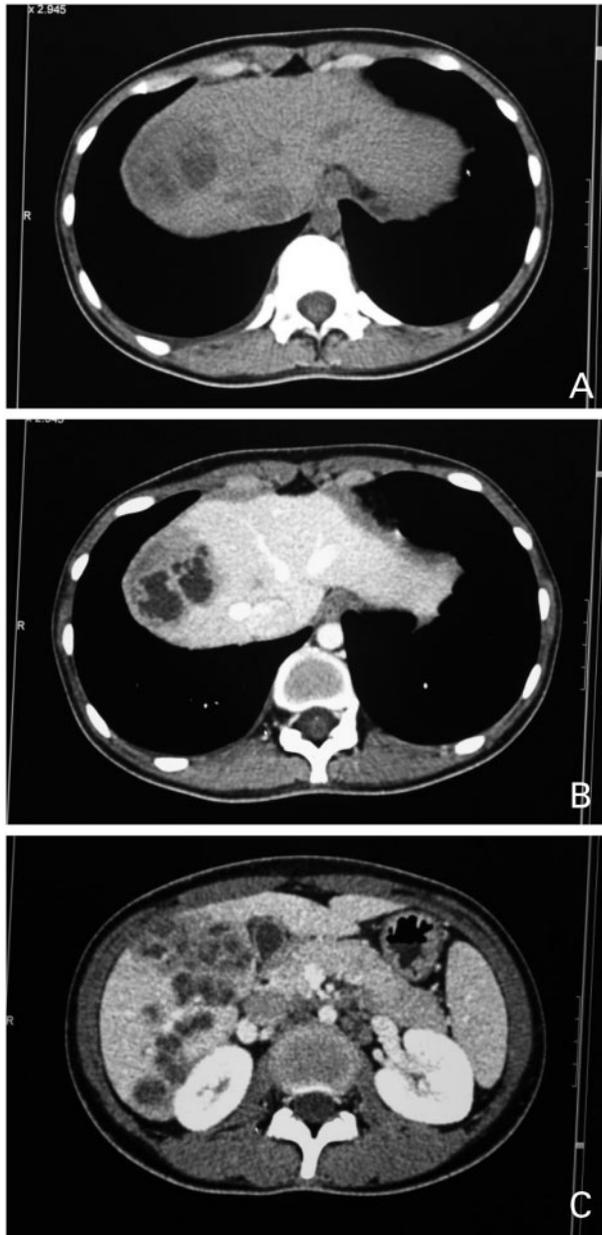


Figure 2. (A) CT scan shows a milder hypodense lesions compared to liver. (B) After injecting contrast agent, we can see mixed low-density solid-cystic lesions nearing the capsule in the portal venous phase. (C) In an enhancement scan, we can see multiple hypodense solid-cystic lesions, like honeycombs.

or hydatid antibody). Therefore, diagnosis by ELISA proved to be inaccurate in our study.

Pathological examination is the most accurate means for making a final diagnosis. Our 32 patients were all diagnosed by postoperative pathology. The visual detection of eggs under the microscope is the best method to confirm HP. However, this finding is not common in all lesions, so we also can diagnose HP by the following observations: (i) the formation of a cyst cavity or tunnel shape that contains coagulative or liquefactive necrosis, (ii) a high level of Charcot-Leyden crystals and (iii) a high degree of eosinophil infiltration with the formation of chronic eosinophilic abscesses. This phenomenon occurs due to mechanical injuries caused by paragonimiasis and the immunopathological response of the body to metabolic products produced

Table 2. Intraoperative and postoperative variables

Variables	Values
Operative treatment, n (%)	
Laparotomy	25 (78.1%)
Laparoscopy	7 (21.9%)
Operative variables, mean \pm SD	
Operative time, minutes	137.4 \pm 25.9
Intraoperative blood loss, ml	294.7 \pm 299.9
Length of stay, days	13.90 \pm 5.24
Postoperative length of stay, days	6.76 \pm 2.24
Total cost, RMB	34 852 \pm 3258
Postoperative complication, n (%)	
Bleeding	0 (0%)
Infection	1 (3.13%)
Hepatic failure	0 (0%)
Bile leak	0 (0%)
Postoperative blood test, mean \pm SD	
Alanine aminotransferase (IU/L)	28.5 \pm 9.6
Aspartate aminotransferase (IU/L)	27.2 \pm 7.7
Albumin globulin ratios	1.40 \pm 0.17
Direct bilirubin (umol/L)	4.70 \pm 1.73
Indirect bilirubin (umol/L)	7.61 \pm 2.99
White blood cells ($\times 10^9/L$)	6.24 \pm 1.50
Eosinophil (%)	5.45 \pm 2.23

by the worm [4]. Notably, chronic cholecystitis was observed in 16 patients. This condition could be caused by parasites migrating through the hepatic parenchyma and invading the cholecyst. In another study, the authors speculate that paragonimiasis can also invade the bile duct and cause chronic cholangitis [6].

Importantly, we need to distinguish HP from cholangiocarcinoma (CCA), abscesses and liver echinococcosis. CCA is the second most common primary hepatic tumor and is derived from epithelial cells of the bile ducts. On CT, mass-forming CCA also usually appears as an inhomogeneous low-attenuation mass with no enhancement. Furthermore, the AFP of CCA is always in a normal range, and both CCA and HP can block the bile duct and cause it to dilate. The symptoms of a liver abscess manifest as fever and abdominal pain, and they always appear as a cystic-solid mass by CT and ultrasound examinations. It is very difficult to distinguish liver abscesses from acute-stage HP. Liver echinococcosis, a common parasitic disease in the liver, presents with increase eosinophilia and abdominal discomfort. CT images also show low-density images and no enhancement. Furthermore, due to ELISA cross-reactions, echinococcosis may show positive results for *Paragonimus* antibodies, while paragonimiasis may show positive results for echinococcosis antibodies. All of these diseases have similar symptoms and laboratory/image findings. As such, when doctors cannot diagnose these diseases by in-depth examinations, we should rely on biopsies.

There are two measures we can choose to distinguish HP from other diseases mentioned above. One is the percutaneous liver biopsy. We diagnosed one patient by this method. However, due to the large lesions, he did not respond to medication and thus required surgery. Therefore, a percutaneous liver biopsy can help diagnose HP, but it comes with risks. For instance, if the liver mass is cancerous, a percutaneous liver biopsy may cause the cancer to spread. Furthermore, if the lesions are large and serious, medication cannot cure HP and patients will ultimately require surgery. The other means is

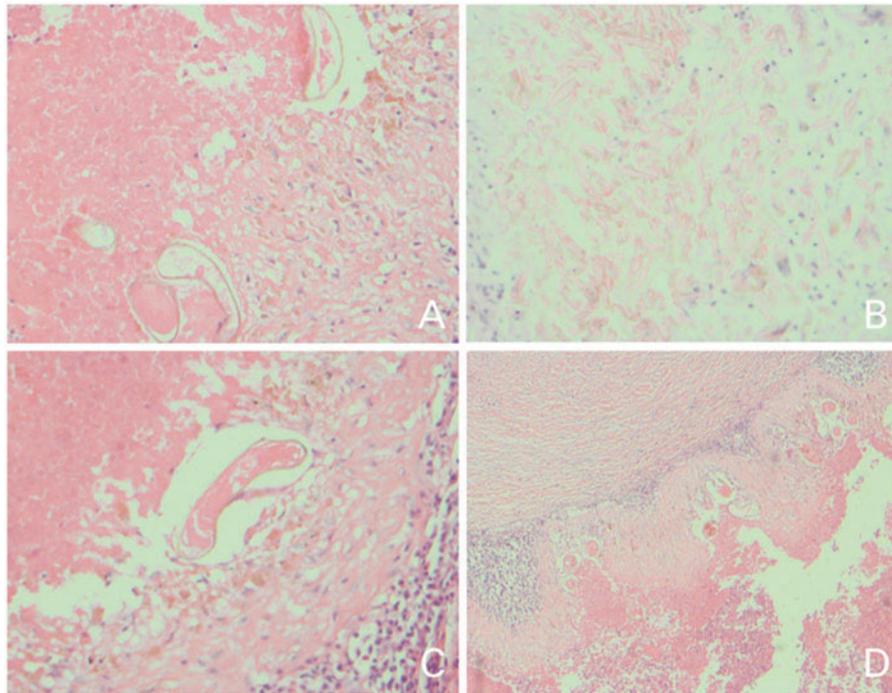


Figure 3. Hematoxylin-eosin staining of surgical specimen showing (A) eosinophils gathering in lesions and eggs; (B) Charcot-Leyden crystals; (C) eggs in lesion; (D) eosinophilic abscess, eggs and necrosis.

surgery. Surgery has two advantages over a percutaneous liver biopsy. First, we can obtain tissues for pathological examination. Second, regardless of the source of the lesion (cancer, abscess, tumor or any other parasite disease), we can eliminate it by a liver resection. Even in the case of cerebral paragonimiasis, surgical resection is sometimes used for treating this disease [13]. Unlike HBV infections, the damage to the liver from HP is local and the functional reserve of the liver is normal. A hepatectomy thus does not have a severe impact on HP patients, as long as their lesions have not invaded the entire liver (in this case, a liver transplantation is required). There were no cases of severe HP in our study. Radiofrequency ablation may be a potential strategy for treating HP, without significant side effects or complications [14].

According to our follow-up, the liver functions of all patients recovered well, including their ALT, AST and bilirubin levels, there was no recurrence of symptoms and lesions did not reappear in liver images or in other organs. All patients were discharged soon after their operations without any complications. The average hospitalization time is 13.90 ± 5.24 days because too much time is spent on diagnosis prior to surgery, delaying treatment and increasing hospitalization costs. In addition, long-term oral medication is associated with a high risk of side effects, including dizziness, headaches, gastrointestinal reactions, rash and even liver/kidney damage [14]. Therefore, when liver masses are observed and their source cannot be determined by laboratory tests and imaging, HP should be considered. We recommend that these patients undergo surgery not only to assist with the diagnosis of HP, but also to cure it.

Conclusion

The diagnosis of HP is difficult due to the absence of specific symptoms and clinical manifestations. Laboratory tests and imaging are less reliable in providing diagnostic evidence.

Pathological examination is the final and most important method for the diagnosis of this disease. Although surgery is invasive, it can provide a rapid means for diagnosis and treatment and may be widely used in the future. Our study includes the largest patient cohort for HP research to date, but the surgical outcomes warrants further investigation and follow-up.

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Conflict of interest statement: none declared.

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