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Inflammatory Liver Tumor Caused by *Fasciola hepatica* Mimicking Intrahepatic Cholangiocarcinoma

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Abstract. *Human fascioliasis is a rare parasitic disease outside of countries in which it is endemic. The diagnosis of hepatic-phase fascioliasis by diagnostic imaging alone is challenging. A 69-year-old female was referred to our hospital for the treatment of a solitary solid cystic mass lesion, 6 cm in diameter, accompanied with mild symptoms and minimal changes in laboratory parameters. Intrahepatic cholangiocarcinoma was suspected, and she underwent extended posterior sectionectomy. Four months later, she was re-admitted because of fatigue, high fever, and epigastric pain. Her eosinophil fraction and immunoglobulin E levels were extremely elevated (49.1% and 6833 IU/ml, respectively). She was found to have two new reticular cystic hepatic tumors. Serum dot enzyme-linked immunosorbent assay for parasites revealed strong positivity for Fasciola hepatica. Praziquantel was ineffective, and multi-cystic tumors rapidly developed in the left lateral section, requiring emergency left lateral sectionectomy. An F. hepatica helminth, approximately 3 cm in size, was observed on the cut liver surface during hepatic resection. Prophylactic triclabendazole (1,000 mg/day) was administered twice. She has been well for over 10 years without relapse of fascioliasis. In patients with hepatic tumors accompanied by inflammatory changes and eosinophilia, detailed medical history and serological testing by dot enzyme-linked immunosorbent assay for parasites are strongly recommended.*

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Fascioliasis is a zoonotic disease caused by liver parasitism by *Fasciola hepatica* and less frequently by *F. gigantica* (1-3). Many people are affected by fascioliasis, and an estimated 2.6 million people are at risk globally. Fascioliasis is endemic in Central and South America, as well as across Eastern Europe and Asia. In contrast, human fascioliasis is less common in nonendemic countries. Generally, patients with fascioliasis show multiple changeable hepatic lesions with systematic inflammation. Eosinophilia is present in almost all patients with fascioliasis (4, 5). Studies have demonstrated challenges in the diagnosis of fascioliasis using diagnostic imaging (5-9). Specifically, fascioliasis appears as an ill-defined heterogeneous low echoic or mixed-type tumor by abdominal ultrasonography and as a well-enhanced tumor with cystic changes by abdominal contrast-enhanced computed tomography (CE-CT) and dynamic magnetic resonance imaging (MRI).

Intrahepatic cholangiocarcinoma (ICC) is a common primary hepatic tumor which likely occurs in patients with chronic liver disease, intrahepatic lithiasis, and certain parasitic diseases as well as in patients with a normal liver (10, 11). ICC is observed as a low-density tumor with mild enhancement, especially in the tumor periphery, by CE-CT.

We herein report the case of a patient with a solitary inflammatory liver tumor caused by F. hepatica mimicking ICC in a nonendemic country. The patient did not have any symptoms of fascioliasis or systemic inflammatory changes at initial admission, which delayed the definitive diagnosis.

Case Report

A 69-year-old female was referred to our hospital to undergo treatment for a solitary solid cystic mass lesion, 6 cm in diameter, in the right posterior sector of the liver (Figure 1). There was no bile duct dilatation; however, several enlarged lymph nodes were identified in the hepatoduodenal ligament

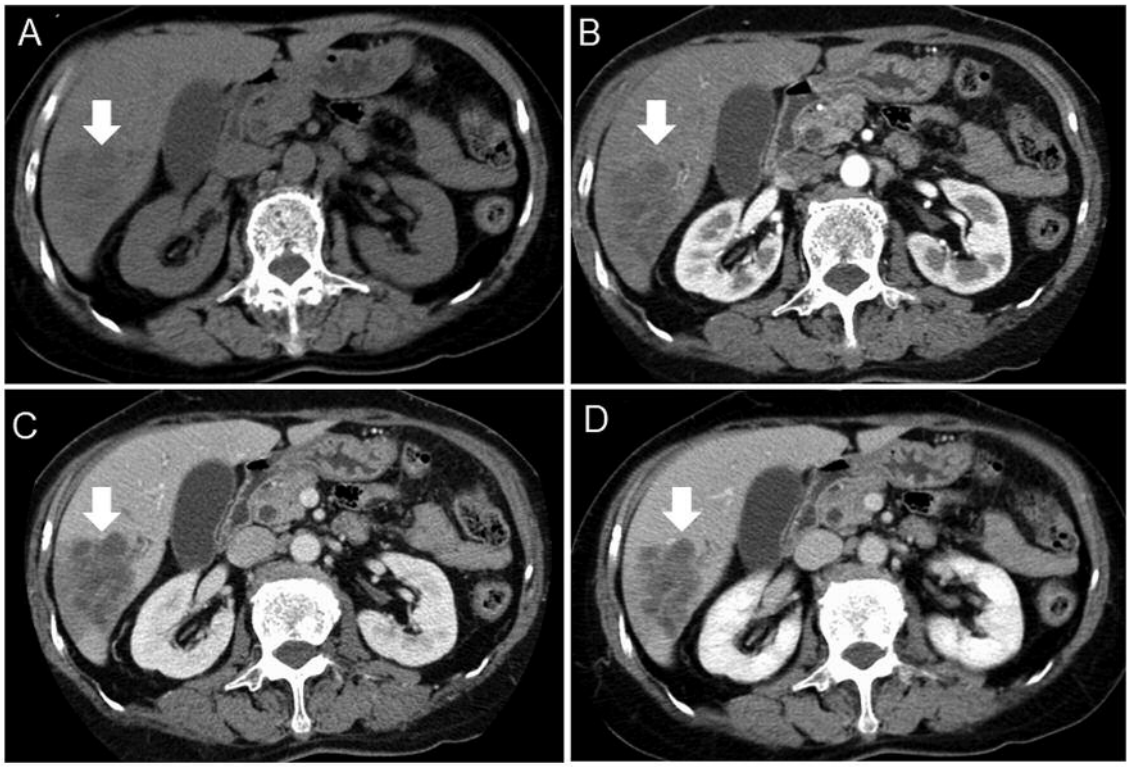

Figure 1. *Plain computed tomographic (CT) findings (A) and arterial-phase (B), portal-phase (C) and venous-phase (D) contrast-enhanced CT findings before first hepatectomy. CT showed a multinodular low-density lesion, 6 cm in diameter, in the posterior sector of liver. The lesion was partially enhanced without washout.*

and peripancreatic space. The patient's chief complaints were general fatigue and epigastric pain; she had no fever and exhibited mild inflammatory changes in blood biochemistry data on admission to our hospital. Her white blood cell count was 7,500/μl, her eosinophil fraction in the peripheral blood was 3.3%, and her C-reactive protein level was 0.26 mg/dl. The levels of tumor markers including carcinoembryonic antigen and carbohydrate antigen 19-9 were within normal limits. Tumor biopsy was not performed to avoid tumor cell seeding. The patient was diagnosed with suspicious ICC and underwent extended posterior sectionectomy. Some of the removed enlarged lymph nodes were determined not to be malignant. Macroscopically, well-defined yellowish lesion was observed and cystic lesions contained bile juice (Figure 2A). The resected liver was comprised of necrotizing lesions varying in size which were surrounded by granulomatous and fibrotic tissue. Eosinophilic infiltrations with Charcot-Leyden crystals, foreign-body giant cells, erythrocytes, and fibrin were confirmed in the necrotizing lesions (Figure 2B and C). Thus, a parasitic inflammatory tumor was suspected; however, the microscopic examination of the feces after surgery failed to show parasite body or parasite eggs. The patient was discharged and was followed-up closely.

Two months after the first hepatectomy, there was no recurrent tumor (Figure 3A). After a further 2 months, the patient developed fatigue accompanied by high fever and epigastric pain and was re-admitted to our hospital. Laboratory data showed an increase in C-reactive protein, white blood cell count, eosinophil fraction, and immunoglobulin E level in the peripheral blood (4.8 mg/dl, 11 900/μl, 49.1%, and 6833 IU/ml, respectively). Additionally, slight elevations in liver and biliary enzymes were detected (total bilirubin, 0.8 mg/dl; direct bilirubin, 0.2 mg/dl; glutamic oxaloacetic transaminase, 51 U/l; glutamic pyruvic transaminase, 44 U/l; alkaline phosphatase, 453 U/l; and γ-glutamyl transpeptidase, 29 U/l). Abdominal CE-CT revealed two new reticular cystic tumors in the left lateral sector and the caudate lobe of the liver (Figure 3B). The patient was treated with antibiotics for 1 week, followed by ultrasound-guided percutaneous drainage of the suspicious hepatic abscess in the left lateral sector. Microscopic examination did not show polypides or parasite eggs in the drainage fluid and the feces to suggest fascioliasis. Serum dot enzyme-linked immunosorbent assay (ELISA) for parasites revealed strong positivity for F. hepatica (12). Praziquantel (1,200 mg/day) was administered for 1 week;

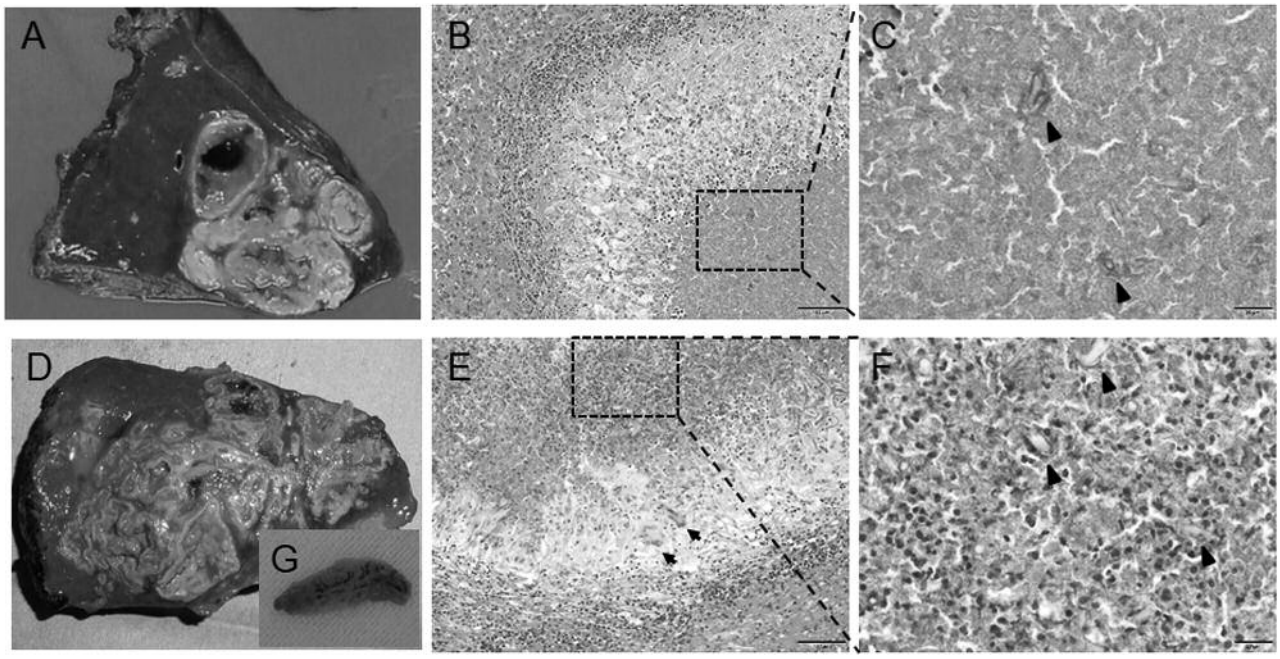

Figure 2. *Macroscopic and microscopic findings of specimens from the first (upper panel) and second (lower panel) resection. A and C: Cut liver surface. B and E: Low magnification (bar=100 μm). C and F: High magnification (bar=20 μm). The solid mass exhibited cystic degeneration (A), demonstrating abscess and parenchymal hemorrhage and scattered Charcot–Leyden crystals (B and C, arrowheads). The cut liver surface exhibited complex granulomatous lesions (D). Charcot–Leyden crystals (arrowheads) phagocytosed by foreign-body giant cells (arrows) and infiltration by numerous inflammatory cells (E and F), eosinophil cells in particular, were observed. A viable Fasciola hepatica helminth, 3.0 cm in length, was observed on the cut liver surface during hepatectomy (inset in D).*

however, her symptoms did not resolve and abdominal CE-CT 1 month after praziquantel therapy revealed a rapidly developing multi-cystic tumor in the left lateral sector and minimal bile duct dilatation. In contrast, most of the caudate lobe tumor had disappeared (Figure 3C). The patient underwent emergency left lateral sectionectomy due to the vanishing hepatic parenchyma. Macroscopically, an irregular whitish lesion with bile duct dilatation was observed (Figure 2D) during hepatic resection. An F. hepatica helminth, approximately 3 cm in size, was observed at the cut liver surface (Figure 2D inset). Pathologically, the second resection liver contained parenchymal hemorrhage, necrotizing lesions with Charcot–Leyden crystals, and granulomas as well as the firstly resected liver specimen. More inflammatory cells and abscessed lesions were observed in the second resected liver than that resected first. However, no eggs were microscopically found in either of the resected liver specimens (Figure 2E and F). Prophylactic triclabendazole (1,000 mg/day) was administered on postoperative days three and four, and the patient was discharged with no morbidity.

The cystic mass in the caudate lobe had completely disappeared 3 months after the second surgery (Figure 3D). The patient's eosinophil fraction and immunoglobulin E level declined to within normal limits at 2 and 7 months after treatment, respectively. Over 10 years after the second surgery, her general condition was good and there was no relapse of fascioliasis.

Discussion

We herein reported the rare case of solitary hepatic fascioliasis in a nonendemic country. The patient worked as a cow breeder in the southwestern part of Japan but had no history of consuming specific products which can contain flatworm metacercariae. Every year, approximately 10-20 patients in Japan are diagnosed with fascioliasis (13).

In the current case, the first hepatic lesion was accompanied by minimal inflammatory symptoms and inflammatory changes in laboratory parameters, suggesting that the patient was in the early hepatic phase of fascioliasis (4). In contrast, the hepatic lesions detected during the second admission were associated with inflammatory symptoms and specific blood chemistry data suggesting parasitic disease. In fact, excessive inflammatory cells infiltration, mainly with eosinophil cells was observed only

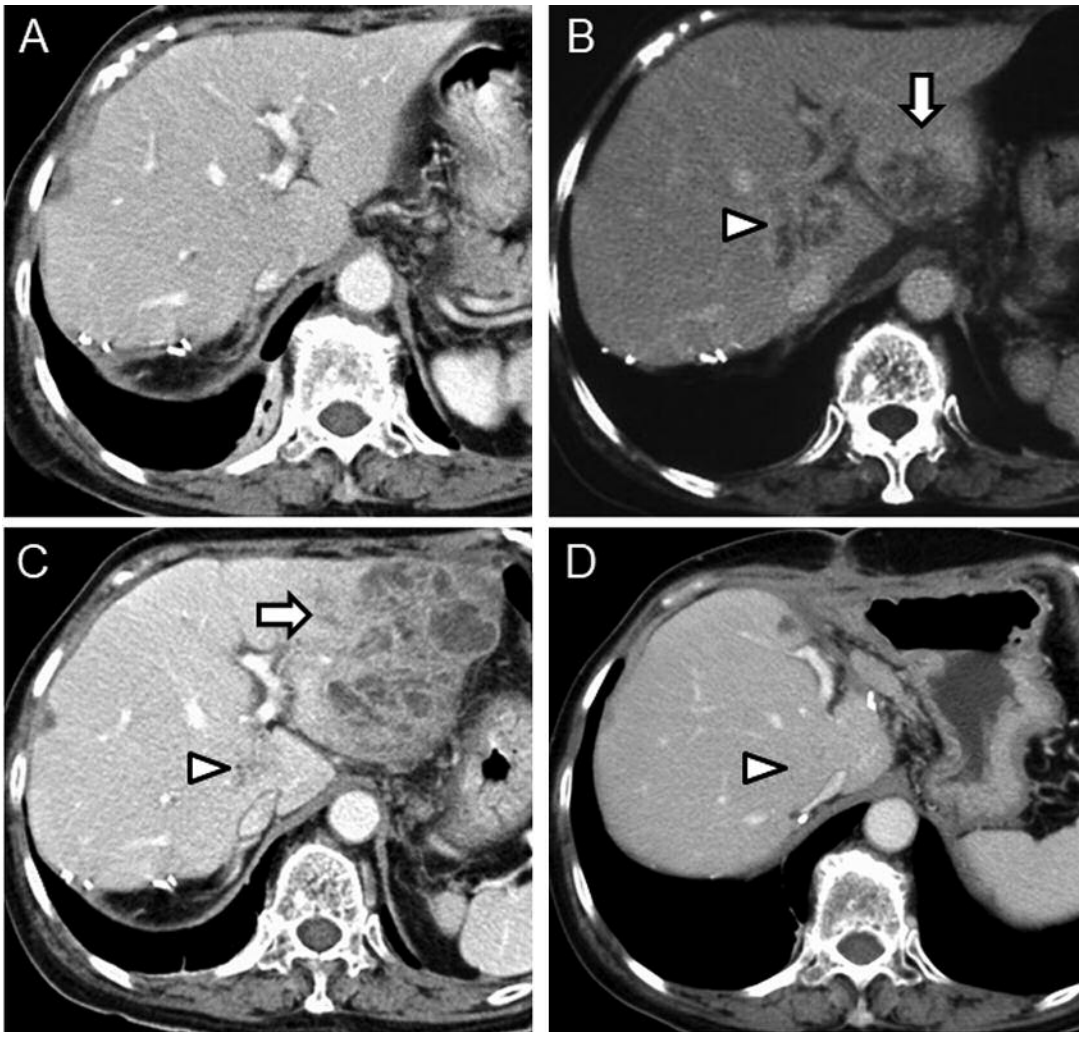

Figure 3. *Contrast-enhanced computed tomographic findings before (A, B, C) and after (D) second hepatectomy. Two reticular mass lesions suddenly appeared in the left lateral sector (arrow) and caudate lobe (arrowhead) 2 months before the second hepatectomy (A and B). The lesion in the left lateral sector rapidly developed within 1 month of the second hepatectomy to occupy most of the hepatic parenchyma (C). The lesion in the caudate lobe gradually vanished within 3 months of resection (D).*

in liver from the second resection. The elevation of eosinophil fraction and immunoglobulin E level in the peripheral blood, albeit important, are not always observed in the early period, similarly to that observed in the present case. The dot ELISA performed before the second surgery revealed the patient's serum was strongly positive against F. hepatica. During the second hepatectomy, a viable helminth was observed on the cut liver surface, and the final diagnosis was F. hepatica infection. Triclabendazole, an orphan drug at the time, was successful in preventing recurrence for over 10 years. Currently, oral triclabendazole is the first-line treatment after the diagnostic confirmation of hepatic fascioliasis (14, 15). Hepatectomy should be performed in patients with large lesions that fail to resolve with anthelmintic drug treatment (16). The recommended triclabendazole dose is 10-12 mg/kg as a single or split postprandial dose, which is effective with few adverse events in approximately 80-90% of patients (4). Although in one study complete clinical and laboratory recovery was observed in all patients 6 months after triclabendazole administration, abdominal CT revealed residual hypodense lesions in almost one-third of the patients (5).

The diagnosis of hepatic fascioliasis by imaging alone is challenging in the absence of clinical information. Hepatic fascioliasis generally appears as multiple hepatic lesions. In previous reports, two types of hepatic fascioliasis were

defined based on CT findings. Firstly, abscess-like lesions with single or multiple hypodense nodular areas and lesions with tunnel-like branching hypodense areas that are better delineated after contrast injection (17-20). The second type is highly suggestive of hepatic fascioliasis. Our patient exhibited a solid mass with cystic changes at the time of first surgery and abscess-like lesions with multiple hypodense nodular areas without peripheral bile duct dilatation at the time of second surgery. Clusters of micro-abscesses arranged in a tract-like fashion accompanied by a reticular pattern of enhancement are one of the findings of fascioliasis. Their case had exhibited a specific phenomenon of subcapsular hepatic hematoma formation and low-attenuation tracks extending from the capsule into the parenchyma along the migration path of maturing helminths. Additionally, a very slow lesion evolution on follow-up examinations has been reported as a characteristic feature (1, 4). However, we suggest that very rapid growth replacing liver tissue is important for differential diagnosis in the early period of infection. Differentiating hepatic-phase fascioliasis from malignant tumors using ^{18}F-fluorodeoxyglucose positron-emission tomography has been reported to be difficult (21).

Several cases were reported of patients who underwent hepatectomy for hepatic fascioliasis mimicking ICC; in all cases, the patients lacked specific symptoms or history suspicious of fascioliasis (8, 22). Mass-forming ICC is observed as a lobulated hepatic mass with arterial-phase peripheral rim enhancement and progressive centripetal enhancement by CE-CT. Conversely, the target appearance on diffusion-weighted MRI and cloud-like central high intensity on hepatobiliary-phase MRI are specific signs of hepatic fascioliasis (23). Contributory features such as hepatic capsular retraction and dilatation of peripheral bile ducts are observed in some patients. However, multimodal diagnostic images have been reported to lead to false-positive and false-negative diagnoses in patients with biliary inflammatory tumors and mucinous type ICC, respectively (24).

Percutaneous tumor biopsy is a useful option but tumor cell seeding can occur if the target lesion is a malignant tumor. In patients with fascioliasis, the larvae usually migrate through the intestinal wall into the peritoneum and pass through the liver capsule to enter the hepatic parenchyma and intrahepatic biliary duct. The hepatic lesions are located close to the liver surface; therefore, laparoscopic biopsy is a beneficial alternative to the percutaneous approach.

In nonendemic countries, the diagnosis of hepatic fascioliasis is challenging in patients without symptoms or inflammatory changes. However, a developing hepatic tumor accompanied with inflammatory changes, especially eosinophilia, should be investigated with detailed evaluation of medical history and serological testing using dot ELISA for the presence of parasites.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

TK and TB identified the concept and wrote the draft of the article; HH, KI, KY, HO, KM, and DY actually treated the patient and collected data; YK examined pathological findings; SA, YIY, KD and HB supervised article preparation.

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