HYPereosinophilia AND liver Mass IN An InMigrant

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Abstract. Human infection with the sheep liver fluke Fasciola hepatica is a global zoonosis that usually parallels the prevalence of infection in sheep and other ruminants. The disease is endemic in South and Central America, Puerto Rico, the Caribbean region, many parts of Africa, Asia, the Middle East, Australia, and China. There have been a number of focal outbreaks reported from Europe, including southern France and the Mediterranean region. Since acute fascioliasis has rarely been reported in the United States, physicians in this country frequently overlook the diagnosis. Therefore, we report a case of acute human fascioliasis and review the pathogenesis, diagnosis, and treatment of this disease in a recently arrived immigrant.

Case REPORT

A 26-year-old woman from the Dominican Republic was well on arrival in the United States in late February 1997. One month later she presented to a local hospital complaining of several hours of severe, sharp, right upper quadrant pain radiating to the right shoulder, with fever and chills. She denied a history of gallstones, jaundice, use of nonsteroidal anti-inflammatory drugs or oral contraceptives, urinary changes, or recent trauma. On admission to the hospital her temperature was normal, and she had mild right upper quadrant tenderness without hepatosplenomegaly or masses. A test result for β-human chorionic gonadotropin was negative, and she had peripheral eosinophilia (27%). An abdominal computed tomography (CT) scan with intravenous contrast demonstrated a 6.0 × 5.0 × 4.0 cm complicated, heterogeneous, necrotic mass in the right lobe of the liver, which extended from the dome to the inferior border, and laterally to the capsule. The mass contained internal septations with surrounding parenchymal hemorrhage (Figure 1A). An IgG-enzyme immunoassay result for antibodies to Echinococcus granulosus was low positive.

The patient was then transferred to our institution for further management. She denied exposure to farm animals, dogs, or fresh water, but she had frequently eaten uncooked “berro” or watercress (Nasturtium officinale). Other family members were well. She had a temperature of 36.9°C, clear lungs, and no liver tenderness or hepatosplenomegaly. One week later her white blood cell was 16,800/mm³ with 5,200/mm³ of eosinophils (31%). She had an alkaline phosphatase of 32 U/liter, and a bilirubin level of 0.5 mg/dL. Review of the CT scan revealed the above noted findings, which were consistent with the rupture of a hepatic hematoma or adenoma; however, a tagged red blood cell scan ruled out the former. Indirect immunofluorescence (IIF) tests for antibodies to Fasciola hepatica performed on serum obtained one and two weeks after the negative FAST-ELISA result revealed increasing titers of 1:80 and 1:160, respectively (1:20 borderline positive; Laboratoire de Parasitologie-Mycologie, Groupe Hospitalier Cochin, Paris, France). The result of an immunoelectrophoresis test was also positive, showing three bands on the first serum and four bands on the latter one.

The patient was treated with a single dose (10 mg/kg, 700 mg) of triclabendazole (Fasinex; Novartis, Basel, Switzerland). A CT scan 12 weeks later (Figure 1B) showed almost complete resolution of the lesion. Subsequent stool examinations remained negative for F. hepatica eggs up to 16 weeks after presentation. Her symptoms have not recurred and the eosinophilia and the other laboratory test results have returned to normal levels. One year later her eosinophil count was 200/mm³ and she remained well.

Discussion

Acute fascioliasis is infrequently recognized in the United States because there are few diagnostic tests available and it is too early in the infection to find the characteristic eggs in the stool. In the present case, hypereosinophilia and a large necrotic hepatic lesion in a patient who frequently consumed fresh watercress were the major reasons to suspect the diagnosis. The history of ingestion of uncooked freshwater plants, especially watercress, is almost always obtained. On occasion, infection can occur by drinking untreated fresh water containing the infective larvae. Urticaria, which is frequently seen in acute fascioliasis, was not evident in this patient.

Mature flukes inhabit the biliary tree where they deposit unembryonated eggs. These immature eggs pass down the bile ducts into the duodenum and eventually to the environment with the feces. After 9–15 days, miracidia hatch and penetrate various species of lymnaeid snails, the first intermediate hosts. After 4–7 weeks, they leave the snail as free-swimming cercariae and either encyst on various aquatic plants or sink to the bottom, in either case, developing into metacercariae. Humans are infected by drinking contaminated fresh or field water, or by consuming uncooked aquatic plants, especially watercress (berro), algae (algas), tortora, and kiosco. Metacercariae excyst in and then penetrate through the duodenal wall. Migrating in the peritoneum, the
invading immature flukes perforate Glisson’s capsule and burrow through the parenchyma, causing focal hepatic necrosis and abscesses. They next invade the bile ducts, mature there in approximately 3–4 months, and initiate egg-laying, which may continue for many years. The presence of mature flukes in the bile ducts may provoke epithelial hyperplasia, desquamation, thickening, and dilatation. Heavy infection may cause extensive periductal fibrosis and hemobilia.

Acute fascioliasis may continue for several weeks to months and coincides with the migration of the larval flukes through the hepatic parenchyma. The acute symptoms subside soon after the larval flukes enter the bile ducts. Acute infection can be associated with mild to severe illness or may be asymptomatic.1,2 This may be related to the number of invading larvae. The manifestations of acute infection include, anorexia, nausea, vomiting, fever, abdominal pain, (especially of the right hypochondrium), hepatomegaly, liver tenderness, urticaria, and hypereosinophilia; icterus is unusual. In chronic fascioliasis, most patients have few or no symptoms. However, a few patients may have right hypochondrium pain. If worms or eggs obstruct the extrahepatic biliary ducts, symptoms of cholecystolithiasis may occur. Occasionally, the worms may invade the gallbladder and their presence may cause symptoms resembling cholelithiasis. Aberrant or ectopic sites of infection are common and include the heart, lungs, brain, skin, and intestinal wall, presenting as visceral larva migrans.

A definitive diagnosis of chronic fascioliasis can sometimes be made by finding characteristic eggs in feces, although this is not a sensitive method of detection.3 Repeated stool examinations may be necessary to find eggs; most often, however, they are never demonstrated.1 In acute fascioliasis, immature worms have not initiated ovipositing; therefore, stool examination is not helpful and, as in ectopic infections, serodiagnosis is required.

Serologic tests are essential to diagnose acute and chronic fascioliasis. These tests include the FAST-ELISA, an ELISA, indirect hemagglutination, complement fixation, IIF, counter-electrophoresis, and double diffusion.1,3–5 Although these tests are quite sensitive, they may cross-react with other parasitic infections such as echinococcus and paragonimus.1 In the present case, the patient initially was referred to our Tropical Medicine Clinic for treatment of hydatid cyst disease when the serologic test result was interpreted at another institution as consistent with echinococcosis. The results of additional laboratory studies for fascioliasis, including the FAST-ELISA on serum obtained at admission, were negative. However, serum obtained one and two weeks later were strongly positive (IIF and immunoelectrophoresis). Recently, immunodiagnosis of human fascioliasis using cysteine proteinases (Fas1 and Fas2) as antigens was shown to be highly specific and sensitive.6 Circulating Fasciola antigen has been detected in both serum and urine samples in patients by testing with monoclonal antibodies. The specificity of this assay was 100% and sensitivities were 98% and 97% for serum and urine, respectively.7 An ELISA and micro-ELISA were used to detect antibodies to Fasciola in humans using excretory-secretory antigen. The sensitivity of each method was 100%; the specificity was 100% for the ELISA and 97% for the micro-ELISA.8 These new diagnostic tests are promising advances in the reliable diagnosis of fascioliasis; however, they are currently not readily available.

Recently, triclabendazole (6-chloro-5-(2,3-dichlorophenoxy)-2-methyl thiobenimidazolo) has successfully (cure rate = 80–100%) eradicated acute and chronic fascioliasis in humans and various herbivores.1,3,9 Praziquantel and bithionol (no longer available in the United States) are frequently ineffective.1 The mechanism of action of triclabendazole has not been established. However, similar to other anthelmintic benzimidazole compounds, i.e., albendazole and mebendazole, it binds to tubulin. It is unclear if this is its major site of action. In this regard, it has been suggested that triclabendazole may inhibit protein synthesis in Fasciola. It is well tolerated and easily administered in one or two doses. Patients may develop mild right upper quadrant pain within 24–48 hours after administration, which is probably due to death of the fluke within the liver or bile ducts. Pharmacologic studies in humans suggest that significantly higher absorption of triclabendazole can be achieved if administered postprandially.10 Recently, a new fasciolicidal agent derived from the stem of the Commiphora molmol tree proved effective in the treatment of Fasciola-infected humans; there were no reported adverse reactions to this agent.11

Individuals who have not been cured by oral drug therapy
have been treated successfully with endoscopic retrograde cholangiopancreatography and flushing of the biliary system with povidone iodide. In this regard, there have been several reports of triclabendazole-resistant *Fasciola hepatica* in ruminants. Although not studied, it is possible that treatment failures in humans may have been due to resistance to triclabendazole.

Acute fascioliasis should be suspected in immigrant patients with marked eosinophilia, liver abscess, and a history of ingestion of uncooked watercress or other aquatic plants. Triclabendazole appears to be the primary drug for treatment of acute and chronic fascioliasis.

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