Imported *Fasciola hepatica* Infection in the United States and Treatment with Triclabendazole

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Infection with *Fasciola hepatica*, a liver trematode, is not frequently reported in the United States. We describe 2 patients, both originally from Cape Verde, who illustrate the spectrum of clinical presentations of *F. hepatica* as well as the means of treating infection with this parasite. Patient 1 had extensive disease and underwent multiple diagnostic procedures before the correct diagnosis was reached. Patient 2, who had few symptoms, had fascioliasis diagnosed by a noninvasive evaluation. Both patients were treated with triclabendazole without experiencing significant side effects. Fascioliasis that has been imported to the United States may elude prompt or accurate diagnosis. Obtaining a detailed travel history and recognizing the clinical presentation early in the course of infection may permit timely and noninvasive identification of infection. Triclabendazole is now the recommended drug for treating for fascioliasis because of its efficacy, safety, and ease of use.

Fascioliasis is a zoonotic disease caused by the trematode *Fasciola hepatica*, a liver fluke [1]. Its usual hosts are sheep or cattle, in which it causes a disease of economic importance called “liver rot.” Humans are accidental hosts who become infected after eating uncooked aquatic plants on which encysted organisms are present. Fascioliasis is distributed worldwide, with a significant number of cases reported from western Europe, the Islamic Republic of Iran, northern Africa, and the Andean countries of South America [2]. A prevalence of human infection of 67% has been reported in the Bolivian Altiplano by use of coprological techniques [2]. Only a few cases of infection native to the United States have been reported; most cases of infection are imported [1, 3].

However, conditions that would allow completion of the life cycle, including the appropriate snail intermediate host, are present in the United States [4]. Hermaphroditic *F. hepatica* adults live in the biliary tree of their hosts and pass eggs out with the host’s feces. When the eggs are in water, ciliated miracidia hatch and subsequently infect an intermediate freshwater snail host. Free-living cercaria leave the snail, attach to aquatic plants (such as watercress), and develop into metacercarial cysts. When humans eat these plants, the metacercaria excyst in the duodenum and migrate through the small intestine wall, the peritoneal cavity, Glisson’s capsule, and into the liver. The larvae migrate to the common and hepatic bile ducts, mature into adult flukes, and begin laying eggs [1].

We describe 2 patients who were originally from Cape Verde who illustrate the spectrum of clinical presentations of *F. hepatica*; we also discuss the treatment considerations for this parasite.

**CASE REPORTS**

**Patient 1.** A 67-year-old man from Cape Verde with a history of atrial fibrillation, congestive heart failure,
and hypothyroidism first came to the United States in December 1996. He visited Cape Verde in the fall of 1997 and then returned to the United States in July 1998. Three months before his return to the United States, he developed abdominal pain that was most pronounced in the right upper quadrant, nausea, anorexia, weight loss of 18 kg (40 pounds), weakness, intermittent diarrhea, and pruritus without fever or chills. Three weeks after his return to the United States, he was admitted to the surgical service at an urban hospital in Boston for evaluation of right upper quadrant tenderness. At that time, he was afibrile, with tender hepatomegaly; he had a WBC count of 9600 cells/mm³, with 46% neutrophils, 16% lymphocytes, 6% monocytes, and 35% eosinophils; hematocrit level, 23.5%; alkaline phosphatase, 299 IU/L (normal range, 40–120 IU/L); aspartate aminotransferase, 40 IU/L (normal range, 0–40 IU/L); alanine aminotransferase, 36 IU/L (normal range, 0–40 IU/L); total bilirubin, 0.6 mg/mL (normal range, 0–1.5 mg/mL); and albumin, 2.4 g/dL (normal range, 3.9–4.8 g/dL). In contrast, laboratory values from February 1997 included a WBC count of 4100 cells/mm³ with no eosinophils and a hematocrit level of 46.2%. CT scan of the abdomen, done with and without iv contrast, demonstrated multiple ill-defined hypodense lesions throughout both lobes of the liver and a small amount of ascites (figure 1). A diagnostic biopsy of a liver specimen was performed that revealed severe active hepatitis with eosinophilic abscesses, marked loss of parenchyma, and areas of fibrosis (figure 2). Masson’s trichrome, periodic acid–Schiff, and Gomori methenamine silver nitrate stains were negative for parasites, fungi, and other organisms. One stool sample was analyzed by means of formalin ethylacetate concentration and polyvinyl alcohol-fixed trichrome staining. Only Entamoeba coli cysts were detected. A duodenal biopsy specimen demonstrated an increased number of plasma cells and prominent lymphoid follicles without evidence of organisms. Duodenal aspirate and biopsy yielded no growth on aerobic, anaerobic, viral, and fungal cultures.

Later that month, the patient presented again with rapid atrial fibrillation and congestive heart failure. He continued to experience abdominal pain, anorexia, and weakness. Physical examination revealed normal temperature, bibasilar crackles, a liver span of 18 cm with a tender edge, and moderate ascites. Laboratory studies disclosed the following values: WBC count, 8400 cells/mm³, with 18% eosinophils; alanine aminotransferase, 48 IU/L; alkaline phosphatase, 172 IU/L; total bilirubin, 0.9 mg/dL; and albumin, 2.2 g/dL. The results of serological testing were negative for antibody to HIV, negative for hepatitis A IgM, and positive for hepatitis B core antibody. A diagnostic paracentesis revealed WBC count of 2444 cells/mm³, with 21% neutrophils, 43% lymphocytes, 7% monocytes, 24% eosinophils, and 3% mesothelial cells; and albumin, 1.2 g/dL. Culture of the fluid did not yield any organisms. An abdominal ultrasound showed stones in the gallbladder, marked ascites, and a slightly heterogeneous liver without focal lesions or ductal dilatation. MRI of the abdomen demonstrated multiple low T1 and high T2 signal lesions within both lobes of the liver; these corresponded to lesions seen on the CT scan. At this second admission, 3 additional stool samples were analyzed for parasites, and a single egg with the typical morphology of F. hepatica/Fasciolopsis buski eggs was detected. The results of serum ELISA, performed with partially purified somatic products of adult F. hepatica as antigens (Parasitic Disease Consultants), were positive at a titer of 1:256 (negative, <1:32).

The patient was discharged from the hospital but readmitted with congestive heart failure shortly thereafter. After he experienced diuresis, he was treated with triclabendazole, 20 mg/kg given in 2 divided doses 12 h apart under close medical supervision (obtained from Novartis, Basel, Switzerland, under their named-patient program). He experienced no significant side effects from the treatment. Two months after his readmission, his abdominal pain and anorexia had resolved, and laboratory studies disclosed the following values: albumin, 3.9 g/dL; alkaline phosphatase, 114 IU/L; WBC count, 6600 cells/mm³, with 3.9% eosinophils; and hematocrit level, 36.9%. He returned to Cape Verde before posttreatment serological testing could be performed.

**Patient 2.** A 33-year-old man from Cape Verde with an unremarkable medical history came to the United States 2 weeks before his presentation with a 10-month history of mild diffuse abdominal pain and intermittent diarrhea. He reported eating watercress in Cape Verde, despite a local physician’s
warning against consumption of “watercress that had small objects on it.” While at the clinic, he was afebrile and experienced mild tenderness in the right upper quadrant of his abdomen without hepatomegaly. His WBC count was 8400 cells/mm³, with 7% eosinophils. His alanine aminotransferase level was 54 IU/L, and the remainder of the results of his liver function tests were within normal limits. The results of serological tests were positive hepatitis B surface antibody and negative for hepatitis A IgM and hepatitis C virus antibodies. An ultrasound of his abdomen revealed 2 poorly defined, irregularly shaped lesions. The results of serum ELISA for *F. hepatica* were positive, with a titer of 1:512. He was given 1 dose of triclabendazole, 10 mg/kg, and observation continued in the outpatient clinic; the patient did not experience side effects. His abdominal pain resolved within the 4 months after treatment. Eleven months after treatment, repeat serological tests demonstrated a borderline positive titer of 1:32. Repeat ultrasound of his abdomen showed interval resolution of all cystic lesions and a decrease in the size of the single remaining poorly defined, irregularly shaped lesion.

**DISCUSSION**

Fascioliasis that originated in Cape Verde has been documented in several case reports [5, 6]. Because of the increase in world travel, physicians in areas where infection is not endemic need to become familiar with the presentation of fascioliasis. Clinical presentation is influenced by the stage of the parasitic life cycle. The duration from ingestion of metacercaria to migration of larvae through the liver is 3–4 months; this is called the “pre-patent period” or “larval stage” [1]. During this period, the immature larvae do not release eggs, and most of the clinical symptoms relate to the destruction by and inflammatory response to the migrating larvae. Common clinical signs and symptoms include abdominal pain, weight loss, fever, and eosinophilia [7, 8]. Other, less common clinical findings include pulmonary infiltrates with pleural effusions, ascites (often with a high eosinophil count, as was seen in patient 1), hepatic subcapsular hemorrhage, and anemia. Larvae can also migrate to the skin (migrating cutaneous nodules), lymph nodes, genitourinary tract, eyes, and brain [9].

The chronic or biliary stage of fascioliasis is characterized by adult flukes that live in the hepatic and common bile ducts of the host. The patient frequently becomes asymptomatic during this phase, with resolution of the eosinophilia, fever, and abdominal pain. Occasionally, infected persons develop symptoms of biliary obstruction, frank ascending cholangitis, acute pancreatitis, or mucosal erosion with hemobilia. Limited data suggest that the incidence of cholangiocarcinoma is not increased among patients with fascioliasis, whereas it is increased among persons with clonorchiasis [10].

During the early larval stage of infection, eggs are not found in the stool. However, stool can be examined for eggs during the biliary stage of infection. Eggs are nonembryonated, ovoid, and large (130–150 μm × 60–90 μm), with a small operculum. The egg looks nearly identical to that of *F. buski* (an intestinal trematode). Because eggs are released sporadically, the number of eggs excreted can vary widely, and it may be necessary to examine multiple concentrated stool specimens [2]. Different stool concentration methods vary with regard to the rate of egg recovery [9]. False-positive test results are possible for patients who have ingested raw or poorly cooked livers of animals that are infected with fasciola; however, the occurrence of these results can be reduced by repeated examination of stool samples after the patient adopts a liver-free diet [9].

Radiographic techniques have been used to aid in the diagnosis of fascioliasis. Ultrasonography has variable sensitivity for hepatic abnormalities and can be unremarkable in the setting of extensive disease, as was seen in patient 1. One study found liver abnormalities on ultrasonography in only 2 of 20 patients with fascioliasis [8]. When ultrasonography does demonstrate abnormalities, ill-defined areas of mixed echogenicity, as seen in patient 2, have been described [7, 11]. Motile flukes can be seen in the gallbladder or in ducts as linear echogenic images [6]. CT scan of the abdomen shows abnormalities in ~90% of patients with acute fascioliasis who seek medical attention. Characteristic findings include the following: multiple, small, indistinct, hypodense lesions; microabscesses arranged in a tunnel-like, branching pattern with contrast; and frequent subcapsular location of lesions [11]. Liver capsule thickening...
and subcapsular hemorrhage have also been described [6]. One report of MRI scan findings in patients with acute fascioliasis described extensive parenchymal destruction of the liver, similar to that seen in patient 1 [12].

Although liver biopsy is not usually indicated when fascioliasis is strongly suspected, typical findings on biopsies obtained from patients with fascioliasis include necrotic debris; tracklike destruction of parenchyma; polymorphonuclear infiltration with abundant eosinophils; Charcot-Leyden crystals; and occasionally granulomas with or without eggs, fibrosis, and bile duct proliferation [13]. Flukes or eggs are only rarely identified on biopsy specimens [13]. If patients proceed to laparoscopy, common findings include short vermiform cords and studding of the liver surface with multiple gray-white to yellow nodules that are 2–20 mm in diameter [9, 13].

Because eggs are not released during the first 3–4 months of acute infection, immunologic techniques play an important role in the diagnosis of fascioliasis. A partially purified whole trematode antigen–based ELISA was used for the serological diagnosis of patients 1 and 2. This assay has a small amount of cross-reactivity with Schistosoma species (Dr. Irving Kagan, personal communication). Sensitivities of similar ELISA assays are reported to be >90% [14]. In regions with higher rates of endemic infection, other assays have been used, including ELISA for coproantigens or excretory-secretory products of adult F. hepatica [9, 15]. Cross-reactivity with Schistosoma, Echinococcus, Paragonimus, and Ascaris species has been reported [9, 16]. In animal models, antibodies are detected within 4 weeks of infection and persist for years [17]. With effective treatment, antibody titers in animal models return to baseline levels within 18–21 weeks [18]. In one series of human subjects with fascioliasis who were treated with triclabendazole, 93% of cured patients had negative ELISA values at 12 months [19].

Many drugs have been used to treat fascioliasis with varying success. Although praziquantel is the treatment of choice for other trematodes, it is ineffective against F. hepatica. Recently, 2 other drugs have been used in the United States. Bithionol has been given successfully to persons with fascioliasis, with a 100% rate of cure, although ~20%–30% of patients required a second course for cure [20]. Unfortunately, bithionol must be administered in 3 divided doses every other day for 10–15 days and has a 50% incidence of side effects, including nausea, abdominal pain, rash, and diarrhea.

The Centers for Disease Control and Prevention has recommended triclabendazole as the first-line agent for treatment of F. hepatica since 1998 because of its ease of administration and good tolerability. Triclabendazole is a benzimidazole [6-chloro-5-(2,3-dichlorophenoxy)-2-methyl thiobenzimidazole] with an active sulfoxide metabolite, which acts as an inhibitor of microtubular and protein synthesis [21–23]. Since 1983, triclabendazole has been used in veterinary practice with high efficacy against both adult and immature flukes of F. hepatica, as well as Paragonimus species. After an epidemic of fascioliasis in the Islamic Republic of Iran in 1989, the World Health Organization worked with Novartis Pharma Inc. to develop a human formulation of triclabendazole [24]. Triclabendazole can be given as a single oral dose of 10 mg/kg or, in cases of severe infection, in two 10-mg/kg doses given 12 h apart. Triclabendazole should be administered with food to increase its bioavailability [25]. One series of 24 patients with chronic fascioliasis who were treated with 1 dose of triclabendazole, 10 mg/kg given after an overnight fast, found a 79% rate of cure [19]. Three patients who consented to a second course of treatment were also cured. No significant side effects were reported. Smaller case series have reported higher rates of cure with side effects of only mild abdominal pain and nausea that occurred immediately after treatment and responded to symptomatic therapy [26, 27]. In the United States, triclabendazole is only available by contacting Novartis Agribusiness (Basel, Switzerland).

In both of our patients, we used triclabendazole for therapy of fascioliasis. Patient 1 was treated as an inpatient with triclabendazole, 20 mg/kg given in 2 divided doses, because of the severity of his infection and the presence of decompensated congestive heart failure. Patient 2 received only 1 dose of triclabendazole in an outpatient setting because he had only mild disease and no comorbid conditions.

Efficacy of treatment of F. hepatica can be monitored by the following: improvement in clinical symptoms during a period of weeks to months; resolution of peripheral eosinophilia; disappearance of eggs in stool; gradual decrease in ELISA titer (during a period of 6 months to 2 years); and improvement in radiographic findings. If these criteria are not met within 6 months of therapy, retreatment should be considered [19].

The difficulty in arriving at the correct diagnosis in patient 1 illustrates the potential delay in appropriate consideration of fascioliasis in the United States. Fascioliasis is not a reportable disease in the United States, so the prevalence in this country is unknown. In 1998–1999, a major reference laboratory in the United States reported only 7 specimens that tested positive for F. hepatica among 58 specimens that were submitted for serological testing (Dr. Irving Kagan, personal communication).

The 2 patients described here and a review of the literature demonstrate the broad clinical spectrum of fascioliasis. The occurrence of infection with F. hepatica in the United States may be greater than previously reported because of lack of health care workers' familiarity with the diagnosis and the difficulty in identification of cases. A detailed travel history and early recognition of the clinical presentation may permit a noninvasive diagnosis. Triclabendazole has become the treatment of choice for fascioliasis because of its ease of administration, minimal side effects, and efficacy.
Acknowledgments

We thank Lindsey Baden, MD, for many helpful discussions during the preparation of this article, and Ionita Ghiran, for assistance with figure preparation.

References