Natural History, Clinicoradiologic Correlates, and Response to Triclabendazole in Acute Massive Fascioliasis

Luis A. Marcos,* Martin Tagle, Angelica Terashima, Alejandro Bussalleu, Cesar Ramirez, Carlos Carrasco, Luis Valdez, Jorge Huerta-Mercado, David O. Freedman, Joseph M. Vinetz, and Eduardo Gotuzzo

The University of Texas Health Science Center at Houston Medical School, Houston, Texas; Institute of Tropical Medicine Alexander von Humboldt (IMTAvH), Universidad Peruana Cayetano Heredia (UPCH), Lima, Peru; Gastroenterology Service, Hospital Nacional Cayetano Heredia, Lima, Peru; Radiology Service, Hospital Nacional Cayetano Heredia, Lima, Peru; University of Alabama at Birmingham, Birmingham, Alabama; Division of Infectious Diseases, Department of Medicine, University of California San Diego, La Jolla, California

Abstract. Fascioliasis is highly endemic in the Andean region of South America. Newer serological assays have improved our ability to diagnose acute fascioliasis. The diagnosis was established by Fasciola hepatica serology (Fas2-ELISA or Western blot) in 10 patients. Identifiable exposure included ingestion of watercress (N = 8), alfalfa juice (N = 5), and lettuce (N = 1). Computed tomography of the abdomen showed hepatomegaly (N = 9), track-like hypodense lesions with subcapsular location (N = 8), and subcapsular hematoma (N = 2). Radiologic sequelae included cyst calcifications detectable at least 3 years after treatment. Stool examinations were negative for F. hepatica eggs; serology was positive (Arc II [N = 2], Fas2-ELISA [N = 6], Western blot [N = 2]). The syndrome of eosinophilia, fever, and right upper quadrant pain, elevated transaminases without jaundice, hypodense liver lesions on CT, and an appropriate exposure history suggests acute fascioliasis. Fascioliasis is specifically treatable with a single dose of triclabendazole.

INTRODUCTION

Fascioliasis, a parasitic disease caused by the trematode (liver fluke) Fasciola hepatica, has a substantial human public-health impact around the world. This disease has spread to >51 countries including Europe, Africa, Asia, the Americas, and Oceania, with ~17 million people infected. Moreover, it has been recognized as an emerging and re-emerging vector (ungulate)-borne disease with the widest latitudinal, longitudinal, and altitudinal distribution known for any zoonotic disease. For these reasons, the World Health Organization has classified fascioliasis as an important human parasitic disease that merits international attention.

The highest prevalence of animal fascioliasis occurs in certain areas of the Andean countries, specifically Bolivia (up to 100%) and Peru (up to 72%). Human fascioliasis is currently expanding as an important public-health problem. The WHO has estimated that at least 7 million people are at risk of this infection in Peru. The most highly endemic areas are the Peruvian Altiplano (35–72%); the Mantaro and Cajamarca valleys (8–36%); and the highlands of Lima (as high as 28%). As one indication of the high incidence of fascioliasis, 277 cases were recently reported in Lima, but only 13% were acute phases, and they did not include radiologic imaging, such CT or MRI.

In the past 5 years, a new serological test to diagnose human fascioliasis has become available, the Fas2 ELISA. The Fas2 ELISA is more specific (86.6–92%) than Western blot (72%) and Arc II (37%). Because the Fas2 ELISA can detect cases that the other tests do not, it has come to replace serologic tests used in clinical practice prior to 2003.

With the increased global burden of fascioliasis and the availability of better serological and radiology study of patients to identify this disease more accurately, we used a clinicoradiologic approach to study the natural history of acute fascioliasis. Data are presented on cases observed in the past 5 years in referral centers in Lima, Peru, with a particular emphasis on liver CT findings.

MATERIALS AND METHODS

Patients. Between 2000 and 2005, 10 patients—9 with abdominal CT scan and 1 with MRI with F. hepatica infection—were diagnosed in Lima at the Institute of Tropical Medicine Alexander von Humboldt of the Universidad Peruana Cayetano Heredia; at the Gastroenterology and Radiology Service of the Hospital Nacional Cayetano Heredia; and at private gastroenterology practices. Detailed histories were obtained from the patients and included solely those with radiologic findings—CT scan or MRI—in the acute phase of the disease plus inclusion criteria (confirmed and suspected case). Abdominal CT scans were carried out at 3 phases, emphasizing the portal phase. All patients were treated with triclabendazole.

Confirmed case. A patient with a clinical picture compatible with acute fascioliasis (fever, hepatomegaly, eosinophilia, CT-determined liver lesions) and positive serological test (Fas2 ELISA or Western blot) was confirmed to have fascioliasis.

Suspected case. A patient had a clinical picture compatible with acute fascioliasis, epidemiologic background (consuming of watercress or raw vegetables from endemic areas), and whose symptoms and eosinophilia resolved with 1 dose of triclabendazole; however, a defined serological test could not be performed (before 2003 or private-practice case). A negative Arc II does not exclude fascioliasis.

Criteria for cure. Parasitological cure was defined as negative stool examinations during a year (at least 3 stool samples), using the rapid sedimentation technique. Clinical cure was defined as resolution of the clinical picture and eosinophilia after 1 week of treatment.

Serological tests. Fas2 is a major cysteine proteinase antigen of F. hepatica (E/S protein of the adult parasite). Fas2 ELISA detects the IgG antibodies against the antigen Fas2. The Arc II detects a mosaic of antigens including the Fas2.
Technical requirements 5μL of the antigenic solution (crude antigen of *F. hepatica*), 150μL of the patient’s serum, and 50μL of a positive control in 3.5mL of agar 1.2%. It is positive when the precipitation bands are visualized in the gel stained with Amido Schwarz. The Western blot technique uses the crude antigen of the parasite (from 14 to 27kDa), separated by molecular mass, which is then transferred to a nitrocellulose gel for electrophoresis, where, after exposure to serum samples, specific antibodies against the *Fasciola* antigens are visualized as bands.

The Fas2 ELISA is more specific (92%) than Western blot (72%) and Arc II (37%). The serological tests performed in this series of cases were carried out in the same research laboratories where the 3 serological tests were compared in a previous study.

RESULTS

Description of enrolled patients. Seven cases had the confirmed criteria, and 3 were suspected. Of these 10 cases, 4 were male and 6 female. Mean age was 47.9 years ± 15.9 (range, 23–70 years). Symptoms lasted on average 7.7 ± 6.7 weeks until presentation but ranged from 0.5 to 22 weeks. Sources of infection were identified in 8 patients; watercress or alfalfa among others; watercress (N = 5), alfalfa juice in emollients (warm beverages made from tender leaves of watercress or alfalfa among others; N = 2), and lettuce (N = 1).

Clinical manifestations and laboratory findings. The main clinical manifestations of the 10 patients are right upper quadrant pain (80%), fever ≥38°C (70%), malaise (60%), anorexia (50%), weight loss >10kg (50%), and nausea and vomiting (30%). The laboratory analysis is summarized in Table 1. The less common symptoms and signs were cough in 2 cases and diarrhea and urticaria in 1 case. A history of gallstones was confirmed in 1 case. Jaundice was not noted. Liver function tests, complete blood count (CBC), and hemoglobin level were analyzed in all patients. International normalized ratios (INRs) and total and direct bilirubin levels were normal. Serological tests (Arc II, Western blot, Fas2 ELISA) were done in all patients. When Fas2 ELISA was positive, Western blot was not done.

CT findings. CT scans of the abdomen were performed in 9 patients, 1 patient had a CT scan plus an MRI scan, and 1 patient had only an MRI scan. The CT scan findings were hepatomegaly (N = 9), subcapsular location (N = 8), nodular hypodense lesions (N = 8), contrast-enhancement of Glisson’s capsule (N = 6), and necrotic granuloma (N = 5), and image compatible with necrotic granulomas, also described by others, splenomegaly (N = 5), subcapsular hematoma (N = 2), dilation of the intrahepatic biliary tract (N = 1), gallbladder stones (N = 1), and periportal lymphadenopathy (N = 1) (Figures 1–5). The MRI without contrast showed a T2-weighted hyperintense signal in the subcapsular image of the right lobe of the liver. In T1-weight images, a low-density serpiginous lesion was seen. The Glisson’s capsule is seen as a high-density signal. One patient was followed up at 6 and 11 months after treatment; this patient’s abdominal CT scan shows calcifications throughout the liver (Figure 6, A and B).

DISCUSSION

In this report, we analyze a cases series of 10 patients with high-intensity, acute infections caused by *F. hepatica*. These
cases were rigorously confirmed and followed for > 1 year. Although 3 cases were formally defined as “suspected” because of the lack of Fas2 ELISA in that time, they were included in the present analysis because of the strong clinical and radiologic evidence of fascioliasis. Diagnosis was strongly supported by response to single-dose triclabendazole treatment: evolution of the hepatic lesions, clinical picture, epidemiologic background, and the dramatic resolution of high degrees of eosinophilia (typically > 5000/mm³). A novel and important finding was the demonstration of cyst calcifications lasting up to 3 years (the largest duration of follow-up) as sequelae after triclabendazole therapy. Although the characteristics of these cyst calcifications seem to be unique to fascioliasis, this finding adds a new agent to the list of infectious diseases that are associated with tissue calcifications, such as echinococcosis, paragonimiasis, histoplasmosis, toxoplasmosis, and others. Detailed study of these 10 patients provides insight into the natural history of acute, massive fascioliasis of substantial importance in the diagnosis and management of this emerging zoonotic infectious disease.

Accurate identification of early fascioliasis has historically been difficult. ArcII serology has been the standard, but this test has previously been shown to be insensitive.¹¹ Accurate assessment of the natural history of early fascioliasis is best based on using the Fas2 ELISA rather than previous, less-sensitive tests.¹¹,¹² Further, we found that resolution of a very high degree of eosinophilia after a single dose of triclabendazole provides strong evidence of fascioliasis; eosinophilia fell to half of previous values within 2 weeks after therapy and resolved after 6–8 weeks. Although a wide range of diseases
might present with hepatic lesions and fever, such as pyogenic or amebic liver abscess, typhoid fever, brucellosis, visceral toxocariasis, or secondary infections in the context of other infections (ascariasis and echinococcosis), resolution of hepatic lesions and eosinophilia after triclabendazole would not be expected with any of these diseases. It is possible that liver flukes such as Opisthorchis might respond to this treatment, but this disease is not present in Peru. Therefore, using the Fas2-based serological test, the present study provides solid information regarding the natural history of early fascioliasis.

The present study also emphasizes the CT findings of multiple hepatic lesions during acute fascioliasis. In the cases reported herein, infection with multiple juvenile larvae paralleled the severity of the disease. Multiple lesions due to Fasciola might be observed during any time of the acute phase (up to 5 months), with changes in position, attenuation, and shape over this time. To determine the natural history of such infections, we grouped the cases to duration of symptoms (early, intermediate, and late stage) and matched them with the 3 most common and distinct lesion types found on CT scan: Glisson’s capsule (contrast-enhanced), multiple hypodense nodular areas, and necrotic granuloma. In the first group, Glisson’s capsule (contrast-enhanced) may be explained as a reaction or inflammatory process caused by the juvenile parasite when perforating the capsule, also described in Ref. 15, and which corresponds to the early stage of the acute infection (first month of infection). In the second group, CT scan images revealed multiple hypodense nodular areas (abscess-like lesions) or low-density serpiginous, tortuous tunnel-like branching lesions, mainly subcapsular in location, ranging from 2 to 10 mm, created as the result of parasite migration through the liver,10,16–21 a later stage of the acute infection (after the first month of infection). Most peripheral lesions corresponded to a shorter time of disease. The third group showed a necrotic granuloma defined as a single (non-contrast-enhanced) hypodense irregular mass in the liver parenchyma, more central than peripheral, also reported and confirmed in Ref. 22 and reported as a liver mass in Ref. 23; this corresponded to the final stage of the acute phase (> 3 months from infection). This latter finding is consistent in our cases with the support of the notorious increasing of ALT (more specific for liver destruction) compared with the other patients without necrotic granulomas (116.8 versus 59.8 U/liter; \( P = 0.016 \)). In MRI, these hypodense lesions were observed as hypointense signals under T1-weighting and hyperintense signals under T2-weighting, also noted in Ref. 13. This strong evidence may suggest that adding any of these radiologic signs to the classic triad of hepatomegaly, eosinophilia, and fever might increase the likelihood of reaching the diagnosis. Another significant radiologic finding was the presence of subcapsular hematomas that compromised the hemody-
as watercress.4,26 The metacercariae hatch, migrate across the cercariae encysted on various kinds of aquatic vegetation such differently than acute fascioliasis.25

Diagnosis can be established in the chronic stage by detecting eggs in the stool.14 Because of the natural history and life-cycle characteristics of F. hepatica, acute infection cannot be diagnosed by stool examination and thus must rest on combination of clinical and radiologic findings, supported by serology.

In the present study, patients were easily cured with a single dose of triclabendazole (except in Patient #3, who required one additional dose to resolve eosinophilia). Indeed, the response to triclabendazole is so reliable that it can be used as a diagnostic criterion. Although confirmatory serology should be obtained prior to treatment, a high index of suspicion might suffice to give a single dose of triclabendazole, a drug with a high therapeutic index, in rural endemic areas where serological and radiologic diagnosis may be difficult to obtain. However, it may be difficult to obtain triclabendazole because it remains a veterinary drug, and efforts need to be made to register the drug for humans in more countries.28 Triclabendazole has been placed on the WHO List of Essential Medicines (http://www.who.int/medicines/publications/essentialmedicines/en/) because of its efficacy and cost-effectiveness.

As exemplified in the present case series, acute fascioliasis presents most commonly with fever, hepatomegaly, and a high degree of eosinophilia. Radiologic findings are characterized by ill-defined hypodense lesions in the liver with rapid resolution of the process after triclabendazole. Calcification of liver lesions may remain after therapy, but a favorable outcome may be defined as disappearance of the symptoms and eosinophilia. Acute F. hepatica infection needs to be considered in patients with eosinophilia, prolonged fever, abdominal pain, and multiple hepatic abscesses or metastasesslike lesions in the peritoneum or liver before starting multiple diagnostic tests. Recognizing the clinical scenario early may allow timely and non-invasive identification of this infection. A highly sensitive serological test should be included to evaluate patients in endemic regions.

The natural history of acute starts with ingestion of metacercariae encysted on various kinds of aquatic vegetation such as watercress.4,26 The metacercariae hatch, migrate across the small intestine wall, enter the peritoneal cavity, and then penetrate the Glisson’s capsule. Typical clinical manifestations at this stage include malaise, anorexia, right upper quadrant pain, vomiting and nausea, fever, and weight loss (Table 1). Hepatic enzymes may be normal or minimally raised,27 as was observed in our patients. Larvae migrate through the hepatic parenchyma for months until they reach the large biliary ducts, where they mature to adults (chronic biliary phase).25

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Authors’ addresses: Luis A. Marcos, Martin Tagle, Angelica Terashima, Alejandro Bussalleu, Luis Valdez, and Eduardo Gotuzzo, Instituto de Medicina Tropical Alexander von Humboldt, Av. Honorio Delgado 430, Urb. Ingenieria, San Martin de Porres AP 4314, Lima 100, Peru; Telephone: 511-3821021, E-mail: Luis.A.Marcos@umtmc.edu. Martin Tagle, Alejandro Bussalleu, and Jorge Huerta-Mercado, Gastroenterology Service, Hospital Nacional Cayetano Heredia, Lima, Peru. Cesar Ramirez and Carlos Carrasco, Radiology Service, Hospital Nacional Cayetano Heredia, Lima, Peru. David O. Freedman, University of Alabama at Birmingham, Birmingham, AL. Joseph M. Vinetz, Division of Infectious Diseases, Department of Medicine, University of California San Diego, La Jolla, CA.
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