

Fascioliasis: 3 cases with three different clinical presentations

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Fascioliasis, which is a zoonotic infestation caused by the trematode Fasciola hepatica (liver fluke), is primarily a disease of herbivorous animals such as sheep and cattle. Humans become accidental hosts through ingesting uncooked aquatic plants such as watercress. It presents a wide spectrum of clinical pictures ranging from fever, eosinophilia and vague gastrointestinal symptoms in the acute phase to cholangitis, cholecystitis, biliary obstruction, extrahepatic infestation, or asymptomatic eosinophilia in the chronic phase. However, it may often be overlooked, especially in the acute phase, because of vague symptoms. As a result of newly introduced serological assays facilitating the diagnosis, there has been an increase in the number of reported cases. Here, we report the clinical and laboratory assessment and therapeutic approach of a series of three cases diagnosed (in order of) one week, three months and one and a half years after presentation of the first symptoms of the disease.

Key words: Fasciola hepatica, hepatitis, triclabendazole

Fasioliasis: Üç farklı klinikle başvuran üç olgu

Fasciola hepatica (karaciğer şeriti) adlı trematodun etken olduğu zoonotik bir infestasyon olan fasiyoliazis, primer olarak koyun ve sığır gibi otçul hayvanların hastalığıdır. İnsanlar, su teresi gibi su bitkilerinin çiğ yenmesiyle konak olurlar. Akut fazda ateş, eozinofili ve silik gastrointestinal semptomlardan kronik fazda kolanjit, kolesistit, safra yolu tıkanıklığı, karaciğer dışı infestasyon veya asemptomatik eozinofili gibi geniş bir yelpazede klinik tablolara neden olabilir. Bununla beraber, özellikle akut fazda silik semptomlar nedeniyle çoğunlukla atlanabilmektedir. Tanıyı kolaylaştıran yeni serolojik testlerin kullanılmasıyla, bildirilen olgu sayısında artış olmuştur. Burada, semptomların başlangıcından sonra sırasıyla bir hafta, üç ay ve bir buçuk yıl sonra tanı koyduğumuz üç olgunun klinik, laboratuvar değerlendirmesi ve tedavi yaklaşımını bildirmekteyiz.

Anahtar kelimeler: Fasciola hepatica, hepatit, triklabendazol

INTRODUCTION

Human fascioliasis is a zoonotic disease caused by the trematodes of the genus *Fasciola* (*Fasciola hepatica* and *Fasciola gigantica*) (1,2). Fascioliasis is distributed worldwide, with cases reported from more than 50 countries, with nearly 17 million people infected (3). Moreover, it has been recognized as an emerging vector-borne disease. The World Health Organization has classified fascioliasis as an important human parasitic disease that requires international attention (4).

The liver fluke eggs are passed out in feces. Each egg hatches, releasing a larva called a miracidium. The miracidia larvae invade aquatic snails (the genus *Lymnaea*). Inside the snails, they develop into cercariae. Cercariae exit the snails and adhere to aquatic plants where they form cysts called metacercariae. Animals or humans are infected through ingestion of water or water plants contaminated with metacercariae. The flukes penetrate through the intestinal walls, enter the abdominal

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cavity, and migrate to the host's liver and bile ducts, causing parenchymal injury with necrosis, biliary fibrosis, dilatation, or obstruction (5).

In accordance with the development of diagnostic procedures, the reported prevalence rates have been increasing (6). The diagnosis could be difficult to confirm in countries where the serological tests are not in routine use because of the absence of ova in the stool in the acute phase and the low and intermittent egg production of the parasite in the chronic phase. Parasites are sometimes detected incidentally during operations or invasive imaging procedures (7). In this report, we present three cases of fascioliasis with different clinical pictures.

CASE REPORTS

Case 1

A 54-year-old woman living in Istanbul presented with one week of fever and chills, anorexia, nausea, vomiting, and colic pain in the right upper quadrant of her abdomen. She did not define any change in the color of the urine or feces. Her medical history was unremarkable except for hypertension. The laboratory analysis demonstrated elevated liver enzymes [aspartate aminotransferase, (AST) 48 U/L (normal range: 15-37 U/L) and serum alkaline phosphatase, (ALP): 156 U/L (normal range: 50-136 U/L)], marked eosinophilia ($4500/\text{mm}^3$, N: $0-400/\text{mm}^3$), and mild leukocytosis ($13500/\text{mm}^3$, N: $4800-10800/\text{mm}^3$). Abdominal ultrasonography showed enhancement in periportal echogenicity consistent with hepatic inflammation. Serological tests for hepatitis viruses (HAV, HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and toxoplasma were negative. Based on the history of daily ingestion of watercress, a serologic test (indirect hemagglutination, IHA) for *F. hepatica* was done, and IgG was positive at a titer of 1/1280. The patient was treated with triclabendazole 10 mg/kg/day once orally (Egaten 250 mg, obtained from Novartis Pharma AG, Switzerland) for two days after informed consent had been obtained. On outpatient follow-up, her symptoms, clinical findings and laboratory findings resolved within two weeks, and no complication or abnormality in laboratory tests was detected in the following six months.

Case 2

A 31-year-old woman from Van, a city in the eastern part of Turkey, had presented to another he-

alth institute with fever, chills, jaundice, and pain in the right upper quadrant of her abdomen for three months. Her blood test results were as follows: AST: 20 U/L, alanine aminotransferase (ALT): 32 U/L, gamma-glutamyl transpeptidase (GGT): 169 U/L, ALP: 266 U/L, total bilirubin: 0.3 mg/dl, hemoglobin: 11 g/dl, hematocrit: 34%, white blood cell (WBC) count: $9300/\text{mm}^3$, eosinophils: $2780/\text{mm}^3$ (30%), C-reactive protein (CRP): 35 mg/dl (normal range: 0-5 mg/L), and erythrocyte sedimentation rate (ESR): 50 mm/h. The abdominal ultrasonography was normal. Evaluation through abdominal computed tomography (CT), magnetic resonance cholangiopancreatography, (MRCP) revealed diffuse periportal enhancement, hypodense areas with ill-defined borders consisting of centrally-located millimetric hyperdense foci (Figure 1). The patient had been referred to our hospital. Her blood tests revealed elevation of liver enzymes (AST: 56 U/L, ALT: 66 U/L, GGT: 151 U/L, ALP: 224 U/L) and eosinophilia ($4000/\text{mm}^3$, 34%) and the CRP was 84 g/L (N: 0-5 g/L). Repeated abdominal ultrasonography revealed six hypoechoic lesions with ill-defined borders (measuring 34×25 mm maximally) and splenomegaly. Stool examinations were positive for *F. hepatica* eggs (Figure 2). The patient recalled ingestion of watercress. The diagnosis was also confirmed by *F. hepatica* serology by enzyme linked immunosorbent assay (ELISA) (IgM antibodies: positive at a titer of 1/250, IgG antibodies: positive >1/1600). Triclabendazole 10 mg/kg/day was given to the patient for two days after informed consent had been



Figure 1. Image of abdominal computerized tomography of the second case, showing diffuse periportal enhancement and hypodense areas with ill-defined borders consisting of centrally-located millimetric hyperdense foci.

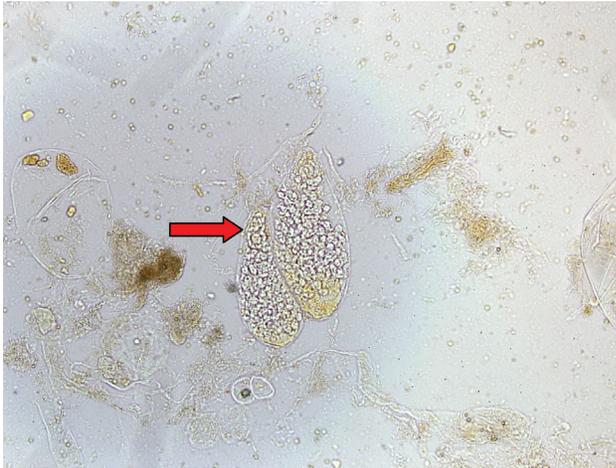


Figure 2. Two *F. hepatica* eggs lying next to each other visualized on stool specimen under light microscopy, x400.

obtained. Her clinical status improved, the laboratory findings returned to normal levels, and the hypoechoic lesions on abdominal ultrasonography disappeared within one week.

Case 3

A 69-year-old woman from Amasya, a city in central Anatolia, had presented to another hospital with fever, nausea-vomiting and abdominal pain 18 months ago. Laboratory data (and reference ranges) were as follows: WBC count: 11000/mm³, eosinophils: 4200/mm³ (28%), AST: 737 U/L, ALT: 614 U/L, GGT: 162 U/L, ALP: 319 U/L, total bilirubin: 1.49 mg/dl, and direct bilirubin: 0.59 mg/dl. No specific finding regarding viral or autoimmune hepatitis was detected despite initial clinical and laboratory investigation. The abdominal ultrasonography was normal. The definitive diagnosis could not be reached at that point. The level of hepatic enzymes spontaneously returned to normal levels within three weeks. However, as her dyspeptic complaints and eosinophilia persisted, she had been under follow-up by hematology and gastroenterology specialists. In this period, a red, itchy skin rash that appeared on the back and abdomen of the patient had been interpreted as idiopathic urticaria and was treated. Later, we consulted the patient to the outpatient clinic of infectious diseases. She had no complaint other than myalgia, and laboratory tests were normal except for eosinophilia (28%, 4200/mm³). Because of the history of watercress ingestion, we performed serological tests for *F. hepatica*. IHA test was positive for IgG at a titer of 1/640. After a two-day treatment with triclabendazole (10 mg/kg/day), her symptoms and

eosinophilia resolved. At the six-month follow-up, the urticarial skin rash had not recurred.

DISCUSSION

Fascioliasis, caused by the trematode *F. hepatica*, is a worldwide parasitic infestation of especially herbivores (cattle, sheep). Humans become accidental hosts through ingestion of water or aquatic plants (watercress, spinach, lettuce, etc.) contaminated with feces of these animals. Eggs are discharged in the stool of the infected animal and they release miracidia, which invade snails (the genus *Lymnaea*). In the snails, miracidia develop into cercaria and are released from the snail. They encyst as metacercaria on freshwater plants. Metacercariae are ingested by humans or animals, and turn into larvae in the intestines. Larvae penetrate the gut wall, enter the peritoneal cavity, and migrate to the liver. They penetrate the liver capsule and mature in the biliary system and begin to release their eggs (1,2,8). In the acute phase of the disease, they cause inflammation, necrosis, and subcapsular hemorrhages in the liver. In this phase, patients present with fever, right upper quadrant pain, nausea, vomiting, urticaria, jaundice, hepatomegaly, and eosinophilia. In the chronic phase, the flukes reside in the bile ducts or extrahepatic locations. In this phase, patients may be asymptomatic or may have symptoms due to cholangitis, cholestasis, pancreatitis, or biliary obstruction (5).

Human fascioliasis has three distinct clinical phases: the acute or hepatic phase, chronic or biliary phase and ectopic or pharyngeal phase (9). During the acute phase, i.e. within 6-12 weeks after ingestion of metacercariae, fever, right upper quadrant pain, hepatomegaly, and marked eosinophilia occur. Moreover, right pleural effusion, Loeffler's pneumonia and cardiac conduction problems have been reported in this phase (9). Although our first case had the clinical symptoms/signs and laboratory findings of the acute phase, her abdominal ultrasonography revealed no abnormality. The reason for this could have been early diagnosis of the disease within a short time (a week) after the first symptoms appeared. Our second case, who had symptoms of the acute phase, had laboratory findings consistent with cholangitis rather than liver parenchymal injury. Multiple hypoechoic lesions with central hyperechoic areas (necrosis) detected on her abdominal ultrasonography were an indicator of the hepatic invasion (acute) stage of the di-

sease. The diagnosis was established within three months of the initial symptoms.

Patients in the chronic or biliary phase of the disease (lasting from 6 months to years if undiagnosed) are commonly asymptomatic (5,9,10). Rarely, they can present with symptoms of biliary obstruction. The most prominent laboratory finding in this phase is the persistence of eosinophilia. Our third case had been investigated for peripheral eosinophilia for a long time, but the initial symptoms of the acute phase occurring a year ago had been overlooked.

The ectopic phase of fascioliasis corresponds to an extrahepatic location of the hepatotropic parasite by means of migration or hematogenous dissemination. The most common extrahepatic location is the subcutaneous tissue (11), followed by the lung, heart, brain, muscle, and genitourinary tract.

Imaging by CT is the suggested radiologic technique in the evaluation of patients with fascioliasis. Especially hypodense nodules, subcapsular hemorrhage and parenchymal calcification can be visualized on CT. Ultrasonography is more useful in the chronic (biliary) phase of the disease (12,13). In the radiologic evaluation of our patients, imaging with CT was used only in our second case, and multiple hypodense lesions were detected. An abdominal ultrasonography confirmed the presence of the same lesions. No lesions were demonstrated on the ultrasonographic examination of the other two patients. We thought this may be explained by the diagnosis of the first case in the early phase of the disease, and in the third case, by application of ultrasonography in both the acute and chronic phases.

The easiest means of establishing the diagnosis is visualization/demonstration of ova in the stool (2), but it has low sensitivity. We could only demonstrate the ova of the parasite in the stool of the se-

cond patient three months after the initial symptoms. We confirmed our diagnosis by means of ELISA using adult or excretory secretory (ES) antigens. Because of no ova release in the stool in the acute phase and intermittent ova release in the chronic phase of the disease, serological tests are necessary to confirm the diagnosis. We confirmed the diagnosis by IHA test in the other two cases whose stool examinations were negative for parasite ova.

Triclabendazole (10-20 mg/kg/day) is the recommended drug for treatment of fascioliasis because of its efficacy and safety (14,15). To our knowledge, it is only available in Switzerland and Germany and licensed for treatment of animal disease. All three cases we followed were treated with a two-day regimen of this drug. We gave two doses of triclabendazole (10 mg/kg/day) with meals after informed consent had been obtained. The drug was tolerated well by our patients and no significant side effect of the drug was observed. Only the second patient had a colic pain 10 days after the treatment. No complication was found with further investigation of the patient.

In conclusion, *F. hepatica* infestation, which is an endemic parasitic infection in our country, may be suspected in patients who exhibit fever, eosinophilia and elevated liver enzymes. We report these cases because fascioliasis should be kept in mind in the differential diagnosis and treatment of patients with vague gastrointestinal symptoms and eosinophilia, especially in endemic but also in non-endemic areas, because of the increase in world travel. As imported cases have been reported, physicians in non-endemic areas of the world also need to become familiar with the presentation, diagnostic work-up and therapeutic modality of fascioliasis, and a detailed travel history of patients must be obtained.

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