Granulomatous hepatitis triggered by liver Fasciola infestation: A case report

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Abstract

Introduction: Liver Fasciola hepatica (FH) infestation is a zoonotic disorder caused by a kind of leaf-like worm.

Case Report: In this article the reported patient is a woman who is 54 years old. She had been suffering from stomachaches after every meal from two years ago. Computed tomography (CT), ultrasonography (US) and magnetic resonance retrograde cholangiography (MRCP), proved that right lobe ducts are dilated although there was not any filling defects in the common bile duct (CBD). These findings were most similar with the manifestations of localized segmental cholangiocellular carcinoma (CCC) or granulomatous hepatitis but at the work up, F. hepatica infection was confirmed. The mentioned disease was diagnosed by means of imaging modalities, laboratory analysis including serology and stool examination and was cured by triclabendazole.

Conclusion: Humans are infected by consuming undercooked vegetables, with the adult worms inhabiting and laying metacercariae in the biliary system. These organisms induce a chronic inflammatory state in the proximal biliary tree, presumably leading to malignant transformation of the lining epithelium.

Introduction

The danger of liver Fasciola (LF) infestation has highly increased in the last ten years. Infestation with this cestode is common all over the world especially in domestic-animal breeding areas and temperate climates including Middle East where our country is located. It is estimated that 2.4 to 17 million people are infected in more than 51 countries and 91 million are at risk worldwide. Snails are intermediate hosts. Humans are incidental hosts and there are several ways that this parasite can infect humans, for example ingestion of unsterilized vegetables or rarely through eating the liver of an infected animal or consumption of dirty water containing undeveloped form of the parasite (metacercariae).1

Incubation period of this disease is about ten weeks. Humans acquire infection by eating vegetables containing metacercariae. After ingestion the metacercariae excyst in the intestine and then the adult worm migrates through the intestinal wall to the peritoneal cavity, and finally reaches liver parenchyma and the biliary ducts, where they develop into adults. In humans this takes three to four months. The adult flukes...
reside in the large biliary ducts of the mammalian host. Acute symptoms usually begin within ten weeks of metacercariae ingestion. At this stage patient feels some fever and abdominal pain at the right subcostal area with hepatomegaly and jaundice is occasionally observed. Other symptoms include nausea, vomiting, cough, and urticaria, malaise, loss of appetite, muscle ache, pruritus. At the laboratory analysis, mild to moderate peripheral eosinophilia in the serum is seen most of the times. A diagnostic triad must be considered for diagnosis of FH which includes abdominal pain, peripheral eosinophilia, and hepatomegaly. In this article we want to report the diagnosis and treatment of an unusual case of FH that is similar to granulomatous hepatitis, and cholangiocellular carcinoma (CCC).

The life cycle of *F. hepatica* starts with release of unfertilized ova into the biliary tract which are then excreted in the stool of grass consuming animals like sheep (definitive hosts) or human being (incidental hosts). Ova become fertilized in water and excrete miracidia which enters a snail (intermediate host), where the parasites undergo developmental maturation. The cercariae are released and develop as metacercariae in water.

Mobile metacercariae cause destruction of hepatic tissue; parasite is entrapped and undergoes necrosis and fibrosis. After this, adult worms can cause obstruction of the biliary tracts, with thickening, dilatation, and fibrosis of the segmental bile ducts. The degree of hepatic destruction is consistent with the number of flukes. The overall time of vitality of mature *F. hepatica* worms in the liver is 10 years.

Majority of patients remain almost asymptomatic after about six weeks. Although major hepatic necrosis can be found with high loud infestation. The chronic stage usually starts almost a few months after infestation and can be found many years later. At this period patient has usually no signs and symptoms, although epigastric and right subcostal area discomfort, loose stool, nausea, vomiting, weight loss, hepatomegaly, and icterus can persist. Extrahepatic infestation can occur, and secondary contamination can lead to cholangitis and cholestatic icterus. Long duration and/or high loud infestation can also induce fibrosing cholangitis and secondary biliary cirrhosis. Peripheral eosinophilia may be present in chronic infection.

The diagnosis can be confirmed by seeing ova in stool, intestinal suction product, or liver tissue. Ova cannot be diagnosed in stool at the early stage of disease or in extrahepatic infections.

Ova of these flukes are oval shaped, with yellow-brown color, and with size of 140 x 70 micrometers. Evaluation of several samples is needed because ova releasing is discontinuous; negative stool examinations do not exclude the diagnosis.

Because ova detection may be negative during the early stage or in the cases of extrahepatic infections, in such patients, confirmation may need serology or evaluation of surgical sample after extraction of the flukes.

Serology may be helpful at the acute phase of liver disease; it is necessary and may be useful for confirming the cause of acute symptoms before the appearance of ova in the stool. It is also helpful in extrahepatic cases, in which ova are not detectable in the stool.

Serologic analysis is with hemagglutination. Generally these finding have better sensitivity, but many have insufficient specificity and simultaneously react with other flukes infestations.

Helpful imaging modalities for this infection include computed tomography (CT), ultrasonography (US), cholangiography, and endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance imaging (MRI). The most common radiologic findings in fascioliasis were several little nodular and ramifying damages which mostly occur in the surface area of the hepatic tissue. They are hypoechoic on US, hypodense on CT, and
hyperintense on T2 and hypointense on T1 on MRI.

Hepatic imaging with CT may note significant hypodense nodules or curvature bands due to moving of the flukes through the liver.\textsuperscript{2} Coarsening of the hepatic capsule, subcapsular blood collecting, or hepatic calcifications may also be noted.

Case Report

A 26 years old woman was referred to our hospital with abdominal pain at the epigastric and right subcostal area for the last two years. The other symptoms and signs of the patient were nausea, vomiting, fever, chills, pruritus, tea colored urine and occasionally watery diarrhea. She had no special drug history. The abdomen was soft with mild tenderness without organomegaly.

At the laboratory evaluation, white blood cell (WBC) count was 4300 cells/ml (55% neutrophils, 36% lymphocytes, 5% eosinophils, 4% monocytes), hemoglobin level was 12.3 g/dl, mean corpuscular volume was 95, platelet count was 345000 cells/ml, erythrocyte sedimentation rate was 13, prothrombin time was 13 seconds with international normalized ratio of 1.2, partial thromboplastin time was 37 seconds, and fasting blood glucose, cholesterol, triglyceride, blood urea nitrogen and creatinine, thyroid-stimulating hormone (TSH) and urine analysis were normal. Liver aspartate transaminase (AST) was 35 IU/l, alanine transaminase (ALT) was 63 IU/l (normal range for female < 32), alkaline phosphatase (ALP) was 458 IU/l (reference range 98-279), albumin was 4.5 g/l, total bilirubin was 0.54 mg/dl with direct bilirubin of 0.19 mg/dl and stool calprotectin was normal faecal calprotectin unit (0-110 µg/g of faeces or stool). Stool exam was negative for ova, parasite, WBC and red blood cells (RBCs). Patient was negative for hepatitis B virus surface antigen and core antibody and hepatitis C virus antibody. Anti-nuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody, serum protein electrophoresis, serum ceruloplasmin, iron, total iron binding capacity and ferritin were in normal range. US of liver was normal and common bile duct (CBD) was 3 mm, splenomegaly was noticed with the span of 14 cm. Abdominal MRI with magnetic resonance retrograde cholangiography (MRCP) was performed to gain more information about the patient which showed that an ill-defined abnormal signal area about 96 x 53 seen at 4\textsuperscript{th} and 8\textsuperscript{th} hepatic segments, which was low signal on T1W and high signal on T2W images. A certain region of bile duct was noticed to be thicker with mild dilatation which might have been localized or segmental cholangitis or CCC. Other hepatic bile ducts were not dilated. CBD and gallbladder were normal but mild splenomegaly was noticed which suggested inflammatory and infiltrative lesions (Figure 1).

Figure 1. An ill-defined abnormal signal area about 96 x 53 is seen at 4th and 8th hepatic segments

Similar data was taken from abdominal CT scan. Several subcapsular hypodense lesions were seen in both lobes of the liver. They enhanced less than peripheral parenchyma after intravenous contrast media. Several enlarged lymph nodes were seen in porta hepatis (Figure 2).

Figure 2. Several subcapsular hypodense lesions were seen

For more evaluation and to rule out F. hepatica from other differential diagnosis,
serology and stool examination were performed for agglutination and ova and parasite which were negative. Image guided liver biopsy was performed. Pathology report showed focal lobular necrosis with peripheral palisading spindle shaped epithelioid cells, surrounded by moderate inflammatory cells mainly eosinophils, and plasma cells beside a few lymphocytes. Ziehl-Neelsen stain did not show acid fast bacilli. There was scattered multinucleated foreign body type of giant cells (FBGCs) form by monocyte-derived macrophage. Diagnosis was eosinophil rich necrotizing granuloma (Figure 3).

Figure 3. Focal lobular necrosis with peripheral palisading spindle shaped epithelioid cells

Discussion
Hepatic granulomas can be seen in a variety of states. Hepatic granulomas may be the early finding to an underlying generalized disease. It may be purely granulomas rarely because of parenchymal liver disease. It is important to diagnose the precipitating and predisposing diseases because it may affect prognosis and treatment. Other clinical findings and the location of hepatic granulomas can lead to the possible diagnosis. Nodular reaction with epithelioid cells (transformed macrophages) are derived from T helper lymphocytes in response to a persistently retained antigen. Sometimes the epithelioid cells adhere to each other and form giant multinucleated cells. Other inflammatory cells may be found within or around the granuloma, including lymphocytes, and eosinophils. They are usually 1-2 mm and very distinct from the surrounding liver tissue. They may coalesce to form up to 40 mm nodules.

Ten percent of liver biopsies and liver autopsies may show granulomas. The pathologic characteristics of the granulomas and their topography may be useful for limiting the differential diagnosis. Five histologic types of liver granulomas have been diagnosed: non-caseating granuloma that are mixture of epithelioid cells, giant cells, and lymphocytes and is classic for sarcoidosis, beryllium, Crohn’s disease, drug reaction and tuberculoid leprosy. Caseating granulomas which are characterized by central necrosis and contain epithelioid cells, giant cells and lymphocytes. They may be palisading and may coexist with non-necrotizing granulomas. They are classic finding for tuberculosis, fungal infections, rheumatoid arthritis, Wegener granulomatosis and Hodgkin disease. A good example is mycobacterium tuberculosis. Fibrin ring granulomas in which epithelioid cells are located at the periphery of a vacuole that usually has a peripheral fibrin ring. Macrophages and lymphocytes that enclose a central empty space (or lipid vacuole) are often encased by a fibrin ring. This type is classic for Q fever and may also be seen in cytomegalovirus and Epstein-Barr virus (EBV) infection, Hepatitis A, leishmaniasis, Lyme disease, boutonneuse fever, toxoplasmosis, Hodgkin disease, non-Hodgkin lymphoma, and drug reaction.

Suppurative granulomas have central micro abscess. They are often large and irregular or may have stellate pattern. They are classic findings in cat scratch fever, lymphogranuloma, tularemia and less often in Yersinia, actinomycosis, nocardiosis, fungal, or mycobacterial infection.

Lipogranulomas are lipid vacuole (without fibrin ring) surrounded by macrophages or lymphocytes, classic finding in mineral oil, ASH (Alcoholic Steatohepatitis), NASH (Nonalcoholic Steatohepatitis), lipid-gold injections. Hepatic granulomatosis is seen with a large number of diseases, their prevalence depends upon topography and geographical status. It may be an accidental finding on
otherwise normal liver biopsy specimen. Thus, an isolated granuloma (or perhaps two on a large liver biopsy specimen) does not necessarily indicate the presence of granulomatous liver disease.\textsuperscript{4} Similarly, granulomas in patients with known liver diseases (such as hepatitis B) may represent an incidental finding that does not alter clinical manifestations or response to treatment.\textsuperscript{5} Other diagnoses should be considered in specific settings. It is helpful to conceptualize the different causes of hepatic granulomas by subdividing them into broad general categories, including those associated with systemic infections, malignancy, drugs, autoimmune disorders and idiopathic.\textsuperscript{9,10}

In this patients, pathologic finding was compatible with parasite infestation of liver bile ducts like fascioliasis but because of negative serologic and stool analysis and high clinical probability and inexpert local laboratories, the patient was referred to the central laboratory at the health institute. Fasciola hepatica (FH) agglutination titer was highly positive and ova of parasite were seen in stool examination.

The patient was prescribed triclabendazole with single dose of 750 milligrams. At the follow up examination the patient was improved and finally was cured. Triclabendazole is an imidazole derivative. It is effective against all stages of fascioliasis with a cure rate of > 90%. Evidence is based on observational studies. Dosing consists of 10 mg/kg orally for one or two days. The drug is relatively well tolerated and absorption is improved by postprandial administration.

Follow up after therapy should include monitoring for resolution of eosinophilia, clearance of eggs in stool, and a decrease in serology titers. It is reasonable to repeat all tests that were initially positive at three months. Resolution of biliary tract findings on ultrasound after therapy may also be helpful. Diagnosis of fascioliasis should prompt screening of family members with serology (stool microscopy is not generally helpful since eggs are often absent early in infection). Asymptomatic patients should be treated to avoid the risk of future complications. Infection can be prevented by avoiding ingestion of raw freshwater plants in endemic areas. Elimination of the snail intermediate hosts has also been attempted by molluscicide application and pasture drainage, but, in general, is not practical. Vaccine studies in animal models have shown reduction in worm burdens and egg production of approximately 70 percent; no vaccines are available for human use.\textsuperscript{11}

Infection with liver fluke is associated with cholangiocarcinoma of the intrahepatic bile ducts. Humans are infected by consuming undercooked vegetables, with the adult worms inhabiting and laying metacercariae in the biliary system. These organisms induce a chronic inflammatory state in the proximal biliary tree, presumably leading to malignant transformation of the lining epithelium. Carcinogens that are taken by patients like smoking, and alcohol might also act as cofactors.\textsuperscript{12,13}

Acknowledgments
We thank to Liver and Gastrointestinal Diseases Research Centre, Imam Reza hospital, Tabriz University of Medical Sciences in Tabriz, Iran, for support of researchers.

Authors’ Contribution
No one did not contribute in preparing in this article.

Funding
No funding source was used.

Conflict of Interest
Authors have no conflict of interest.

Ethic approval
There was no need for ethic approval for case reports.
Granulomatous hepatitis

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