Case Reports

Human Fascioliasis: Diagnosis by Typical Computed Tomography Features and Response to Nitazoxanide in 16 Patients from India

Fascioliasisis a food-borne hepatic trematode zoonosis caused by the liver fluke Fasciola hepatica (FH). Though common in developing countries and not uncommon in Europe[1], there have been very few reports from India.[2-5] It is suspected that FH may be far more prevalent in India than it appears.[2] Although Triclabendazole is the drug of choice it is not available in India. Nitazoxanide has been reported to be effective in FH. Computed tomography (CT) has been reported to have characteristic features of FH. We present a case series of 16 patients, the largest so far from India to the best of our knowledge, diagnosing FH cases by characteristic CT findings against a background of typical clinical features and demonstrate its response to treatment with Nitazoxanide.

Methods

16 patients, from the year 2010 to 2016, presented to us with chronic pain in the right hypochondrium. Several had fever and significant weight loss. Blood investigations, chest xray, urine and stool examinations were ordered. All patients had ultrasound (USG) of the abdomen done elsewhere which showed indeterminate liver lesions. Hence a triphasic contrast enhanced 64 slice CT (Aquilion One, Canon, Tokyo, Japan) was performed with intravenous contrast of 1 to 1.5 ml/Kg of iopromide (Ultravist 370; Schering, Berlin, Germany) upto a maximum of 100 ml at a rate of 4 mL/s. Scans were obtained during the arterial, portal and hepatic venous phases with a section thickness of 0.5 mm. 9 patients had an ERCP with examination of the aspirated bile. As triclabendazole was not available to us, all our patients received Nitazoxanide for two weeks. 43% of the patients also received other drugs like Ivermectin, Praziquantel and Albendazole from their treating physicians. In 15 patients clinical follow up and in 9 patients post treatment imaging and AEC were available.

Results

Of the 16 cases, 7 were male and 9 female between 15 and 71 years of age. 15 were from northeastern India. All patients habitually consumed raw vegetables and leafy greens. All had pain in the right hypochondrium of half to several months duration. 31% reported significant weight loss and 56% had fever. All had significant eosinophilia with a mean AEC of 2305. Stool examinations revealed ova or parasites in none. In 4 cases adult worm or ova were detected in bile. **Table 1** gives the details of the confirmed cases of FH and **Tables 2A** and **2B** of the unconfirmed cases.

56% patients had abnormal liver function tests with elevation predominantly of the GGTP and serum alkaline phosphatase. ESR was raised in 33% and WBC count in 31%.

Typical CT features included hepatomegaly, grapelike clusters of cystic lesions 2 to 3 cm in diameter with uniform thickness moderately enhancing walls beginning at the liver periphery and radiating towards the hilum of the liver in the distribution of bile ducts, subcapsular fluid at the point of entry of parasite, mild dilatation of the proximal segmental ducts, inflammatory changes in the adjacent liver in the form of edema and increased enhancement, periportal reactive adenopathy, mild dilatation of the common bile duct (CBD) with diffuse mild wall thickening and lucent filling defects suggestive of parasite or sludge containing ova and meandering linear tunnel like hypodense channels in liver suggestive of the parasite burrowing through liver tissue to reach biliary radicles. In one of our patients the meandering channels were also found in an enlarged spleen **(Figures 1 and 2)**. We have named the cystic lesions “fasciola cluster of grapes sign” and the meandering linear lesions “fasciola tunnel sign”. Treatment in the unconfirmed cases was started based on the characteristic clinical and CT features.One patient had a segmental resection of the lesion, which showed dense eosinophilic infiltrates.

94% patients symptomatically improved remarkably. 100% patients who had post treatment repeat blood investigation showed resolution of eosinophilia.

100% patients who had post treatment imaging showed remarkable radiological regression of disease.

Discussion

Human fascioliasis is caused by the trematodes Fasciola hepatica and Fasciolagigantica. It is reported worldwide.[6] FH is a flat, leaf-shaped hermaphroditic parasite, and needs two hosts to complete its life cycle. The definitive hosts are herbivorous mammals. Humans are accidental hosts who acquire infection by consumption of contaminated raw vegetables or drinking water.[6] Intermediate hosts are freshwater snails. Fasciola flukes live in the hepatic bile ducts of their definitive hosts and eggs pass out with the host's feces. The eggs hatch into ciliated miracidia on contact with water and infect fresh water snails. Free cercaria leave the snail, attach to aquatic plants like watercress and develop into metacercarial cysts. Infection of the definitive host consists of two stages, the hepatic and the biliary stage. After ingestion, the metacercaria ex-cyst in the duodenum and migrate through the intestine wall into the peritoneum, and via the Glisson's capsule into the liver. The larvae then migrate through the hepatic parenchyma. This hepatic phase lasts for 4 months and patient presents with fever, nausea, vomiting, urticaria,

Table 1: Clinical and radiological Features of proved cases of Fasciola hepatica.

Case No	1	2	3	4
Age/Sex	25/F	43/F	35/F	71y/m
Occupation	Housewife	Housewife	Housewife	Retired
Consumption of raw vegetables	Yes	Yes	Yes	Yes
Clinical features	RH pain 1 year, Fever 3 months, Weight loss 8 kg in 1 year	RH pain 6 months	RH pain 6 months, loss of weight 7 kgs in 6 months	RH pain 1 Year
AEC at start of treatment	1080	1056	2086	2548
Abnormal lab findings	None	None	WBC 14900, Eosinophil 14 %	None
CT Abdomen at start of treatment	Fasciola cluster of grapes sign positive segment 8. 5.3 X 4.7 cm. Linear filling defects in ducts. CBD filling defects.	Fasciola cluster of grapes sign positive segments 5, 6 and 7. Measuring 9 X 10 cm. CBD lucent filling defects. Mild intrahepatic biliary dilatation.	Fasciola cluster of grapes sign positive segments 4a, 8 and 2 measuring 8cm. Segmental bile ducts dilated with filling defects. CBD mildly dilated with filling defects.	Fasciola cluster of grapes sign positive in right lobe of liver
Stool examination	No ova or parasites	No ova or parasites	No ova or parasites	No ova or parasites
Bile examination	Adult dead worm of Faciola	Adult dead worm of Faciola	Adult dead worm of Faciola	Adult dead worm of Faciola
Nitazoxanide	500 mg TDS x 14 days	500 mg TDS x 14 days	500 mg TDS x 14 days	500 mg TDS x 14 days
Other medication	Ivermectin 12 mg OD x 7 days	None	None	None
Repeat Imaging after therapy	Not done	USG done 8 moths later - reduction in size of cystic lesions from 10 cm to 4.5cm.	CT 3 months later - significant reduction in size from 8cm to 3cm with no dilatation of CBD.	Not done
AEC 3 months after therapy	288	530	Not done	Not done

RH - right hypochondriac, AEC - absolute eosinophil count range 30-350 cells/cu mm, ALP - serum alkaline phosphatase range 45 to 115 U/L, GGTP range 10-50 U/L, SGOT range 5-40 U/L, SGPT range 5-35 U/L.

Table 2A: Clinical and radiological Features of unproved cases of Fasciola hepatica.

Case No	1	2	3	4	5	6
Age/Sex	24 /M	46/M	22/F	44/F	26/F	41/F
Occupation	Student	Farmer	Student	House wife	House wife	Housewife
Consumption of uncooked vegetables	Yes	Yes	Yes	Yes	Yes	Yes
Clinical features	RH pain 1 month	RH pain1 month. Pruritus 4 months. Fever 1 day.	RH pain 15 days. Fever 15 days. Significant weight loss.	RH pain 1 month	RH pain. Fever 1 month	RH pain and fever low grade 3 months.
AEC at start of treatment	2001	2040	1596	3546	2875	3150
Abnormal lab findings	ALP 110, Eosinophil 15%, ESR 27	ALP 205, GGTP 63, Eosinophil 15%, WBC 13600	Eosinophil 17%	ALP 117, GGTP 41, Eosinophil 30%, ESR 64	ALP 470, Eosinophil 25%, WBC 11500	ALP 132, GGTP 47, Eosinophil 35%, Globulin 5.3
CT Abdomen at start of treatment	Fasciola cluster of grapes sign positive segment 8	Fasciola cluster of grapes sign positive segments 5 & 6	Fasciola cluster of grapes sign positivein segment 5, mild intra-hepatic biliary dilatation	Fasciola cluster of grapes sign positivesegment 5 and 6	Fasciola cluster of grapes sign positiveright lobe. Fasciola tunnel sign positive in liver and spleen.	Fasciola cluster of grapes sign positive segments 4 and 5 measuring 6 cm
Stool exam	No ova or parasites	No ova or parasites	No ova or parasites	No ova or parasites	No ova or parasites	No ova or parasites
Bile exam	Normal	Normal	Not done	Normal	Normal	Normal
Nitazoxinde	500 mg TDS for 14 days	500 mg TDS for 14 days	500 mg TDS for 14 days	500 mg TDS for 14 days	500 mg TDS for 14 days	500 mg TDS for 14 days
Other medications	Ivermectin 12 mg OD x 7 days	Ivermectin 12mg OD x 7 days, Albendazole 400mg BD x 7 days	Ivermectin 12 mg OD x 5 days, Albendazole 400 mg BD x 14 days	Ivermectin 12 mg OD x 7 days, Albendazole 400mg BD x 14 days	Praziquantel 600mg TDS x 2 days	Nil
Repeat Imaging after therapy	USG 8 months later was normal	USG 2 years later was normal	Not done	CT showed regression in the size of the cyst	CT 5 months later showed significant resolution of hepatic lesions	Not done
AEC 3 months after therapy	152	Not done	Not done	310	288	Not done

RH- right hypochondriac, AEC-absolute eosinophil count 30-350 cells/cu mm, ALP- serum alkaline phosphatase range 45 to 115 U/L, GGTP range 10-50 U/L, SGOT range 5-40 U/L, SGPT range 5-35 U/L.

Table 2B: Clinical and radiological Features of unproved cases of Fasciola hepatica.

Case No	7	8	9	10	11	12
Age/Sex	35/M	53/M	38/M	58/M	15/F	36/F
Occupation	Civil worker	Civil worker	Farmer	Farmer	Student	House wife
Consumption of uncooked vegetables	Yes	Yes	Yes	Yes	Yes	Yes
Clinical features	RH pain 1 year	RH pain 6 months, Fever low grade 3 months	RH pain and nausea 5 months, Weight loss 10 kg in 5 months	RH pain and low grade fever 5 months	RH pain, 9 kg weight loss in 3 months, Fever	RH pain for 6 months, Fever high grade
AEC	972	3588	1170	900	2400	3570
Abnormal lab findings	Not done	WBC 13800, Eosinophil 26%, ESR 56	ALP 308, Globulin 4.6, GGTP-56, ESR 81	ALP 163, SGOT 45, SGPT 66, GGTP 90, ESR 57	ALP-255, SGPT-146, GGTP 91, Eosinophil 29%, ESR-22	ALP 645, WBC 10200, Eosinophil 35%
CT Abdomen at start of treatment	Fasciola cluster of grapes sign positive measuring 1.8 x 1 cms, in segment 8.	Fasciola cluster of grapes sign positive in segments 5, 7 and 8.	Fasciola cluster of grapes sign positiveright lobe measuring 10x7 cm, CBD showed filling defects.	Fasciola cluster of grapes sign positiveright lobe.	Fasciola cluster of grapes sign positivein segment 2, 3, 4 measuring 7 x 4.5cm. Wall thickening CBD	Fasciola cluster of grapes sign positivein right lobe of liver. Fasciola tunnel sign positive both lobes.
Stool exam	No ova or parasites	No ova or parasites	No ova or parasites	No ova or parasites	No ova or parasites	No ova or parasites
Bile exam	Not done	Not done	Not done	Not done	Not done	Not done
Nitazoxinde	500 mg TDS x14 days	500 mg TDS x 14 days	500 mg TDS x14 days	500 mg TDS x 14 days	500 mg TDS x 14 days	500 mg TDS x 14 days
Other medications	Nil	nil	Nil	Albendazole 400mg BD x 14 days	Nil	Nil
Repeat Imaging after therapy	Not done	Not done	Not done	CT 1 month later reduced perilesional edema. USG 5 months later reduced size.	USG-resolution of disease	Not done
AEC 3 months after therapy	Not done	800	500	450	620	Not done

RH- right hypochondriac, AEC-absolute eosinophil count 30-350 cells/cu mm, ALP- serum alkaline phosphatase range 45 to 115 U/L, GGTP range 10-50 U/L, SGOT range 5-40 U/L, SGPT range 5-35 U/L.

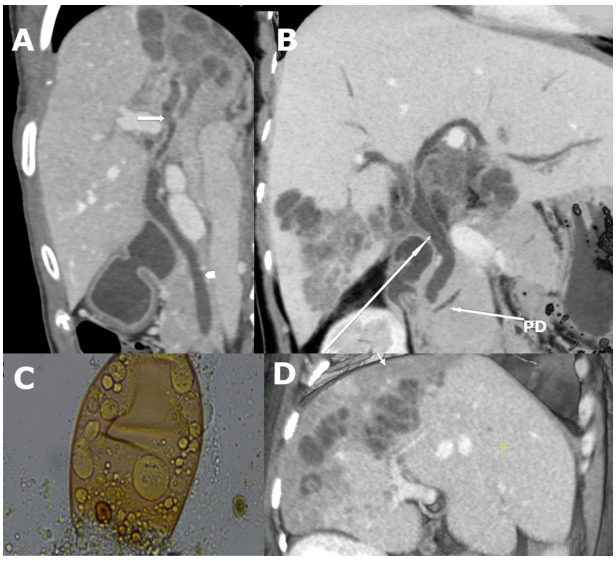

Figure 1: Panel A shows CT volume rendered sagittal oblique image. Clustered grapelike cystic lesions are seen in the right lobe of the liver in the superior subcapsular region leading to a dilated segmental duct (arrow) with filling defects within representing parasite. The common bile duct is mildly dilated (arrowhead). Panel B is a CT minimum intensity projection in coronal plane demonstrating a lucent filling defect within the mildly dilated common bile duct representing the dead parasite (arrow). The adjacent segments 5 and 4 of liver show the typical fasciola cluster of grapes sign. PD- pancreatic duct. Panel C shows the fasciola egg on microscopic examination of bile. Panel D is a volume rendered oblique coronal CT image showing clustered cysts with low density areas around them suggestive of edema of the surrounding liver parenchyma.

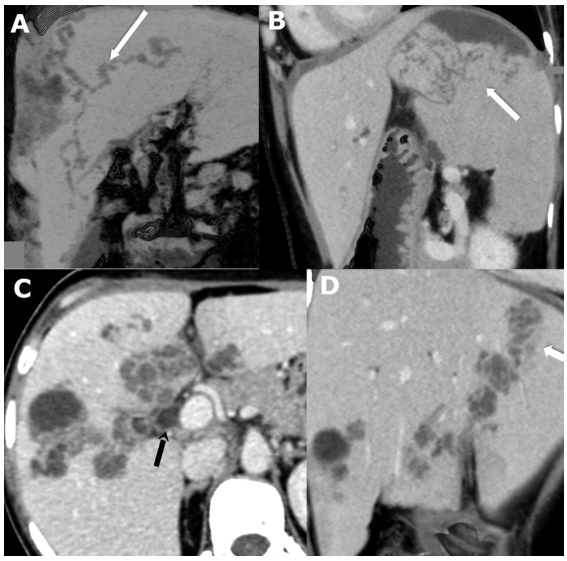

Figure 2: Panels A and B are oblique coronal CT images in minimum intensity projection showing meandering linear channels within the liver (A) and spleen (B) representing the parasite tunneling through tissues – fasciola tunnel sign. Panels C and D are axial and coronal volume rendered CT images showing the typical clustered cysts. The common bile duct is dilated in C with lucent filling defects suggestive of dead parasite (black arrow).

right hypochondriac pain, hepatomegaly, hypergammaglobulinaemia, anaemia and marked eosinophilia. All our patients had right hypochondriac pain and marked eosinophilia.

The chronic biliary stage occurs in the months following ingestion when adult flukes mature in the biliary tract and begin laying eggs. This can result in intermittent right hypochondriac pain, with or without cholangitis or cholestasis due to chronic bile duct inflammation. Eggs appear in the stool during this phase. Demonstrating the eggs in stool sample may need repeat samples with concentration procedures. Since we did not do this it may explain the negative stool exam in all our confirmed cases.

Imaging can play a definitive role in the noninvasive diagnosis of FH. USG, which is the first investigation of choice, may show hypoechoic areas in the liver in the hepatic stage. However these are not specific to FH and may also be found in hepatic neoplasia. All our patients had indeterminate findings on USG. CT at this stage shows characteristic grape like clusters of cysts, which represent granulomas in the biliary distribution radiating from the liver capsule where the parasite enters to the central biliary tree. Oblique reformations are especially useful for demonstration of above findings. All our 16 patients had these typical findings proving the "fasciola cluster of grapes sign" on CT to be a reliable sign.To our knowledge, only FH can produce the "facsiola tunnel sign" which is another specific sign on CT making CT a definitive imaging tool for FH. A contrast enhanced MRI may show similar findings but is less easily available and less amenable to dynamic multiplanar reformations. A biopsy though considered definitive at this stage can be avoided if these characteristic features are picked up on meticulously performed and analysed CT. In the biliary stage gall bladder and CBD may show echogenic leaf like filling defects on USG, which when showing motility suggests adult live worms.[7]

One of the reasons for FH being reported less than its prevalence in India could be due to the non-availability of CT as well as inaccurate interpretation of the CT findings.[8]

Endoscopic retrograde cholangiopancreaticography (ERCP) may demonstrate the adult worm within the CBD or gall bladder, can obtain ova in biliary and duodenal aspirate and aids in the management by sphincterotomy and removal of the adult worms.[9]

Triclobendazole[10], a benzimidazole, is the current drug of choice. Unfortunately, the drug is not available for human use in India. Nitazoxanide, a thiazolide derivative is active against a variety of protozoa and has been studied for FH with reasonable success.[11-14] Although, 43% of our patients had received albendazole, praziquantel and ivermectin empirically, these drugs have not been shown to have any effect on fasciola as per previous studies.[6,15] In addition, all our patients that receivednitazoxanide alone showed remarkable clinical improvement as well. Those who had blood and imaging investigation showed resolution of eosinophilia and regression of disease. The good response to treatment in all our patients can therefore be attributed to nitazoxanide.

We acknowledge the limitation of our case series in that only four cases were proven on the basis of demonstration of the adult worm or larva.

Conclusion

Human fascioliasis should be suspected in patients who present with right hypochondriac pain, significant weight loss, eosinophilia, fever, elevated serum alkaline phosphatase, GGTP, ESR and WBC count with characteristic imaging findings of the "fasciola cluster of grapes sign" and the "fasciola tunnel sign"on CT scan. ERCP is useful for retrieval of adult worms and ova as stool examinations are often negative. If triclabendazole is not available, nitazoxanide should be the drug of choice.

ROCHITA VENKATA RAMANAN[1]
UBAL DHUS[2]
ANAND RAMAMURTHY[3]
SAROJINI ASHOK PARAMESWARAN[2]
PARAMASIVAN PIRAMANAYAGAM[3]
RAM GOPALAKRISHNAN[4]

[1]Department of Radiology,
[2]Department of Medical Gastroenterology,
[3]Department of Liver transplantation and Hepatobiliary surgery,
[4]Institute of Infectious Diseases,
Apollo Hospital, Chennai, India

Corresponding Author: Dr Rochita Venkata Ramanan
Email: rochitav@yahoo.com

References

1. Marcos LA, Terashima A, Gotuzzo E. Update on hepatobiliary flukes: Fascioliasis, opisthorchiasis and clonorchiasis. CurrOpin Infect Dis 2008;21:523-30.
2. Ramachandran J, Ajjampur S, Chandramohan A, Varghese G M. Cases of human fascioliasis in India: Tip of the iceberg. J Postgrad Med 2012; 58:150-2.
3. Elhence V, Mehta B, Gupta RK. Fascioliasis: A case from central Uttar Pradesh. Indian J Gastroenterol 2001; 20:164.
4. Narain K, Biswas D, Rajguru SK, Mahanta J. Human distomatosis due to Fasciola hepatica infection in Assam, India. J Commun Dis 1997; 29:161-5.
5. Madhumitha R, Gohel S, Vishwanathan L, Gopalakrishnan R. Liver Lesions, Fever and Eosinophilia Caused by Fasciola hepatica in a 15-year-old Girl. Indian J Pediatr. 2015 Oct;82(10):967-8.
6. WHO headquarters, Geneva, Switzerland 17–18 October 2006. Report of the WHO Informal Meeting on use of triclabendazole in fascioliasis control. Available online: www.who.int/neglected_diseases/preventive.../WHO_CDS_NTD_PCT_2007.1.pdf
7. Kabaalioglu A, Ceken K, Alimoglu E, Saba R, Cubuk M, Arslan G et al. Hepatobiliaryfascioliasis: sonographic and CT findings in 87 patients during the initial phase and long-term follow-up. American journal of roentgenology. 2007 Oct;189(4):824-8
8. Nyindo M, Lukambagire AH. Fascioliasis: an ongoing zoonotic trematode infection. BioMed research international. 2015 Aug 31;2015.
9. Gulsen MT, Savas MC, Koruk M, Kadayifci A, Demirci F. Fascioliasis: A report of five cases presenting with common bile duct obstruction. Neth J Med. 2006 Jan 1;64(1):17-9.
10. Tolan RW. Fascioliasis due to Fasciola hepatica and Fasciolagigantica infection: an update on this 'neglected'neglected tropical disease. Laboratory Medicine. 2011 Feb 1;42(2):107-16.
11. Ortiz JJ, Ayoub A, Gargala G, Chegne NL, Favennec L. Randomized clinical study of nitazoxanide compared to metronidazole in the treatment of symptomatic giardiasis in children from Northern Peru. Alimentary pharmacology & therapeutics. 2001 Sep 27;15(9):1409-15.
12. Kabil SM, Ashry EE, Ashraf NK. An open-label clinical study of nitazoxanide in the treatment of human fascioliasis. CurrTher Res 2000;61:339-45.
13. Favennec L, Jave Ortiz J, Gargala G, Lopez Chegne N, Ayoub A, Rossignol JF. Double-blind, randomized, placebo-controlled study of nitazoxanide in the treatment of facioliasis in adults and children from northern Peru. Aliment PharmacolTher 2003;17:265-70.
14. Rossignol JF, Abaza H, Friedman H. Successful treatment of human fascioliasis with nitazoxanide. Trans R Soc Trop Med Hyg 1998;92:103-4.
15. Fang W, Chen F, Liu HK, Yang Q, Yang L. Comparison between albendazole and triclabendazole against Fasciolagigantica in human. Zhongguoxue xi chongbing fang zhizazhi= Chinese journal of schistosomiasis control. 2014 Feb;26(1):106-8.