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

Fascioliasis is 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.\(^2\)\(^-\)\(^4\) 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 pain 1 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 | 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 positive in segment 5, mild intra-hepatic biliary dilatation | Fasciola cluster of grapes sign positive segment 5 and 6 | Fasciola cluster of grapes sign positive right 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 |
| **Nitazoxinide** | 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, 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 400 mg 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.
| 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, Fever low grade 3 months | RH pain 6 months, Fever low grade 3 months, Weight loss 10 kg in 5 months | RH pain 6 months, Fever low grade fever 5 months | RH pain, 9 kg weight loss in 3 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 cm, in segment 8. | Fasciola cluster of grapes sign positive in segments 5, 7 and 8. | Fasciola cluster of grapes sign positive in right lobe measuring 10x7 cm, CBD showed filling defects. | Fasciola cluster of grapes sign positive in right lobe. | Fasciola cluster of grapes sign positive in 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 |
| Nitazoxinide | 500 mg TDS x 14 days | 500 mg TDS x 14 days | 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 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.
right hypochondriac pain, hepatomegaly, hypergamma-globulinaemia, 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 “fasciola 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 cholangiopancreatography (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.\(^9\)

Triclabendazole\(^{10}\), 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 received nitazoxanide 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.

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