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Eosinophilia in an Indian Patient with Helminthic Infection Unresponsive to Albendazole and Diethylcarbamazine: An Enigmatic Case of Human Fascioliasis

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Abstract

Human fascioliasis is a zoonosis caused by *Fasciola hepatica* and *Fasciola gigantica*. Population migration, globalization of food trade, climate change, and drug resistance are contributing to the re-emergence of *Fasciola* infection in several countries with increased recognition even in nonendemic regions. Helminthic infections are prevalent in India and are a common cause of eosinophilia in Indian patients who are often empirically treated with antihelminthic agents. However, human fascioliasis is rarely reported in India and does not respond to commonly used antihelminthic agents like albendazole, mebendazole, praziquantel, and diethylcarbamazine (DEC). We report a case of a young female with abdominal pain and eosinophilia who did not respond to empirical treatment with albendazole and DEC. She was diagnosed with *Fasciola hepatica* on endoscopic retrograde cholangiopancreatography and was treated with nitazoxanide that led to complete resolution of symptoms and normalization of eosinophil counts.

Keywords
- hypereosinophilia
- *Fasciola hepatica*
- fascioliasis
- trematode

Introduction

Eosinophilia is a common finding in clinical practice and has numerous causes. It is defined as absolute eosinophil count (AEC) more than 500/µL and clinical manifestations may vary from asymptomatic incidental detection of eosinophilia, hypereosinophilia (AEC > 1500/ µL) without end-organ damage, to life-threatening hypereosinophilic syndrome (HES). Common etiologies include allergic disorders, parasitic infections like helminths, fungal infections (allergic bronchopulmonary aspergillosis, histoplasmosis, etc.), human immunodeficiency virus (HIV), adverse drug reactions, immunological disorders (sarcoidosis, connective tissue diseases, etc.), eosinophilic granulomatosis with polyangiitis, idiopathic HES and neoplastic conditions like primary HES, acute and chronic eosinophilic leukemia, systemic mastocytosis, and lymphoid malignancies.[1] Although identifying the cause of eosinophilia often requires a battery of investigations,

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patients residing in endemic countries such as India are often empirically treated with antihelminthic agents. We report a case of a young female with abdominal pain and eosinophilia who did not respond to empirical treatment with albendazole and diethylcarbamazine (DEC).

Case Report

A 20-year-old Indian woman, currently residing in Chandigarh, with no chronic medical illnesses presented with a history of recurrent episodes of abdominal pain for the past 6 weeks. The pain was dull in nature over the right upper quadrant and epigastrium, nonradiating, not related to food intake or posture, unrelieved by antacids, and responsive to analgesics. She also experienced anorexia for 4 weeks but had no significant weight loss. The patient denied any history of jaundice, diarrhea, hematemesis, melena, allergic conditions, dyspnea, pruritus, skin rashes, or intake of over-the-counter or herbal medications. She consumed a mixed nonvegetarian diet and admitted to frequent travels to her ancestral village in Kullu District of Himachal Pradesh. Physical examination was unremarkable. Laboratory findings revealed mild leukocytosis (white blood count: 10,300/mm3) with hypereosinophilia (AEC: 1730/μL). Serum bilirubin, aspartate aminotransferase, and alanine aminotransferase were within normal limits, but alkaline phosphatase was elevated (278 IU/L). An ultrasonogram (USG) of the abdomen showed normal findings.

She was extensively evaluated for common etiologies of hypereosinophilia including peripheral blood film examination, stool examination for ova, cysts and parasites, serologies for HIV, hepatitis B, hepatitis C, *Entamoeba histolytica*, *Echinococcus granulosus* and filariasis, serum immunoglobulin E and angiotensin-converting enzyme levels, antinuclear antibody, antineutrophil cytoplasmic antibody, bone marrow examination, chest X-ray, and abdominal USG that were unrevealing. The patient was empirically treated with albendazole followed by DEC for 2 weeks. However, the hypereosinophilia persisted. A hepatology consultation was sought due to the abdominal pain and deranged alkaline phosphatase. Although abdominal USG was normal, magnetic resonance cholangiopancreatography (MRCP) revealed an undilated biliary system with a linear filling defect in the distal common bile duct (CBD). These MRCP findings were confirmed on endoscopic retrograde cholangiopancreatography (ERCP), and multiple (at least 3) live, flat, leaf-shaped "flukes" were extracted from the CBD using a stone-extraction balloon (►**Fig. 1**). One of the flukes was removed using Roth's net and confirmed as *Fasciola hepatica* upon parasitological examination based on the morphological findings of cephalic cone, two prominent shoulders, converging margins, and small-size (13 × 9 mm). The patient was treated with nitazoxanide (500 mg twice daily) for 7 days. Eosinophil counts and alkaline phosphatase normalized, and the patient remained asymptomatic during follow-up after 1-month.

Discussion

Fasciola hepatica is a trematode that infects the liver and biliary ducts of humans and other mammals, mainly ruminants. Humans are accidental hosts who acquire the infection by consuming contaminated water or raw vegetables such as watercress, containing the metacercarial stage of the parasite. It is particularly common in parts of Latin America, Eastern Europe, and Middle East and is a re-emerging zoonosis in many other countries worldwide.[2,3] Traditionally, human fascioliasis was considered to be uncommon in India, though it is being increasingly recognized in the past two decades.[4–9] Indeed, *fasciola* among ruminants is a significant problem in the livestock sector of India and the intermediate snail host, *Lymnaea auricularia,* is also common in the tropical plains and Kashmir valley.[10]

Fasciola gigantica is the prevalent species in India, although both *F. hepatica* and even hybrid intermediate forms have been described in humans.[10,11] *F. hepatica* has been reported in the Kashmir valley and vertical transhumance may have led to spread to lower altitude areas in Himachal Pradesh and the neighboring Chandigarh. A similar situation has been recently described in the neighboring Pakistan.[12] In our patient, speciation of *F. hepatica* was based on the morphological findings of cephalic cone, two prominent shoulders, converging margins and small size (13 × 9 mm). Other morphological clues for differentiation from *F. gigantica* include the position of the testes, branching pattern of caeca, ovaries and testes, and the size of the eggs. Nonetheless, it should be noted that there may be significant variation in the morphology that may be further compounded by hybridization. Thus, molecular techniques like polymerase chain reaction are the gold standard for accurate speciation in *Fasciola.*

The clinical manifestations of human fascioliasis depend on the phase and intensity of the infection.[8] In the acute phase, when the immature flukes migrate through the liver parenchyma, patients may experience abdominal pain, hepatomegaly, nausea, vomiting, intermittent fever, urticaria, malaise, and weight loss. Peripheral eosinophilia is ubiquitous in the acute phase. The maturation of metacercaria into adult fluke takes approximately 3 to 4 months in humans. In the chronic phase, when the adult flukes reside in the biliary ducts, patients may have intermittent abdominal pain, cholelithiasis, cholangitis, obstructive jaundice, or pancreatitis. It should be noted that both phases can sometimes co-exist. Heavy or prolonged infection can lead to sclerosing cholangitis and biliary cirrhosis. Ectopic lesions may occur in other organs, such as the lungs or intestines.[2,3] Peripheral eosinophilia may be absent in the chronic phase but may often be present as was seen in our patient. Elevation in alkaline phosphatase is also common. Indeed, peripheral eosinophilia and elevation in alkaline phosphatase were observed in 100% and 56% of patients in a series of 16 cases of human fascioliasis from India.[9] Elevation in biochemical markers of cholestasis like serum alkaline phosphatase and gamma-glutamyl transferase has been shown to correlate with the fluke burden and parasite biomass in experimental studies of fascioliasis in sheep.[13]

The diagnosis of fascioliasis is based on serology or detection of eggs in stool, duodenal aspirates, or bile specimens. The diagnostic kits for *Fasciola* serology are not commonly available in India and was unavailable at our institute. Stool examination in our patient was unrevealing.

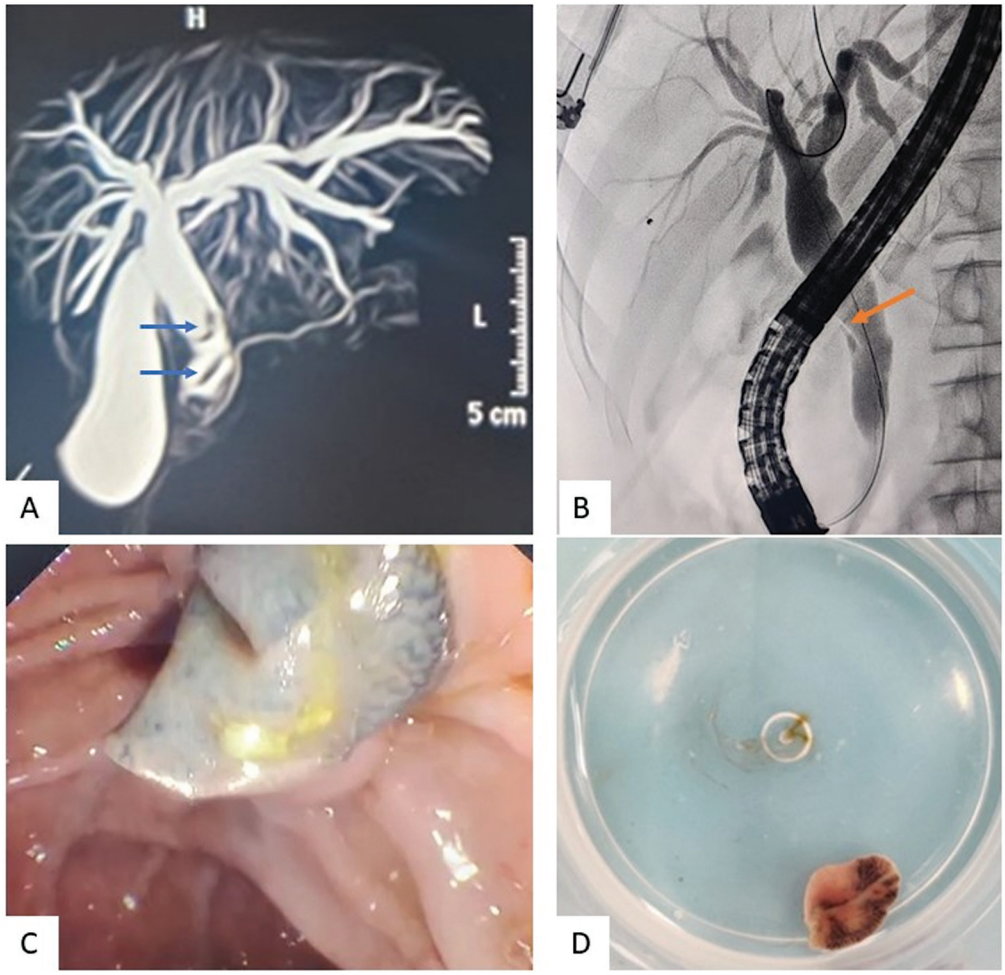

Fig. 1 Filling defects in common bile duct on magnetic resonance cholangiopancreatography (**A**; blue arrow) and cholangiogram (**B**; orange arrow); *Fasciola* being trawled out of common bile duct during endoscopic retrograde cholangiopancreatography (**C**) that was subsequently extracted for morphological analysis (**D**).

In the biliary phase, the infection can be suspected on imaging by the presence of linear echogenicity in the bile duct without posterior acoustic shadowing on USG or linear filling defects on MRCP. ERCP is both diagnostic and therapeutic in the chronic biliary phase and a definitive diagnosis can be established by removing adult flukes during ERCP. The diagnosis of *F. hepatica* in our patient was made by morphological examination of the fluke that was extracted during ERCP.

With regard to pharmacotherapy, it is important to note that *Fasciola* does not respond to commonly used antihelminthic agents like albendazole, mebendazole, praziquantel, or DEC.[3] The drug of choice is triclabendazole that is not routinely available for human use in India. A randomized controlled trial from Peru showed that nitazoxanide is a well-tolerated and effective alternate agent for human fascioliasis. Our patient was treated with 7 days of nitazoxanide with complete resolution of clinical symptoms and normalization of eosinophil counts.[14] Nitazoxanide may be particularly suitable as empirical therapy for areas where fascioliasis is endemic in humans due to its broad-spectrum activity against variety of intestinal protozoa (including Giardia) and helminths, high rates of cure, and low cost.[15]

Conclusion

Human fascioliasis is an emerging zoonoses. It should be suspected as a cause of eosinophilia even in nonendemic countries particularly in patients with abdominal pain, hepatomegaly, deranged liver function, and nonresponse to common antihelminthic agents like albendazole, mebendazole, praziquantel, or DEC.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Ethical Statement

The authors followed applicable EQUATOR Network (www.equator-network.org/) guidelines, notably the CARE guideline, during the conduct of this report.

Author Contributions

D.R. helped in manuscript writing; G.C.P. contributed to data collection and manuscript writing; Y.K. was involved in data collection; D.P.D. helped in data collection and critical revision; A.M. contributed to parasitological analysis, data collection, and critical revision; A.D. helped in manuscript writing, data collection, and critical review. The manuscript has been read and approved by all the authors, and each author believes that the manuscript represents honest work.

Note

The case was presented at the 31st annual conference of the Indian National Association for Study of the Liver (INASL), August 3–6, 2023.

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Conflict of Interest

None declared.

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