Original Research Paper

Volume - 16 | Issue - 06 | June - 2026 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

General Medicine

HEPATIC HISTOPLASMOSIS PRESENTING AS GRANULOMATOUS CHOLESTATIC HEPATITIS WITH SECONDARY HLH IN IMMUNOCOMPETENT PATIENT

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ABSTRACT Histoplasma capsulatum, a dimorphic fungus, is an endemic mycosis prevalent in developing countries. It typically presents as a disseminated infection in immunosuppressed host. It is rare in immunocompetent individual and can have varying presentation. It is an uncommon cause of Granulomatous Cholestatic hepatitis in India. We report a case of hepatic histoplasmosis in immunocompetent individual, manifesting as granulomatous cholestatic hepatitis complicated by secondary hemophagocytic lymphohistiocytosis (HLH). The patient presented with fever, cholestatic pattern of jaundice, hepatosplenomegaly. Subsequent workup for common causes of cholestatic jaundice was negative. Liver Biopsy, prompted by cholestatic liver enzyme pattern and normal biliary system imaging, revealed granulomatous hepatitis, raising suspicion for hepatic histoplasmosis.

KEYWORDS : Hepatic Histoplasmosis, Granulomatous Cholestatic Hepatitis, Secondary HLH

INTRODUCTION

Histoplasma capsulatum, a dimorphic fungus, is an endemic mycosis prevalent in developing countries. It typically presents as a disseminated infection in immunosuppressed host. It is rare in immunocompetent individual and can have varying presentation. It is an uncommon cause of Granulomatous Cholestatic hepatitis in India. We report a case of hepatic histoplasmosis in immunocompetent individual, manifesting as granulomatous cholestatic hepatitis complicated by secondary hemophagocytic lymphohistiocytosis (HLH).

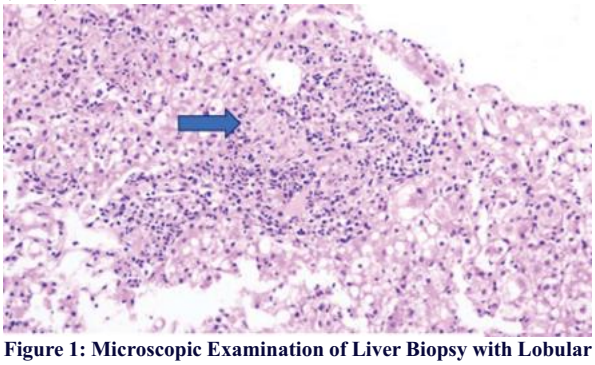

Figure 1: Microscopic Examination of Liver Biopsy with Lobular ill-Formed Granuloma (HE-20X)

Case Study

45-year-old gentleman presented with high-grade intermittent fever associated with chills for a duration of 10 days along with yellow discoloration of eyes and high colored urine for 3 days. There was no significant past medical, surgical, drug history or any history of addictions. There is no history of recent travel and cattle exposure. On examination he was febrile and icteric. Abdominal examination revealed tender hepatomegaly with splenomegaly, rest systemic examination was normal.

On admission investigation done revealed Hemoglobin – 11.2 g/dL, Total Leucocyte Count —3120/mm^3 Platelet Count —81,000 /mm^3, Polymorphs 54%, Lymphocyte — 35%, Aspartate transaminase (AST)-72 units/L, Alanine Transaminase (ALT) -57 units /L, Gamma Glutamyl Transferase (GGT)-143 units/L, Alkaline phosphatase (ALP)- 383 units/L, Total Bilirubin-7.87mg/dl, Direct Bilirubin-5.96 mg/dl, Total Protein-6.0g/dl, Albumin—3.1 g/dl, Procalcitonin- 0.38 ng/dl, C-Reactive Protein— 115.4 mg/dl, Peripheral Smear-Normocytic Normochromic red blood cells, Leukopenia with Thrombocytopenia. Serology for Hepatitis B, Hepatitis C, Hepatitis E, Hepatitis A and Human immunodeficiency Virus 1 and 2 were negative. Chest X-Ray was normal. Ultrasound Whole abdomen revealed hepatosplenomegaly with dilated portal vein of 16mm with no evidence of ascites.

Based on initial clinical evaluation and investigation patient was started on broad spectrum antibiotics after considering local endemic pattern of various diseases. Tropical Infection workup (Malarial Antigen, Leptospira IgM, Scrub IgM and Dengue IgM) were also negative. Initially antibiotics were started empirically but de-escalated, once urine and blood cultures remained negative.

1. In view of cholestatic jaundice magnetic resonance cholangio-pancreatography (MRCP) was done which revealed hepatosplenomegaly with periportal inflammation.

Patient continued to have fever spikes with worsening of liver enzymes. Autoimmune workup was negative. To widened the scope of etiologies Positron Emission Tomography- Computed Tomography (PET-CT) and bone marrow aspiration and biopsy were done. PET-CT revealed gross hepatosplenomegaly with minimal ascites and absence of FDG avid significant lymphadenopathy or focal/diffuse bone marrow uptake in regions of body surveyed. Given persistent fever, cytopenia (Hb-8.8 g/dl, Total WBC count-2930/mm^3, Platelet-132000/mm^3), hepatosplenomegaly and deranged liver function tests, Hemophagocytic Lymphohistiocytosis was suspected. Investigations showed- Serum Ferritin – 1354 ng/ml, Serum Fibrinogen – 131 mg/dl, Triglyceride-347mg/dl and hemophagocytic cells in bone marrow aspiration, with H score of- 239, indicating 98% probability of Hemophagocytic Lymphohistiocytosis. Bone Marrow Mycoreal was also negative for tuberculosis. Serum Rk-39 antigen test was negative for Leishmaniasis.

Increasing trend of liver enzyme -Total Bilirubin – 12.69 mg/dl, Direct Bilirubin – 9.3 mg/dl, AST-141 Units/L, ALT– 58 units/L, GGT– 82 units /L, ALP– 329 units/L and normal biliary system on imaging, prompted a liver biopsy, to rule out infiltrative and granulomatous liver diseases.

Percutaneous Liver biopsy revealed ill formed non-necrotizing granulomas with scattered intracellular and extracellular oval organisms with peripheral halo are noted throughout the core, some within Kupffer cells (Figure 1). Ziehl-Neelson stain for acid fast bacilli and immunohistochemistry for cytomegalovirus was also negative. These organisms were highlighted on Periodic acid Schiff-diastase (PAS-D) and Grocott's Methamine Silver (GMS) staining (Figure 2 and 3) with weak staining on Giemsa Stain suggesting possibilities of a.) Histoplasmosis b.) Leishmaniasis.

Urine for Histoplasma Galactomannan Antigen test came strongly positive. Liver biopsy in conjunction with urine for Histoplasma

Galactomannan Antigen test established the diagnosis of Hepatic Histoplasmosis. Patient was started on Liposomal Amphotericin B but developed hypersensitivity reaction. Liposomal Amphotericin B was stopped and after stabilization patient was started on intravenous Isavuconazole, with loading dose of 200 mg thrice daily for 2 days followed by 200 mg one daily for 6 months. Subsequently, patient showed marked improvement in clinical status and normalization of laboratory parameters including cytopenias. Patient was managed only with antifungal therapy alone, without immunosuppression and demonstrated significant clinical and laboratory improvement in secondary hemophagocytic lymphohistiocytosis.

DISCUSSION

Histoplasma capsulatum is a dimorphic fungus. It is most common cause of endemic mycosis in developing countries. It is a self-limited and asymptomatic disease in immunocompetent individuals but remains a frequent cause of opportunistic infection in patients with compromised immune status. Liver involvement as a part of disseminated histoplasmosis is well known. However, liver infection as a primary manifestation of histoplasmosis without evidence of primary lung involvement is rare. [1] While histoplasmosis is endemic in certain regions in the world including North and South America, Africa and parts of Asia, it is considered rare in India. Given the appropriate clinical context, histoplasmosis should be considered in both immunocompetent and immunocompromised patients, regardless of pulmonary symptoms in non-endemic as well as endemic areas. [1,2]

Patients with isolated hepatic histoplasmosis usually present with nonspecific symptoms, such as fever, fatigue, nausea, vomiting, weight loss, and elevation of liver enzymes. They may present with stigmata of chronic liver disease, portal hypertension, ascites, and/or varices. These features may be due to chronic parenchymal liver injury resulting from histoplasma. The full spectrum of hepatic manifestations of this disease is unknown but spans the range in the literature from mildly abnormal liver enzymes to severe icteric cholestasis with fever and pain. [3-5] Laboratory values are highly variable for this disease. High total bilirubin is usually associated with a concomitant rise in direct bilirubin, and GGT is significantly elevated as demonstrated. [6] A liver biopsy is often obtained in conjunction with serum and urine antigen studies to establish the diagnosis. GMS and PAS-D stain are useful for visualizing Histoplasma organisms in tissues. The early lesions in the tissue specimen contain a large number of macrophages and lymphocytes, with occasional epithelioid cells and multinucleated giant cells. [7]. The agents most commonly used for the treatment of histoplasmosis are amphotericin B and itraconazole. [8] however Isavuconazole has also demonstrated efficacy against histoplasmosis. [9]

CONCLUSION

In conclusion, clinicians should maintain high vigilance for histoplasmosis presenting as granulomatous cholestatic hepatitis-even in healthy individuals, with confirmation of diagnosis via tissue histopathology and antigen testing. One should consider secondary HLH in febrile patient with pancytopenia or bicytopenia, hepatosplenomegaly, and elevated triglyceride or hypofibringenemia. Prompt antifungal treatment alone is often sufficient-immuno-suppressants/steroids can be avoided.

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