

## Case Report

# Langerhans cell histiocytosis of liver

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### ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disorder of unknown etiology caused by proliferation of Langerhans cells. It can involve single organ system to multi organ systems and clinical presentation is variable depending on the organ involved and have different prognosis. LCH is common in children when compared to adults. Hepatic involvement in adults is relatively rare. Liver involvement has considerable impact on survival rates. Histopathology and immunohistochemistry provide the definitive diagnosis. Authors report a case of Langerhans cell histiocytosis in a young adult with hepatic involvement.

**Keywords:** Corona, Histiocyte, Immunohistochemistry, Langerhans cell histiocytosis, Transplantation

### INTRODUCTION

Langerhans cell histiocytosis (LCH) is characterized by the abnormal overproduction of histiocytes which infiltrates the tissues and organ systems predisposing to organ damage. It is a rare systemic disease.<sup>1</sup> LCH was previously coined as histiocytosis X. The term histiocytosis denotes the proliferation of histiocytes and other inflammatory cells, and "X" refers to the unknown cause of the disease. Lichtenstein in the year 1953 classified LCH into three main morphologically similar lesions namely eosinophilic granuloma, Hand-Schuller-Christian syndrome, and Letterer-Siwe syndrome.<sup>2</sup>

### CASE REPORT

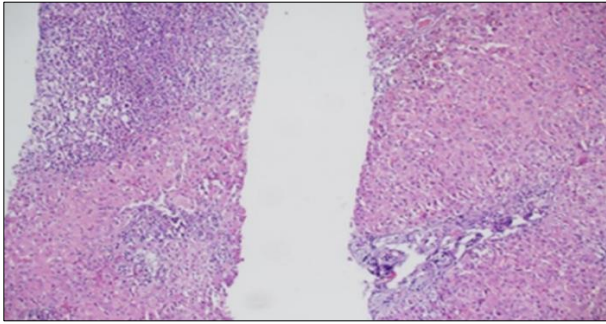
A 18 year young adult male from Bangladesh came to the hospital with non-specific symptoms such as of progressive lethargy, fatigue, anorexia and weight loss with few weeks history of progressive yellowish discoloration of eyes. His family history was unremarkable and no toxic habits were present. Physical examination showed that he was febrile and having deep

jaundice. Systemic examination showed moderate hepatomegaly. The laboratory data shows leucocytosis-16600 cells/mm<sup>3</sup>, moderate anaemia with hemoglobin 8.7 g/dl, total bilirubin 18.4 mg/dl, direct bilirubin 11.1 mg/dl, indirect bilirubin 7.3 mg/dl, alkaline phosphatase 499 U/L, SGPT-76 U/L, SGOT-100 U/L. Hepatitis B virus surface antigen, hepatitis C antibodies and human immuno-deficiency virus antibody were negative.

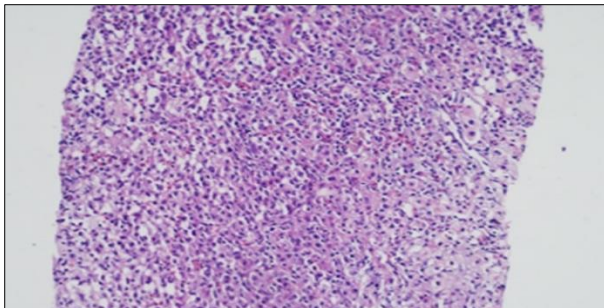


**Figure 1:** CT scan shows hepatomegaly with hypoenhancing small lesions in both lobes of liver.

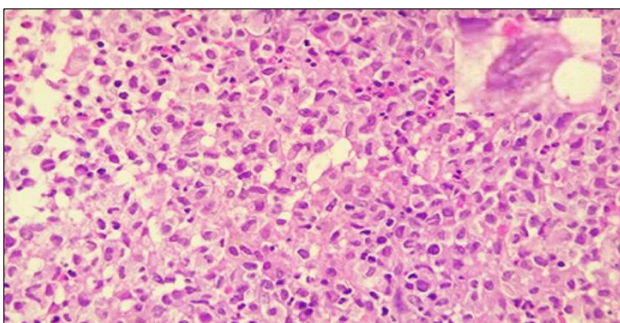
USG abdomen shows patchy to diffuse altered hypoechoic areas in both the lobes of liver largest measuring 43×21 mm. Significant periportal lymphadenopathy and moderate ascites. CT scan shows liver is enlarged in size (21.0 cm) and showed homogenous attenuation and enhancement with enumerable hypo-enhancing small rounded lesions (6×8 mm) in both lobes (Figure 1). No intrahepatic biliary duct dilatation. Multiple enlarged pericardiac, paraesophageal, periportal, portocaval, perigastric, periceliac, pre and para-aortic lymphadenopathy.



**Figure 2: Liver biopsy showing and portal tracts expanded by inflammation (H and E-4X).**



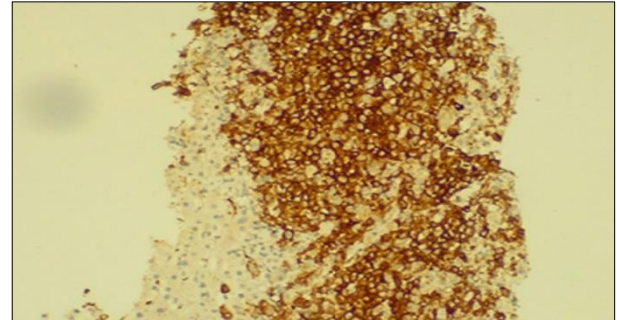
**Figure 3: Portal tract expanded by mixed inflammatory infiltrate and few histiocytes (H and E-10X).**



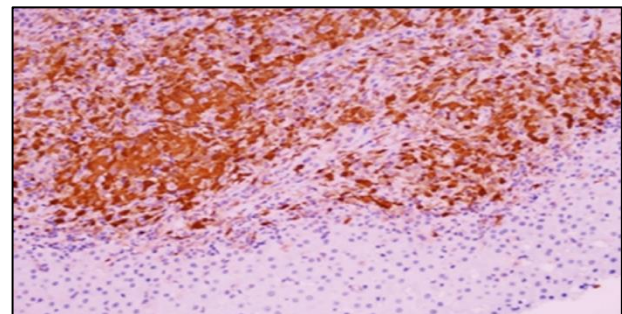
**Figure 4: Lesional cells shows vesicular nuclei, irregular nuclear membrane. Inset occasional cell showing groove (H and E-40X).**

Possibilities considered are 1. Langerhans cell histiocytosis 2. Tuberculosis (However less likely as there was no necrosis in the lymph nodes).

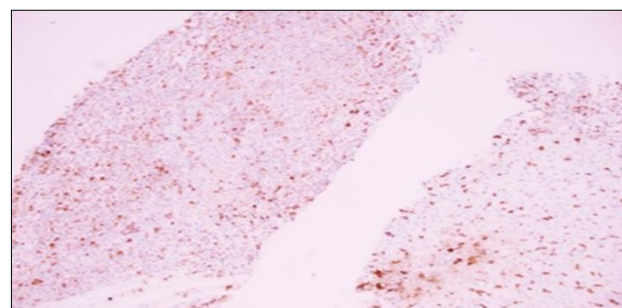
Perigastric lymphnode, mesenteric lymphnode and liver biopsy were sent for histopathological examination. Liver biopsy shows few portal tracts expanded by inflammatory cells comprising of lymphocytes, neutrophils, eosinophils and few histiocytes (Figure 2, 3). Few cells are with vesicular to hyperchromatic nuclei, irregular nuclear membrane, few with small nucleoli, moderate amount of eosinophilic cytoplasm. Occasional cells are showing intra-nuclear grooves. (Figure 4: Lesional cells shows vesicular nuclei, irregular nuclear membrane, moderate eosinophilic cytoplasm. Occasional cell showing groove in a background of inflammation H and E 40X).



**Figure 5: Liver biopsy showing cytoplasmic positive for CD1a in lesional cells within portal tract (IHC-10X).**



**Figure 6: Liver biopsy showing cytoplasmic positive for S-100 in lesional cells within portal tract (IHC-10X).**

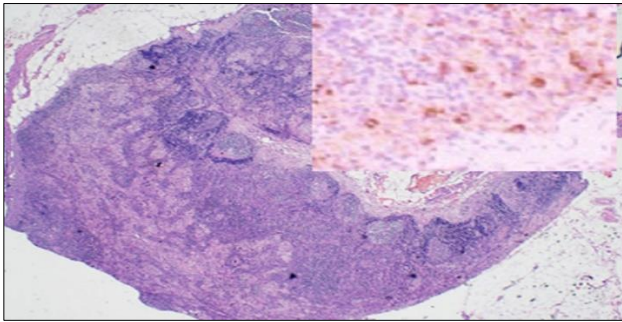


**Figure 7: CD 68 is positive in histiocytes in liver (IHC-4X).**

Immunohistochemistry shows positive staining of histiocytes with Cd1a and S-100 and CD 68 (Figure 5, 6,

7) confirming the diagnosis as Langerhans cell histiocytosis. Perigastric and mesenteric lymphnodes show few histiocytic aggregates. CD68 highlights few histiocytes and are negative for CD1a in lymphnode (Figure 8).

He was initiated with most accepted protocol for multi organ involvement high risk LCH which include prednisolone (40 mg/m<sup>2</sup>/day orally for four weeks, and then tapered over two weeks) and vinblastine (6 mg/m<sup>2</sup> weekly intravenous bolus for six weeks).<sup>3</sup>



**Figure 8: Lymphnode biopsy with few histiocytes which highlights CD 68 (IHC 10X).**

Unfortunately, at the end of six weeks it was evident that his disease has progressed. Bilirubin increased from baseline level of 18 mg/dl to 22 mg/dl at the end of 8th week with development of ascites. Repeat ERCP did not reveal any obstructive component which can be relieved by stent placement. He was deemed refractory to the first line chemotherapy and was initiated with second line chemotherapy cytarabine.<sup>4</sup>

The patient returned to his native country (Bangladesh) after the chemotherapy. Since neutropenia and thrombocytopenia was expected after the chemotherapy, he was expected to return. However, due to corona lockdown he could not return and due to logistic limitation succumbed to progressive disease and myelo-suppression.

## DISCUSSION

Langerhans cell histiocytosis (LCH) is a disease due to clonal proliferation as well as migration of dendritic antigen presenting histiocytes.<sup>5</sup> LCH is common in males than in females and the ratio ranges from 1.1:1 to 4:1. It is more common in children and young adults.<sup>2</sup> Incidence of LCH in adults is 1 to 2 cases per million when compared to children with 3 to 5 per million.<sup>1</sup>

Exact pathogenesis of LCH is unclear whether it is of neoplastic or reactive nature. In case when there is spontaneous remission it is considered to be reactive. In case when there is organ involvement by monoclonal population of aberrant cells and based on response to

cancer-based modality indicates probably neoplastic process.<sup>6</sup>

The clinical presentation may be variable depending on the organs involved. The LCH is divided into two major categories: “single system” and “multisystem.” Single system is further subdivided as Single site (unifocal bone, skin) and multiple site (multifocal bone, skin, lung, liver, spleen, lymph nodes, hypothalamus, pituitary gland, gastrointestinal tract). When two or more organs are involved with or without organ dysfunction it is of multisystem category. Multisystem is categorized into “low-risk” and “high-risk” groups depending on the organ involvement. Involvement of any organ viz liver, lungs, spleen, and hematopoietic system indicates “high risk” category (constitute 80% of multisystem LCH)” and has a bad prognosis. “Low risk” category is when there is no risk organ involvement (approx. 20%) and has a good prognosis.<sup>7</sup>

Multisystem LCH in children with liver involvement has reported incidence values of 19-60% which has poor prognosis. Chemotherapy is effective in early stages of liver involvement.<sup>8</sup> Multisystemic liver involvement in adults although seen in 87% but it is overlooked and poorly recognized with incidence reported values range from 16% to 27%.<sup>9</sup>

Liver involvement in LCH is categorized into two distinct forms: first, an early LCH liver involvement which is secondary to infiltration of the liver by Langerhans cells, and presents with liver nodules and hepatomegaly, and respond to immunosuppressive/chemotherapy treatment. If cholestasis is seen, it is usually mild. And a second form is described as late and shows chronic fibrosis centered on bile ducts with little or no histiocytic infiltration, progressing to sclerosing cholangitis.<sup>9</sup> The CD1a-positive cells helps to differentiate it from primary sclerosing cholangitis, and it is difficult to diagnose with biopsy if done in late stages with fibrotic lesions only.<sup>10</sup>

The confirmatory diagnosis is by histological examinations and immunohistochemistry. Histopathology shows LCH cells with irregular nuclei with prominent folds and grooves, fine chromatin, indistinct nucleoli with abundant eosinophilic cytoplasm and are 12 to 15 µm in diameter. Expression of CD1a, S100 protein and langerin (CD207) are the characteristic IHC markers. Expression of CD68 is variable. Electron microscopy shows birbeck granules which are elongated zipper-like cytoplasmic structures and measuring 200 to 499 nm.<sup>11</sup>

Differential diagnosis of LCH are histiocytic/dendritic lesions, primary or secondary tumors of liver, lymphoma, and Langerhans cell sarcoma.<sup>11</sup> In early stages with liver nodules LCH has to be differentiated from primary or secondary tumors of the liver. It is more complicated when associated with malignant tumors.<sup>12</sup> In later stages the differential diagnosis is chronic non suppurative destructive cholangitis or primary sclerosing cholangitis.

Prognosis is worst with liver involvement and has a fatality rate of 30% versus 10% without liver involvement. Early LCH responds to treatment with nodules or hepatomegaly with complete resolution. Late LCH liver involvement with sclerosing cholangitis, cirrhosis, or liver insufficiency is difficult to treat with partial response to treatment. The only treatment is the liver transplantation in the end stage.<sup>13</sup> LCH has a varied clinical spectrum, therapy is customized according to site and extent of disease. Treatment of patients with low risk multisystem LCH is 1-year systemic therapy with vinblastine and prednisone whereas for high risk multisystem patients are treated with mercaptopurine in addition to above. Clofarabine, cytarabine and cladribine are options for salvage therapy. Treatment of patient's single system LCH depend on the location of disease. Treatment of patients with hepatic LCH is systemic chemotherapy and is ineffective once cirrhosis develops. Liver transplantation is the curative option in advanced stages.<sup>14</sup>

BRAF or MAP2K1 mutations in most cases of LCH provides evidence of not only neoplastic nature but also shows its implications in risk stratification and treatment. Patients with hematopoietic progenitor cell with BRAF V600 mutation are at high risk whereas mutation limited to differentiated dendritic cell are at low risk. Treatment is effective with inhibitors of this BRAF V600.<sup>10</sup>

## CONCLUSION

LCH is a rare disease, making its diagnosis difficult. In adults the liver involvement is uncommon. Liver involvement is seen in multisystem as well as in single system. Liver biopsy with specific immunohistochemistry such as CD1a leads to the definite diagnosis. Diagnosis of liver involvement in early reversible stage is important for improved outcomes and better prognosis and need liver transplantation in the later stages.

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