

Langerhans Cell Histiocytosis (LCH) Presenting as Decompensated Liver Disease: Case Report

Chhagan Bihari, Archana Rastogi, Apurba Rajbongshi, Vikrant Sood, Rajeev Khanna, Seema Alam

Chhagan Bihari, Archana Rastogi, Apurba Rajbongshi, Department of Pathology, Institute of Liver and Biliary Sciences D-1, Vasant Kunj, New Delhi, 110070, India

Vikrant Sood, Rajeev Khanna, Seema Alam, Department of Pediatric Hepatology, Institute of Liver and Biliary Sciences D-1, Vasant Kunj, New Delhi, 110070, India

Correspondence to: Archana Rastogi, Associate Professor, Department of Pathology, Institute of Liver and Biliary Sciences, D-1, Vasant Kunj, New Delhi, 110070,

India. drarchanarastogi@gmail.com

Telephone: +911146300000 (6049)

Received: May 1, 2013

Revised: May 31, 2013

Accepted: June 3, 2013

Published online: August 21, 2013

ABSTRACT

Langerhans' cell histiocytosis (LCH) is a rare disease characterized by clonal proliferation of Langerhans cells. It manifests as single system unifocal, multifocal or multisystem disease. The diagnosis is always on histological assessment. We report a case of Langerhans' cell histiocytosis in a young child with clinical signs of decompensated liver disease whom the histological and immunohistochemical analysis of the liver biopsy, lymph node biopsy and radiology formed the diagnosis of multisystemic LCH.

© 2013 ACT. All rights reserved.

Key words: LCH; Decompensated liver disease; Sclerosing cholangitis

Bihari C, Rastogi A, Rajbongshi A, Sood V, Khanna R, Alam S. Langerhans Cell Histiocytosis (LCH) Presenting as Decompensated Liver Disease: Case Report. *Journal of Gastroenterology and Hepatology Research* 2013; 2(8): 750-752 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/458>

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease of unknown etiology that mainly affects young children. The clinical spectrum ranges from solitary or few indolent and chronic lesions in bone,

skin or other organs called as Eosinophilic granulomas to a fatal, acute, fulminant, disseminated disease with multiorgan involvement (Litterer-Siwe Disease). The intermediate clinical form, called Hand-Schüller-Christian disease, is characterized by multifocal, chronic involvement and classically presents as a triad of diabetes insipidus, proptosis and lytic bone lesions. These all are characterized by accumulation of proliferating Langerhans cells (LC) which have surface markers and ultrastructural features similar to cutaneous LC and variably admixed with eosinophils^[1,2]. Less commonly LCH can involve lung, spleen, bone marrow and rarely liver and gastrointestinal tract^[1].

Sclerosing cholangitis in children is a rare pathology of varied etiology which is characterized by chronic inflammation, and progressive fibrosis of extrahepatic and intrahepatic bile duct system. Sclerosing cholangitis may occur in 10-15% of patients with the multivisceral form of LCH^[3]. LCH related sclerosing cholangitis and subsequently progressive fibrosis and parenchymal involvement leads to biliary cirrhosis, portal hypertension and even chronic liver failure^[4]. Only few cases of LCH presenting with liver failure have been published in English literature so we find this rare case worth reporting; who initially presented as decompensated liver disease and found to be a case of underlying multisystemic LCH.

CASE REPORT

A three years 7 months old male child without any prior co morbidity presented with complaints of jaundice for last 5 months, abdominal distention for last 2 months. He had no history of neonatal cholestasis, umbilical or neonatal sepsis. There was no history of copper utensil usage. On general physical examination he was having pallor, Icterus, clubbing, ascites and generalized lymphadenopathy. On upper gastrointestinal endoscopy he had grade 2 esophageal varices. On abdominal ultrasound examination revealed an enlarged liver (span 13.6 cm) with irregular, lobulated outlines, coarse echo texture with periportal cuffing, intra-hepatic biliary radicals showed diffuse irregular thickening of walls, enlarged spleen and ascites. On laboratory examination he was found to have high total bilirubin of 14.6 mg/dL with direct fraction of 8.9 mg/dL, high alkaline phosphatase (392 IU/L, normal value 32-92 IU/L) and low albumin (1.7 g/dL). All viral, autoimmune and metabolic markers were negative. The liver biopsy showed distortion of acinar architecture with formation of parenchymal nodules separated by thick fibrous septae. Portal

tracts and septae showed loose edematous connective tissue, periductal concentric fibrosis, and moderate excess of mixed inflammation including neutrophils and eosinophils. There were periportal mixed inflammatory cell spill over and moderate ductular reaction with ductular bile plugs seen. Few large periportal histiocytic granulomatous collections seen admixed with fair number of neutrophils and eosinophils also seen. The hepatocytes showed cellular and canalicular cholestasis. Zeihl-Neelson staining done for mycobacterium was non-contributory. Immunohistochemically (IHC) these histiocytes were positive for S-100 and CD 1a (Figure 1 A-D). In view of presence of histiocytic granulomas in the liver biopsy and generalized lymphadenopathy, excisional biopsy of cervical lymph node was done which showed complete effacement of follicular architecture with diffuse sinusoidal and paracortical infiltration by sheets of mononuclear atypical histiocytes along with fair number of eosinophils in between and few multinucleated histiocytic giant cells. These histiocytic cells showed enlarged, folded, focally reniform nucleus with prominent nuclear grooving, irregular clefted nuclear membrane, conspicuous nucleoli and moderate amount of eosinophilic cytoplasm. There were few areas of necrosis seen with eosinophilic infiltration. On IHC examination the atypical histiocytic cells were positive for S-100 and CD1a (Figure 2 A-D). The histopathological diagnosis on liver

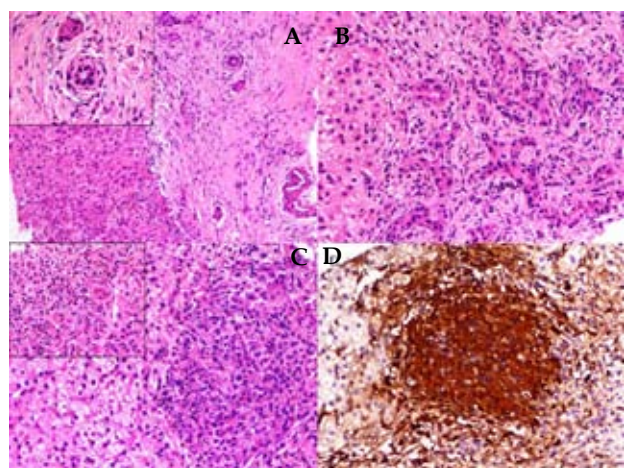


Figure 1 Liver Biopsy. A: Sclerosing fibrosis of portal tracts (Inset-periductal concentric fibrosis); B: Ductular reaction with mixed inflammatory infiltrate; C: Periportal granulomatous lesion -showing histiocytic collection (large arrow) admixed with eosinophils (small arrow) (H and E, 200 \times); D: Histiocytes are positive for CD1a (200 \times).

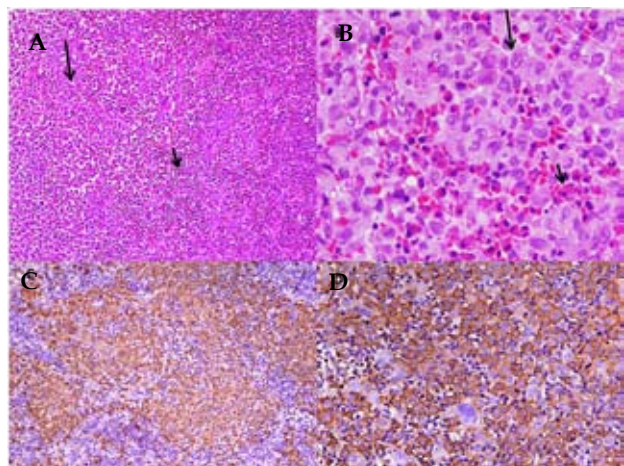


Figure 2 Lymph Node Biopsy. A: Sheets of atypical histiocytes (large arrow) eosinophils (small arrow) (H and E, 100 \times); B: Sheets of atypical histiocytes with irregular nuclei, nuclear grooving (large arrow) admixed with eosinophils (small arrow) (H and E, 200 \times); C: Histiocytes are positive for S-100 (200 \times). D: Histiocytes are positive for CD1a (200 \times).

biopsy; Cirrhosis due to Langerhan's Cell Histiocytosis (LCH) related secondary sclerosing cholangitis was rendered and the Lymph node biopsy was diagnosed as LCH. Later on skeletal survey revealed multifocal osteolytic bone lesions in the skull and ilium. On further investigations saddle shaped sphenoid with hypothalamus-pituitary axis involvement were noted. There was no evidence of lung involvement seen on X-ray chest and computed tomography chest examination. The patient was discharged in a stable condition to the oncology centre for further management with a final diagnosis of multisystem LCH.

DISCUSSION

Histiocytic syndromes are divided into three classes: class I is LCH, class II comprises of histiocytosis other than LCH and class III includes malignant histiocytic disorders^[3]. LCH is a group of diseases that have widely disparate clinical manifestations from asymptomatic to clinically significant symptoms and consequences. It can involve any organ and the clinical symptoms depend upon the site, organ or systems involved and their functional impairment. The common sites of involvement in LCH are bone, skin, lymph nodes, lung, thymus, bone marrow, liver, spleen, central nervous system (hypothalamic-pituitary region) and gastrointestinal tract. LCH is broadly divided in two categories: single system and multi system disease. The Eosinophilic granuloma, Hand Schuller-Christian disease and Litterer-Siwe disease are all examples of clinical spectrum of this disease but not the specific disease entities^[5]. These all are characterized by accumulation of proliferating cells with surface markers and ultrastructural features similar to cutaneous Langerhans cells (LCs)^[2]. Neoplastic cells are actively proliferating, round rather than dendritic in shape, functionally defective in antigen presentation and show a deviant regulation of cell division and the tissue distribution^[3].

Pathogenetically, LCH is a neoplastic condition, thought to be arising from epidermal LCs. These epidermal LCs in response to some external hyper inflammatory stimulus or as a result of cell-autonomous genetic event get activated. The activated LCs undergoes transcriptional reprogramming and which subsequently leads to epithelial-mesenchymal transformation (EMT) of these cells. The activated LCs express CD2, CD11b, CD24, CD44, CD54, CD58, CD80, CD86, β 1 and β 2 integrins along with down regulation of E cadherin. Activation and EMT are necessary for the spread and invasion of these cells to the particular site^[2]. Accumulated LCs along with other inflammatory cells create cytokine cascade through autocrine and paracrine amplification of cell signals, resulting into development of LCH through recruitment, maturation, and proliferation of LCs. The cytokines also causes development of other characteristic features of LCH such as fibrosis, necrosis, osteolysis^[6]. At the molecular level there are frequently recurring oncogenic BRAF mutations, along with rare KRAS and TP53 mutations have been reported, suggesting the neoplastic nature of this entity^[7,8].

The liver lesions can be due to direct or indirect effects of LCH. Indirect effects on the liver of LCH elsewhere in the body are mediated through an accompanying macrophage activation syndrome that is most likely responsible for hepatomegaly, splenomegaly and hypoalbuminemia but without direct infiltration. These indirect effects are completely reversible^[9]. Whereas in case of direct liver involvement by LCH are in two forms: first, one is a portal tract inflammation without LCH infiltration due to cytokines and the second one is the infiltration of the portal tracts and bile ducts with LCH. Laboratory findings in such cases are of cholestasis which reflects the damage of large or medium sized bile ducts. In these

patients, the disease is usually chronic and progressive and the liver biopsy may demonstrate infiltration of the portal area and basement membrane of the bile ducts with LCH cells^[9].

The portal tracts inflammation either due to massive release of cytokines or due to proliferating LCs infiltration leads to sclerosing cholangitis and subsequently biliary cirrhosis in cases of LCH. Although a portal lymphohistiocytic infiltrate is most characteristic, probably cytokine-mediated hepatocellular damage also contribute to substantial functional impairment of liver or even hepatic failure as a presenting feature^[9,10,11].

Portal tracts injury causing occurrence of sclerosing cholangitis due to Langerhans cell histiocytosis (LCH) is a rare cause of end-stage liver disease, seen mainly in children^[4]. On average, sclerosing cholangitis develops 2 years after diagnosis in children. Liver involvement is a factor of poor prognosis. It precipitates the occurrence of biliary cirrhosis and later on manifestations of decompensated liver disease. Usually, sclerosing cholangitis secondary to LCH responds poorly to the treatment^[4,10,12]. In the indexed case there were periportal granulomatous collection of histiocytic cells admixed with eosinophils seen.

For definitive diagnosis of LCH alongwith characteristic light microscopy, there is a requirement of CD1a positivity and/or presence of Birbeck granules on electron microscopy according to the Writing Group of the Histiocyte Society^[5]. In our patient S-100 and CD1a were positive in atypical histiocytes seen both in liver and lymph node biopsies.

To conclude the discussion decompensated chronic liver disease can be the initial presenting feature of LCH in young patients. And the liver biopsy findings of periportal histiocytic granulomas collections alongwith eosinophils in presence of sclerosing cholangitis may be considered as histological pointers that liver disease is secondary to LCH and should be confirmed by immunohistochemistry.

REFERENCES

- 1 Uday Shankar, Monika Prasad and Om P Chaurasia. A rare case of langerhans cell histiocytosis of the gastrointestinal tract. *World J Gastroenterol* 2012; **18**: 1410-1413
- 2 Badalian-Very G, Vergilio JA, Fleming M, Rollins BJ. Pathogenesis of Langerhans cell histiocytosis. *Annu Rev*

- Pathol* 2013; **24**: 1-20
- 3 Sabib M, Ettair S, Erreimi N, Mouane N. Sclerosing cholangitis revealing Langerhans cell histiocytosis in a 15-month-old child. *Arch Pediatr* 2011; **18**: 974-978
- 4 Braier J, Ciocca M, Latella A, de Davila MG, Drajer M, Imventarza O. Cholestasis, sclerosing cholangitis, and liver transplantation in Langerhans cell Histiocytosis. *Med Pediatr Oncol* 2002; **38**: 178-182
- 5 Judit Muller. Langerhans Cell Histiocytosis in childhood. *Journal of pediatric sciences* 2010; **2**; e28
- 6 Egeler RM, Favara BE, van Meurs M, Laman JD, Claassen E. Differential in situ cytokine profiles of Langerhans like cells and T cells in Langerhans cell histiocytosis. *Blood* 1999; **94**: 4195-4201
- 7 Badalian-Very G, Vergilio JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML, Kuo FC, Ligon AH, Stevenson KE, Kehoe SM, Garraway LA, Hahn WC, Meyerson M, Fleming MD, Rollins BJ. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood* 2010; **116**: 1919-1923
- 8 Weintraub M, Bhatia KG, Chandra RS, Magrath IT, Ladisch S. p53 expression in Langerhans cell histiocytosis. *J. Pediatr. Hematol. Oncol* 1998; **20**: 12-17
- 9 Gey T, Bergoin C, Just N, Paupard T, Cazals-Hatem D, Xuan KH, Tavernier JY, Wallaert B. Langerhans cell histiocytosis and sclerosing cholangitis in adults. *Rev Mal Respir* 2004; 997-1000
- 10 Kannourakis G, Abbas A. The role of cytokines in the pathogenesis of Langerhans cell histiocytosis: *Br J Cancer* 1994; **70**: 537-540
- 11 Honda R, Ohno Y, Iwasaki T, Okudaira S, Okada M, Kamitamari A, Ohshima K, Moriuchi H, Kanematsu T. Langerhans' cell histiocytosis after living donor liver transplantation: report of a case. *Liver Transpl* 2005 Nov; **11**: 1435-1438
- 12 Griffiths W, Davies S, Gibbs P, Thillainayagam A, Alexander G. Liver transplantation in an adult with sclerosing cholangitis due to Langerhans cell histiocytosis. *J Hepatol* 2006; **44**: 829-831

Peer reviewer: Jia-Ren Sun, MD, PhD, Associate Professor and Director, Department of Microbiol Immunol, Flow Cytometry Core Lab, Univ Texas Medical Branch, 301 Univ Blvd, Galveston, the United States.