Short Communication

Langerhans cell histiocytosis: report of a single organ involvement in a child

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Abstract

Langerhans cell histiocytosis is a rare disorder characterized by abnormal proliferation of Langerhans cells that can affect various organ systems. The disease usually presents as a unifocal lytic bone lesion and can affect any age group. Less frequently it presents as a disseminated disease with multisystem involvement. Hepatic manifestation in Langerhans cell histiocytosis is relatively rare and usually presents as a part of a disseminated process. We report a case of Langerhans cell histiocytosis involving only the liver in a 9-years-old child.

Keywords: Langerhans cell histiocytosis • histiocytosis X • liver • sclerosing cholangitis

Introduction

Langerhans cell histiocytosis (LCH; formerly called Histiocytosis X) is a rare disorder with several different forms of clinical presentation. Majority of the cases presents as uni- or multifocal bone lesions, visceral involvement is less frequent and usually seen in patients with disseminated LCH [5,11]. The most frequent sites of unifocal visceral manifestation are the lungs, followed by the skin and lymph node [1,4,11,14]. LCH can occur at any age, although the majority of the

cases - especially those with multisystem involvement - affects children [1,4,10,11,14]. The lesions in different organs have the same histopathologic appearance; i.e. granulomatous collection of histiocytes (mostly Langerhans cells) admixed with a variable number of lymphocytes, eosinophil and neutrophil granulocytes. However, some morphologic variability may occur depending on the affected tissue site and the stage of the disease [5].

Solitary hepatic manifestation of LCH is rare, although the liver maybe involved in the multisystemic form of the disease. Besides its rarity, it also deserves attention because of its remarkable prognostic value and special pathologic characteristics. We present a case of a solitary LCH of the liver with emphasis on the special histopathologic features.

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Clinical history

A 9-year-old African-American girl was in good health until December 2003 when she presented to the emergency room with abdominal pain, vomiting, fever and fatigue of several days duration. Her past medical history was unremarkable; she was a full term baby of 8 lbs weight. She had neither serious childhood illness nor any prior hospitalization. On physical examination the patient had scleral icterus and marked hepatomegaly. The liver filled the right upper and almost completely filled the left upper quadrant of the abdominal cavity, extended down on the right and in the midline to about 2 cm below the level of the umbilicus; its texture was firm-to hard. The extremities showed mild edema, but no ascites was observed. The spleen was not enlarged. Neither skeletal abnormalities, nor skin lesions were seen.

The laboratory tests revealed hepatic dysfunction: aspartate-aminotransferase (AST) 199 U/L (normal 10–30 U/L); alanine-aminotransferase (ALT) 112 U/L (normal 10–40 U/L); alkaline-phosphatase (ALP) 534 U/L (normal 69–325 U/L); total bilirubin 2.5 mg/dl; direct bilirubin 2.0 mg/dl; total protein 5.9 g/dl; albumin 1.9 g/dl. Mild anemia was also detected (Hgb 10.4 g/dl, Hct 31.6%). Serological examinations for hepatitis and respiratory viruses were negative. Skin test for tuberculosis was also negative.

The computed tomography (CT scan) showed diffuse, hypodense infiltrative process in the right lobe of the liver, possibly sparing the left lobe. The chest X-ray was normal, no mediastinal enlargement was seen. The chest CT showed only minimal atelectatic changes at the base, no infiltrate, no effusion and no pneumothorax was reported. The skeletal survey did not show bone involvement. The bilateral bone marrow core biopsies and aspirates did not show any evidence of LCH.

Histopathologic findings

The liver needle biopsy revealed diffuse infiltration of the liver by histiocytes with marked expansion of portal tracts and acinar involvement with areas of bridging necrosis (Fig. 1a). Within the portal tracts the histiocytes formed small granulomatoid aggre-

gates (Fig. 1b). Scattered lymphocytes, eosinophils, neutrophils and rare multinucleated giant cells were seen admixed with the histiocytes. Most of the histiocytes had abundant pink cytoplasm, elongated nuclei with central folding (coffee bean shaped) or contorted nuclei with fine chromatin consistent with Langerhans cell histiocytes. Neither cellular atypia, nor mitotic figures were seen. Marked destruction of large and small sized bile ducts by these histiocytes was seen in most portal areas. Bile ductular proliferation was also observed. The bile duct injury pattern was reminiscent of secondary sclerosing cholangitis. Immunohistochemical stains for S-100 protein (Fig. 1c) and CD1a (Fig. 1d) showed strong immunoreactivity with the histiocytes confirming that these were Langerhans cell histiocytes. Special stains for acid fast bacilli and fungal organisms were negative.

Clinical course

After the diagnosis of Langerhans cell histiocytosis was established, the patient was treated with oral steroids and combined chemotherapy. A rapid response was noted and 4 months after the initial symptoms the patient is doing well. There is no hepatomegaly on physical exam, and the abdominal CT showed only mild liver enlargement without any parenchymal abnormality. The hepatic biochemical profile was within the normal ranges. At this time a second liver biopsy was performed that showed no evidence of residual LCH. The liver showed a mild non-specific portal inflammation with severe portal fibrosis (Fig. 2a) and extensive bile duct damage. Residual Langerhans cells could not be identified even with the CD1a immunohistochemical stain (Fig. 2b).

Discussion

Isolated liver involvement by LCH in childhood is extremely rare. In our case the liver was massively infiltrated by Langerhans cell histiocytes. Immunohistochemical stains for S-100 protein and CD1a confirmed their histogenetic origin. The Langerhans cells selectively involved portal tracts,

Fig. 1 First (pretreatment) liver needle biopsy. *a*: Diffuse portal histiocytic infiltration with marked expansion of portal tracts [H&E, original magnification 120x]. *b*: The histiocytes form small granulomatoid aggregates in the portal tracts. Most of the histiocytes have elongated, coffee bean shaped or folded nuclei. The histiocytes are infiltrating and destroying a bile duct (arrow) [H&E, original magnification 360x]. *c*: The histiocytes are expressing positive immunoreactivity to immunohistochemical stain S-100 protein. [original magnification 120x]. *d*: The Langerhans cell histiocytes express positive immunoreactivity to immunohistochemical stain CD1a. [original magnification 360x].

surrounded and infiltrated the bile ducts irrespective of size and caliber and eventually destroyed them. CT scan did not show any enlarged portal lymph nodes, nor was the common bile duct involved by the disease process. This histological pattern is reminiscent of two autoimmune biliary diseases, primary sclerosing cholangitis and primary biliary cirrhosis. It is interesting to note that several authors have speculated, that LCH may represent a disorder/dysfunction of the immune system and not a true neoplastic process [4,5,11,12]. This hypothesis might provide an explanation for the

hepatic injury seen in multi-system LCH where the liver is indirectly involved, namely that pro- and anti-inflammatory cytokines may play a role in the pathogenesis of hepatic fibrosis, even without the local presence of Langerhans cells [2,7,9]. Others have challenged this theory and have put forward the concept of LCH being a neoplastic condition producing large array of cytokines and chemokines [3]. Either way, the issue of pathogenesis is not as yet clear.

In 1998 Levy et al. described the first reported case of isolated hepatic involvement by LCH in an

Fig. 2 Second (post-treatment) liver needle biopsy. *a*: Severe portal fibrosis is well demonstrated with Masson's trichrome stain. [original magnification 60x]. *b*: Portal tract showing mild, non-specific inflammation. Langerhans cell histiocytes are not present. [H&E, original magnification 240x].

adult [10]. Kaplan et al. reported nine cases of liver involvement; five of those had hepatic involvement only [9]. To our knowledge, no other cases of single organ liver LCH have been reported.

Hepatic involvement in a disseminated disease is less uncommon, although the rate of involvement is much lower than in most other organs [1,6,11]. The macroscopic appearance of the hepatic lesions in LCH as reported in the literature varies from single to multiple small to large, subcapsular or deeply located nodules, some authors reported solid tumor-like or occasionally multicystic masses [2,9,10]. Microscopic examination of liver in LCH generally showed two forms. 1) Langerhans cells directly infiltrated the liver forming small granulomatous foci or larger nodular aggregates in the portal areas, while in other cases they formed tumor-like masses of histiocytes [6,7,9,10]. The overall histologic appearance in most of the cases, especially in the advanced stage of the disease, was reminiscent of sclerosing cholangitis [2,7,15].

2) Indirect involvement of liver in the absence of Langerhans cells: nonspecific portal inflammation, portal/periportal fibrosis; bile ductular proliferation; ductopenia; and eventually biliary cirrhosis [2,5,7,9,10].

The course of the disease may show extreme case-to-case variation [5]. In the majority of the cases, especially in those with localized osseous lesions, LCH is considered as a benign, reactive

process [11]. Supporting this presumption, single bone lesions are known to tend to resolve spontaneously [4]. In contrast, multi-system LCH, especially with lung, liver, or other visceral organ involvement is usually associated with poorer prognosis and a fulminant disease process [8]. The late, potentially lethal sequel of liver involvement is biliary cirrhosis [9]. In liver, unlike in other organs involved by LCH, after an initial injury the fibrotic disease process can be self-perpetuating even without the presence of Langerhans cells [9]. The treatment of hepatic LCH consists of systemic chemotherapy, but the therapy does not seem to be effective once cirrhosis is present [8,13]. In those cases liver transplantation can be performed [2,13].

Our young patient is doing well 4 months after the diagnosis. There is no serologic evidence of hepatic dysfunction and there is no sign of hepatomegaly on physical examination. Although the second liver biopsy did not show Langerhans cell infiltration, the periportal fibrosis seems to be persistent together with a mild non-specific periportal inflammation and bile duct injury. Since the disease process in the liver can be self-perpetuating even without the presence of the Langerhans cells, regular laboratory and radiographic examinations will be performed during her follow-up, in order to reveal the changes in her liver function status as well as the possible recurrence or dissemination of the disease.

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