Hepatic Langerhans cell histiocytosis: A review

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Abstract

Hepatic Langerhans cell histiocytosis (LCH) is characterized by proliferation and accumulation of Langerhans cells in the liver, causing liver dysfunction or forming a mass lesion. The liver can be involved in isolation, or be affected along with other organs. A common clinical hepatic presentation is cholestasis with pruritis, fatigue and direct hyperbilirubinemia. In late stages, there may be hypoalbuminemia. Liver biopsy may be required for the diagnosis of hepatic LCH. Histologic finding may be diverse, including lobular Langerhans cell infiltrate with mixed inflammatory background, primary biliary cholangitis-like pattern, sclerosing cholangitis-like pattern, and even cirrhosis at later stages. Because of its non-specific injury patterns with broad differential diagnosis, establishing a diagnosis of hepatic LCH can be challenging. Hepatic LCH can easily be missed unless this diagnosis is considered at the time of biopsy interpretation. A definitive diagnosis relies on positive staining with CD1a and S100 antigen. Liver involvement is a high risk feature in LCH. The overall prognosis of hepatic LCH is poor. Treating at an early stage may improve the outcome. Systemic chemotherapy is the mainstay of treatment and liver transplantation may be offered. New molecular markers involved in pathogenesis of LCH are being explored with a potential for targeted therapy. However, further studies are needed to improve outcome.

Key Words: Langerhans cell; Liver; Cholangitis; CD1a
INTRODUCTION

Langerhans cell histiocytosis (LCH) is characterized by proliferation and accumulation of dendritic antigen-presenting histiocytes, Langerhans cells, in tissue. Langerhans cells express CD1a, S-100 and langerin proteins, and show Birbeck granules on ultrastructural examination[1]. LCH is a rare disease with an annual incidence of about 5 cases per 1 million population. The disease is more common in Caucasian population of northern European descent, with a male predominance. It can affect any age group but most cases occur in children[1,2]. The etiology is unknown. However, there is a strong association between pulmonary LCH and smoking[34].

Some authors have considered that LCH is an abnormal reactive process to an inciting event, such as viral infection, given the fact that multiple cytokines are involved in the process and LCH has been reported to regress spontaneously when it’s an isolated lesion[5,6]. However, the revised 4th edition World Health Organization[1] classified LCH as a clonal neoplastic process. Recently, Murakami et al[7] proposed that both BRAF mutation and Interleukin-1 Loop amplification play important roles in the pathogenesis of LCH[7]. More recently, other groups found that BRAFV600E mutation or alternative activating MAPK pathway gene mutations are almost universally identified in LCH[8,9]. These studies provide a potential for molecular alteration-based targeted therapy for LCH.

LCH demonstrates a variable clinical picture and course. It can involve a single organ system (SS-LCH) or multiple organ systems (MS-LCH). While any organ can be affected, bone is the most frequent site occurring in 80% of cases of LCH; it can be unifocal or multifocal. A third of LCH cases involve the skin and a quarter involve the pituitary gland. Other organs, such as liver, spleen, lungs, lymph nodes, gastrointestinal tract, and rarely parotid glands and nails, can also be involved[10].

When LCH involves a single organ, the course may be indolent and have a favorable survival. Su et al[11] reported 100% 5-year survival in pediatric LCH patients when the disease involved only bone[11]. In a long-term (over 17 years) follow-up study of pediatric LCH, SS-LCH showed a 100% regression rate and low relapse vs 73% regression in MS-LCH[12].

LCH involving the skin, bone, lymph nodes or pituitary gland is considered “low-risk” because of its good response to treatment. Involvement of the lungs, hematopoietic system and spleen, and liver is considered “high risk” with an unfavorable outcome[1,6,12,13].

In this review, we focus on hepatic LCH and provide a brief overview of its clinical presentation, laboratory/imaging findings and current treatment. Its pathologic findings and differential diagnosis are also reviewed.

DIAGNOSIS OF HEPATIC LCH

The diagnosis of hepatic LCH in a patient with known LCH requires one or more of the followings: (1) hepatomegaly, defined as a liver edge greater than 3 cm below the costal margin at the mid clavicular line (confirmed by ultrasound); (2) liver dysfunction defined either by abnormal serum biochemical tests including bilirubin greater than 3 times the upper limit of normal, protein less than 55 g/L, albumin less than 3 g/dL, transaminases [alanine aminotransferase (ALT)/ aspartate aminotransferase (AST)] greater than 3 times normal, or by clinical entities including an
intrahepatic nodular mass or ascites or edema, not as a result of other causes; or (3) histopathological findings of active disease[14,15].

**INCIDENCE OF HEPATIC LCH**

The liver may be affected in isolation[16-19], or involved along with other organ systems such as lymph nodes, skin and lungs.

In pediatric LCH, the frequency of liver involvement is variable but may be high (15%-60%). It carries a poor prognosis. In adult LCH, liver involvement is relatively uncommon with an incidence of 16%-27%. However, it is probably under recognized. One study of multisystemic LCH in adults reported liver involvement in 87%[14,18,20].

**CLINICAL MANIFESTATION**

There are 2 stages of hepatic LCH: An early stage with liver parenchymal infiltration by Langerhans cells and a late stage with biliary sclerosis[18,20]. Clinical manifestations differ based on the stage.

A common presentation is jaundice with direct hyperbilirubinemia and hypoalbuminemia. Patients may present with fatigue and pruritus[21]. Clinically, hepatic LCH may mimic other conditions such as chronic destructive cholangitis, metabolic disease, hepatitis, neoplasia obstructing biliary tract and inherited deficient conjugation of bilirubin. It can also present as Reye syndrome, chronic inflammatory bowel disease, or hemochromatosis[14]. In late stages, patients may present with severe sclerosing cholangitis and liver failure. A subset of patients progresses to develop cirrhosis, which may lead to portal hypertension and secondary hypersplenism[22,23].

**LABORATORY/IMAGE FINDINGS**

Laboratory tests show abnormal serum liver tests with mild to moderately elevated ALT and AST. Cholestatic biochemical profiles are seen with increased total bilirubin, γ glutamyl transferases and anaplastic lymphoma kinase phosphatase. The albumin level is often low. The prothrombin time may be prolonged due to decreased clotting factor. Depending on liver function, clotting factors may be depleted. Complete blood count is usually normal, although the platelet count may be low in patients with portal hypertension and splenomegaly. Abdominal contrast-enhanced computed tomography may demonstrate hepatomegaly with solitary or multiple hypodense hepatic nodules, which can be confluent[18]. At a late stage, magnetic resonance imaging may show biliary tree abnormalities[20].

**PATHOLOGY FINDINGS**

Liver biopsy is the cornerstone of the diagnosis of LCH and disease staging. Liver biopsy can show various injury patterns. In an early stage, lobular Langerhans cell infiltrate mixed with lymphocytes can be seen. The Langerhans cells may form focal aggregates or be multinucleate[18]. In addition to lymphocytes, mature eosinophils, neutrophils and plasma cells can also be noted. A definitive diagnosis can be rendered based on positive immunohistochemical staining with CD1a and S100 antigen of the Langerhans cells.

At a later stage, Langerhans cells may infiltrate the bile ducts and cause sclerosing cholangitis. In some cases, histologic features of sclerosing cholangitis may be seen in a biopsy without identifiable Langerhans cells[17,22,24]. This may be due to selective involvement of the major bile ducts by Langerhans cells; large ducts are unlikely to be sampled in the usual needle biopsy[25]. Chronic non-suppurative destructive cholangitis injury pattern has been also reported[26].

Notably, hepatic LCH may mimic primary biliary cholangitis (PBC). Rush et al[19] reported hepatic LCH presenting as a small noncaseating granuloma in the portal tract with rare multinucleated epithelioid giant cells within the portal inflammatory infiltrate. The patient underwent a liver transplantation for the presumed diagnosis of advanced anti-mitochondrial antibody (AMA)-negative PBC. However, the disease
recurred in the allograft. The diagnosis of hepatic LCH was finally rendered three years after transplantation in the allograft biopsy. Four years later (7 years after the transplantation), the patient lost the liver graft. LCH diagnosis was confirmed in the explanted allograft liver[19].

Similarly, our group reported a case of hepatic LCH that histologically and pathologically mimicked PBC. A 65-year-old man presented with intermittent pruritus with cholestatic biochemistry profile for years. The liver biopsy showed portal histiocytic aggregate (non-necrotizing granuloma) encasing a damaged bile duct (Figure 1). Tests for autoantibodies including AMA were negative, therefore AMA-negative PBC was suspected. One month later, multiple skin lesions developed and a diagnosis of LCH was rendered on a skin biopsy. In light of the positive skin biopsy, the previous liver biopsy was re-examined. The histiocytes surrounding the duct were positive for CD1a and S100, confirming the diagnosis of hepatic LCH, retrospectively[21].

These two cases highlight the difficulty of rendering a diagnosis of hepatic LCH without appropriate clinical context.

In summary, hepatic LCH may present as a non-specific inflammatory process with varying injury pattern. Therefore, the diagnosis of hepatic LCH can easily be missed when this diagnosis is not considered. In addition, its patchy nature and limited sampling may further hinder the diagnosis of hepatic LCH[21]. In late stage MS-LCH, even though the clinical picture may be strongly indicative of hepatic LCH, it may be difficult to render a definitive diagnosis on the initial biopsy and a repeat biopsy may be necessary[6].

DIFFERENTIAL DIAGNOSIS
There are a variety of differential diagnoses for hepatic LCH due to its nonspecific presentations and morphologic features.

The morphological and clinical findings of hepatic LCH may resemble primary sclerosing cholangitis (PSC). A classic “beaded” appearance of extrahepatic biliary tree by endoscopic retrograde cholangiopancreatography and periductal onion-skin type fibrosis with negative stains for S100 and CD1a may be helpful in the diagnosis of PSC. Granulomatous reaction with ductular proliferation raises a differential diagnosis of PBC. The presence of a dense portal lymphoplasmacytic infiltrate, mild degree of interface activity, and negativity for S100 and CD1a in conjunction with positivity for AMA can be helpful for PBC diagnosis. However, as demonstrated above, it can be very difficult to differentiate hepatic LCH from AMA negative PBC in a small liver biopsy, especially in the absence of appropriate clinical context.

In hepatic LCH, the presence of granulomatous inflammation also raises a differential diagnosis of infection. Grocott (or Gomori) methenamine silver and acid-fast bacteria stains may help to rule out infectious etiology, although they have low sensitivity[27-30]. Tissue culture may be helpful in these scenarios. Other differential diagnosis includes sarcoidosis, foreign-body type giant cell reactions, drug-induced liver injury, and non-Hodgkin’s and Hodgkin’s lymphoma.

Additionally, myeloproliferative disorders and myeloid leukemias can express CD1a and/or S100 protein, mimicking LCH. However, these are distinguished by sinusoidal infiltrative pattern of the neoplastic cells[25].

TREATMENT
Depending on clinical course and degree of organ dysfunction, variable treatment options are offered for LCH. Usually, patients with single site SS-LCH are observed only or offered monotherapy, such as oral 6-mercaptopurine and methotrexate, indomethacin, bisphosphonates, and hydroxyurea. Patients with MS-LCH usually benefit from systemic therapy, such as the vinblastine-prednisone combination [6,15,20].

NOVEL MOLECULAR TARGETS
Recently, molecular markers such as \(BRAFV600E\) and \(MAP2K1\) have been identified in LCH pathogenesis. These markers may serve as molecular targets for precision therapy in the future. For instance, vemurafenib, a \(BRAF\) inhibitor, had prolonged
efficacy in patients with BRAF V600-mutant LCH[31]. In addition, MEK inhibitors showed near-universal responses in patients with histiocytoses, including LCH, regardless of tumor genotype[32]. However, prospective clinical trials would be required to determine optimal duration of therapy and to explore a potential for combination with other targeted or cytotoxic therapies.

The optimal treatment for hepatic LCH remains to be determined. Currently, systemic chemotherapy is the mainstay of treatment. Yi et al[33] reported that earlier systemic chemotherapy has led to a relatively better outcome in hepatic LCH. However, the therapy was not effective once cirrhosis developed[33]. Therefore, early diagnosis and treatment of hepatic LCH would be crucial. Unfortunately, a subset of hepatic LCH patients develops severe sclerosing cholangitis that progresses to cirrhosis. In this case, liver transplantation may be the treatment of choice and should be considered early in the disease course[34]. Tang et al[35] reported a case of hepatic LCH that was successfully treated by liver transplantation with subsequent tacrolimus and mycophenolate mofetil as immunosuppressants[35].

Further collaborative studies regarding the biology, clinical presentation and outcome of hepatic LCH would be required to explore and refine variable treatment options.

**PROGNOSIS**

In LCH, liver involvement has a significant bearing on survival. The overall prognosis of hepatic LCH is poor with a fatality rate of 30%-50% (versus < 10% without liver involvement) and median survival of 9 years[6,18,20]. The 3-year survival rate of LCH with liver involvement is 51.8%, compared with that of 96.7% without liver involvement[6]. In Abdallah et al[20]’s study, 30% of patients died due to sclerosing
chlolangitis complicated by secondary cirrhosis[20]. Therefore, it is very important to identify liver involvement at an early reversible stage. Early detection and treatment may improve the outcome[6,18].

CONCLUSION

While hepatic LCH is relatively uncommon, it portends a poor prognosis. Early detection and treatment of hepatic LCH may allow a better prognosis. Liver biopsy plays an important role in the diagnosis and management of hepatic LCH. Unfortunately, the histomorphology is non-specific and needs to be differentiated from other granulomatous processes, such as PBC or infection. A definitive diagnosis requires confirmatory immunohistochemical staining with CD1a and S100. Currently, systemic chemotheraphy is the mainstay of treatment for hepatic LCH. Further studies are required to explore other treatment modalities including molecularly targeted therapy.

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