Cholestasis as manifestation of langerhans cell histiocytosis in an 18-months-old boy

Leao Lurdes, Ariawati Ketut

ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease of unknown etiology. It can occur at any age but is more frequent in the pediatric population at young age. Because of its infiltration nature, the disease varies widely in clinical manifestation from localized to a multisystem involvement. Owing to the relative rarity of the condition and varies in clinical presentation, it remains a disease in which the diagnosis is often delayed or missed. Jaundice in LCH is a manifestation of liver dysfunction. However, a case of cholestasis has been very rare described. We report an 18-months-old boy with LCH involving multiple systems whose present earlier as cholestasis and recurrent fever. The patient was diagnosed following a clinical manifestation of LCH and skin biopsy that revealed Langerhans cells. The patient was in partial remission following chemotherapy and died at fourth months of chemotherapy. In conclusion, any patient presenting to pediatric clinic with jaundice must to be ruled out the possibility of liver involvement in LCH. Jaundice might be an earlier clinical manifestation of liver disease in LCH and can be a clue for diagnosis. Early diagnosis and proper management would contribute to a better outcome.

Keywords: Langerhans cell histiocytosis, cholestasis, liver dysfunction

Cite This Article: Lurdes, L., Ketut, A. 2017. Cholestasis as manifestation of langerhans cell histiocytosis in an 18-months-old boy. Medicina 48(2): 133-137. DOI:10.15562/medi.v48i2.42

INTRODUCTION

Langerhans cell histiocytosis (LCH) is a rare disease characterized by clonal proliferation with unknown etiology. The current nomenclature used for LCH indicates the disease extent, which may involve a single organ system (unifocal or multifocal) or multiple organs (involving a limited number or they maybe disseminated).1,2

The annual incidence of LCH has been estimated to be 2 to 10 cases per 1 million children aged 15 years or younger. The male and female ratio is close to one and the median age is 30 months. Any organ or system of the human body can be affected. Liver, spleen and hematopoetic systems are affected in a small percentage (5 to 10% cases).3,4 Several risk factors have been identified for LCH but strong and consistent associations have not been confirmed.5 The LCH prognosis depends on the extent of disease at presentation. Some prognosis factors have been identified. Age at diagnosis < 2 years portend a worse prognosis but response to therapy at 6 to 12 weeks has been shown to be a more important prognostic factor than age. The overall response to therapy is influenced by the duration and intensity of treatment. Involvement of the high-risk organs

ABSTRAK


Kata kunci: Histiositosis sel Langerhans, kolestasis, disfungsi hati

(liver, spleen, and/or bone marrow) is linked to the extent of the disease.\textsuperscript{6,7}

One of the most serious complications of LCH is cholestasis and sclerosing cholangitis. This usually occurs months after initial presentation, but on occasion may be present at diagnosis, the median is 23 months.\textsuperscript{8-10}

**Case illustration**

An 18-months-old boy was admitted to our hospital with a history of jaundice for last 2 months, chronic cough and recurrent fever for an uncertain duration and. He had no history of neonatal cholestasis or neonatal sepsis. Liver function test (LFT) showed total serum bilirubin 1.43 mg/dL with direct fraction of 1.36 mg/dL; serum albumin 2.85 g/dL; Alkaline phosphatase (ALP) 590 mg/dL; Alkaline aminotransferase (ALT) 51.98 U/L; Aspartate aminotransferase (AST) 21.41 U/L; Gamma GT (GGT) 511 U/L. He was treated as a case of pulmonary tuberculosis and intrahepatal cholestasis. He was discharged one month later with antituberculosis and ursodeoxycholic acid (UDCA) with no marked response. Blood test including liver function test were performed periodically. During outpatient visits, parents complained on and off skin problem. He was referred to skin doctor and was diagnosed as seborrhoic dermatitis and treated accordingly.

At 22 months old, patient was readmitted to pediatric ward for 3 weeks due to poor oral intake and was assessed as severe malnutrition according to WHO standards. He underwent severe malnutrition protocol. Antituberculosis and UDCA were continued. Two months later, the patient became deeply jaundice (figures 1 and 2) and LFT revealed: total serum bilirubin 16.42 mg/dL with direct fraction of 14.22 mg/dL; Total protein 5 g/dL; serum albumin 2.23 g/dL; ALP 623 mg/dL; ALT 91.1 U/L; AST 101.2 U/L; GGT 826 U/L. Case was suspected as drug induced hepatitis and antituberculosis drugs were suspended for 2 weeks. Patient then was seen regularly at outpatient basis. Patient also attended ENT clinic due to chronic and recurrent ear discharge. During that time period, clinical and laboratory findings showed no remarkable improvement which led to discontineuation of antituberculosis drugs.

At 26-months-old, patient was hospitalized due to generalized edema. He was febrile, tachipnic with RR 62x/mnt, deeply jaundice on sclera and skin, abdominal distention, generalized lymphadenopathy, multiple erythematous papules with desquamation on head, chest, back and abdominal area. The anthropometric measurements showed severe malnutrition according to the WHO standards. Laboratory findings as shown in tabel 1 revealed mild anemia with normal total leucocyte and platelet count; peripheral smear revealed microcytic hypochromic anemia; Liver chemistries revealed elevated AST, ALT, ALP and GGT; Total serum, direct fraction and indirect serum bilirubin were increased; urine was positive for bile; Faal hemeostasis, and electrolytes were within normal limits; HbsAg and Anti HCV were non reactive; FNAB showed atypical lymphoid hyperplasia with eosinophylia; abdominal Doppler ultrasonography revealed chronic liver disease with signs of portal hypertention, splenomegali, thickening of gallblader wall and ascites (figure 3). Histology staining from skin punch biopsy was consistent with langerhans cell histiocytosis protocol. Patient was discharged after 1 month on oral chemotherapy of 6-Mercaptopurine 25mg/m\textsuperscript{2} daily, prednison 20 mg/m\textsuperscript{2}. Clinical presentation and laboratory parameter were improved as

**Figures 1 and 2** Slight jaundice noticed at first admission and became deeply jaundice

**Table 1 Laboratory examinations**

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin/TLC</td>
<td>9 g/dL; 8.300/μL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>241,000/μL</td>
</tr>
<tr>
<td>HbsAg/Anti HCV (Elisa)</td>
<td>0.41/0.10 (non reactive)</td>
</tr>
<tr>
<td>AST/ALT/ GGT/ALP</td>
<td>AST 38.9 U/L; ALT 77.6 U/L; GGT 293 U/L; ALP 518 mg/dL</td>
</tr>
<tr>
<td>Serum bilirubin/direct fraction/indirect</td>
<td>Total serum bilirubin 11.82 mg/dL with direct fraction of 11 and indirect fraction 0.82 mg/dL</td>
</tr>
<tr>
<td>Total serum protein/albumin/globulin fraction</td>
<td>TP 5 g/dL; albumin 2.24 g/dL; globulin 2.76 g/dL</td>
</tr>
<tr>
<td>Na/K/Cl and Ca</td>
<td>132/3.43/103.8 mmol/L and 8.2 mg/dL</td>
</tr>
<tr>
<td>INR; PTT/control; APTT/control</td>
<td>1.14; 13.3/11.3; 33.5/56.9 (seconds)</td>
</tr>
<tr>
<td>FNAB of colli lymphadenotaphy</td>
<td>Atypical lymphoid hyperplasia with eosinophylia</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>hypochromic microcytic anemia; normal leucocytes and platelet count; no abnormal cells</td>
</tr>
</tbody>
</table>

Anti HCV, anti hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutayl transferase; ALP, alkaline phosphatase; Na, natrium; K, potassium; Ca, calcium; INR, international normalized ratio; PTT, prothrombin time; aPTT, activated partial thromboplastin time; FNAB, fine needle aspiration biopsy; TLC, Total leucocyte count
shown in the following data (figures 6 to 7 and table 2). In the fourth month on chemotherapy, patient died due to the complication of CLD.

**DISCUSSION**

Langerhans cell histiocytosis is a heterogeneous disease, characterized by accumulation of dendritic cells with features similar to epidermal langerhans cells in various organs. The annual incidence of LCH has been estimated to be 2 to 10 cases per 1 million children aged 15 or younger. The median age of presentation has been found to be 30 months. The male and female children are affected in equal proportions.\(^1,2\) Any organ or system of the human body can be affected but those more frequently involved are the skeleton (80% cases), the skin (33% cases) and the pituitary (25% cases). The other organs involved are the liver, spleen, lungs and hematopoietic systems in a small percentage (5 to 10% cases).\(^3,4\) The clinical course may vary from a self-limiting disease to a rapidly progressive one that might lead to death. One of the most serious complications of hepatic LCH is cholestasis and sclerosing cholangitis, considered as a rare case with poor prognostic factor.\(^5,10\)

The case was an 18-months-old boy who presented with mild jaundice, recurrent fever and cough. Examination done one year later, showed involvement of more than two organs including liver and spleen as high risk organs. The disease was rapidly progress into liver dysfunction with signs and symptoms of chronic liver disease (CLD). Patient underwent chemotherapy for 4 months and died due to a massive gastrointestinal bleeding. According to Histiocyte Society, this is a case of high risk multisystem LCH.

Literature analysis in pubmed showed twenty-eight cases of pediatric gastrointestinal LCH have been reported. The cause of liver pathology in LCH is due to either direct or indirect effects of the langerhans cells. The indirect effects are reversible and occur due to activation of macrophages in the body leading to hepatomegaly, splenomegaly and hypoalbuminemia; however the langerhans cells are absent on liver biopsy. Whereas in case of direct liver involvement, there are two types of reported liver pathology on biopsy. The first one is an infiltration of portal tracts without langerhans cells and the second one is characterized by the domination of langerhans cells in the portal tracts and bile ducts.\(^11,12\) In our case, we did not perform liver biopsy due to poor condition of the patient.

In a case study of LCH, jaundice has been described rarely. However, LCH can present with earliest features of liver dysfunction. On laboratory investigations, the direct liver involvement is characterized by cholestasis due to the damage of medium to large size of bile ducts with increasing serum of total bilirubin and direct fraction of bilirubin. Liver function test showed elevation of AST, ALT, ALP and GGT. In these patients, the disease is usually chronic and progressive. The portal tract inflammation either due to massive release of cytokines or due to proliferating LCs infiltration leads to the development of sclerosing cholangitis and subsequently biliary cirrhosis. 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. Portal tract injury causing occurrence of sclerosing cholangitis due to langerhans cell histiocytosis is a rare cause of end-stage liver disease, seen mainly in children. Liver involvement is a factor of poor prognosis. Usually, sclerosing cholangitis secondary to LCH responds poorly to treatment.10,11,13

In our case, first clinical presentation were mild cholestasis, recurrent fever with cough. Liver function test (LFT) showed total serum bilirubin 1.43 mg/dL with direct fraction of 1.36 mg/dL; serum albumin 2.85 g/dL; ALP 590 mg/dL; ALT 51.98 U/L; AST 21.41 U/L; GGT 511 U/L. Laboratory findings done periodically showed chronic progressive disease (table 2). LFT revealed increased total serum bilirubin and direct fraction; elevated AST, ALT, ALP and GGT; decreased total serum protein and albumin. The finding of abdominal Doppler ultrasonography was consistent with chronic liver disease (CLD) with signs of portal hypertension, splenomegaly, thickening of gallblader wall and ascites.

Children and adults may develop a red papular rash in the groin, abdomen, back or chest that resembles a diffuse candidal rash. Seborrheic involvement of the scalp may be mistaken for a severe case of dandruff in older individuals. Ulcerative lesions behind the ears, involving the scalp, under the breast, genitalia or perianal region are often misdiagnosed as bacterial or fungal infections. Vesicular lesions may be seen and need to be differentiated from herpetic lesion.16 In our case, patient has had chronic skin problem with persistent rash and was attended skin clinic for various time. He has been treated as seborrhic dermatitis and fungal infection. Skin punch biopsy was performed and sent for histopathology examination. The result showed morphologically consistent with langerhans cell histiocytosis.

Since LCH may affect any organ or system of the body, the condition should be considered whenever suggestive clinical manifestations occur in the skin, bone, lung, liver or CNS. The diagnosis is clinicopathologic. In addition to clinical and radiological features, LCH diagnosis should always be based on histological and immunophenotypic examination of lesional tissue that should be taken from the most easily accessible, yet representative lesion. Based on the International Histiocyte Society recommendations, the presumptive diagnosis established based on conventional histological findings. The presence of this findings, coupled with immunohistochemical results showing positive S-100 protein staining supported probable diagnosis. The definitive diagnosis made if positive CD1a and/or CD207 antigen expression by way of immunohistochemistry.17-19

Diagnosis of LCH is usually made by skin biopsy performed for persistent skin lesions. A liver biopsy is only recommended if there is clinically significant liver involvement and the result will alter treatment. Liver disfunction is suspected when liver enzymes > 5-fold upper limit of normal; bilirubin > 5-fold upper limit of normal and evidence of hypoalbuminemia. Diagnostic confirmation may be a challenge in some circumstances. In rare cases the risk of biopsy may outweigh the need for a definitive diagnosis, and therefore the risk/benefit ratio should be carefully assessed. In our case, patient was diagnosed as multisystem high-risk LCH based on clinical presentation, laboratory and radiographic findings (table 1), the skin punch biopsy showed morphologically consistent with LCH. Immunohistochemical analysis of the skin biopsy showed positive result for S-100, whereas CD1a and/or CD 207 were not available.

There are general considerations for treatment and criteria for definition of organ involvement in LCH as per histiocytosis society. For liver involvement, the patient may show a combination of symptoms which includes: liver enlargement > 3 cm below the costal margin at the midclavicular line, confirmed by ultrasound or disfunction documented by hyperbilirubinemia > 3 times normal, hypoalbuminemia (< 30 g/dL), GGT increased > 2 times normal, ALT (SGPT)-AST (SGPT) > 3 times normal, ascites, edema, or intrahepatic nodular mass. Spleen involvement if spleen enlargement > 3 cm below margin at the mid clavicular line, confirmed by ultrasound. Skin involvement if any rash documented by histological examination or any lesion (erythematous and crustated macules, papules, or nodules with or without ulceration, or petchiae, or seborrheic-like picture) compatible with the diagnosis, if LCH is confirmed by biopsy of another organ. As mentioned before, clinical challenges of multisystem LCH are mortality in young children with involvement of risk organs, and bouts of reactivation resulting in morbidity and permanent consequences which can occur in all age group. Patients with risk-organ involvement are at risk of death and a poor response to therapy defines a subgroup with a particularly poor prognosis. Several international protocols for MS-LCH treatment have been designed within the framework of the HS.7,8,20 Their main conclusions are: (i) standard treatment is based on steroids and Vinblastin (VBL); (ii) clinical response after first 6 weeks of treatment is a good marker of further disease evolution; (iii) Prolonged treatment for at least 1 year reduces the risk of disease reactivations. Front line treatment of MS-LCH are VBL 6 mg/m² i.v. weekly bolus for 6 weeks, with prednisone 40 mg/m²/day given orally in 3 divided doses for 4 weeks and then tapered over the following 2 weeks. After 6 weeks of treatment, disease status should be reevaluated and treatment continued accordingly. Refractoty disease in patients with liver disfunctions is rare but life threatening situation. Therapeutic
options include combination chemotherapy should be given. A subset of young children with liver involvement may subsequently develop sclerosing cholangitis that progresses to cirrhosis. Treatment for this children may includes liver transplantation. In our case, we used a histiocytosis protocol by given combination of prednisone and vinblastin as recommended with 6-MP 50 mg/m2/day orally for 6 weeks, Methotrexate 500 mg/m2 intravenously every 2 weeks for 6 weeks and leucovorin 12 mg/m2 every 2 weeks for 6 weeks. After 6 weeks on chemotherapy, clinical status was reevaluated and showed no improvement. Again chemotherapy was continued based on protocol. This situation would prone the patient to a poor prognosis.

Prognosis is closely linked to the extent of disease at presentation when high-risk organs such as liver, spleen and/or bone marrow are involved and to the response to initial treatment. Risk refers to the risk of mortality. Although age younger than 2 years was once thought to portend a worse prognosis, data from the LCH study showed that patients age 2 years or younger without high-risk organ involvement had the same response to therapy as older patients. The high risk designation comes from the high mortality rate (35%) in those who did not respond well to chemotherapy. Clinical status was reevaluated and showed no improvement. Again chemotherapy was continued based on protocol. This situation would prone the patient to a poor prognosis.

CONCLUSION

Langerhans cell histiocytosis can occur at any age but is more frequent in the pediatric population. The annual incidence of LCH has been estimated to be 2 to 10 cases per 1 million children aged 15 years or younger. Owing to the relative rarity of the condition, it remains a disease in which the diagnosis is often delayed or missed. Any patient presenting to pediatric clinic with jaundice must be ruled out the possibility of liver involvement in LCH. Jaundice might be an earlier clinical manifestation of liver disease in LCH and can be a clue for diagnosis. Involvement of liver is considered as high risk which might lead to serious complication and death. Therefore the early recognition and promptly treatment would reduce the number of serious complication and even death.

REFERENCES