

# Langerhans Cell Histiocytosis and Choledocholithiasis: A Causal Relationship or Coincidence?

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**L**angerhans cell histiocytosis (LCH), previously known as histiocytosis X, encompasses a diverse group of proliferative disorders characterized by infiltration and accumulation of histiocytes and other immune effector cells within various tissues.<sup>1</sup> Clinical manifestations of LCH are varied and depend on the sites and extent of involvement; LCH can range from solitary disease of the bone to severe multivisceral involvement including the lungs, bone, liver, spleen, lymph nodes, hypothalamus, pituitary gland, and gastrointestinal tract. LCH typically occurs in children and adolescents, but it can develop in all age groups, and it has a male predominance.<sup>2</sup> Manifestations of LCH vary depending on whether the patient has single-system or multisystem involvement, but hepatobiliary disease due to LCH is uncommon. This case reports LCH in a male child with neurologic symptoms (diabetes insipidus) and obstructive jaundice.

## Case Report

An 11-year-old boy, who was known to have LCH but was in remission, presented with a history of yellowish discoloration of the eyes and dark-colored urine associated with polydipsia and polyuria for 1 year. He had infiltration of Langerhans cells in the lungs and a seborrheic rash on the skin. The diagnosis of LCH was confirmed by a chest radiograph and skin biopsy. Jaundice was nonprogressive, painless, and was not preceded by prodromata. The patient was on a maintenance dose of cyclosporine (12 mg/kg/day in 2 divided doses given daily). There was no history of gastrointestinal bleeding, pruritus, or fever. On physical examination, mild scleral icterus, moderate hepatosplenomegaly, and mild

tenderness in the right hypochondrium were observed. There was no free fluid.

A complete blood count, renal function test results, and serum amylase levels were normal. Liver function tests showed elevated levels of serum bilirubin (total bilirubin, 16.6 mg/dL [normal, 0.3–1.9 mg/dL]; direct bilirubin, 7.8 mg/dL [normal, 0–0.3 mg/dL]), transaminases (aspartate transaminase, 110 IU/L [normal, 7–53 IU/L]; alanine transaminase, 80 IU/L [normal, 11–47 IU/L]), serum alkaline phosphatase (680 IU/L; normal, 130–550 IU/L), and serum gamma-glutamyl transpeptidase (90 IU/L; normal, 11–55 IU/L). Tests for hepatitis B virus surface antigen, hepatitis C antibodies, and HIV antibodies were negative. An upper endoscopy revealed grade III esophageal varices.

An ultrasound of the abdomen showed a dilated biliary system (common bile duct [CBD], 16 mm in diameter) and multiple large calculi in the CBD. Intrahepatic biliary radicles were dilated. A magnetic resonance cholangiopancreatography confirmed the ultrasound findings. In addition, the dilated CBD was filled with multiple stones, the largest of which was 3.8 cm in diameter. One large calculus measuring 20 mm × 18 mm was seen in the mid-CBD. An intrahepatic biliary calculus (8 mm × 8 mm) was seen in the dilated left hepatic duct. The distal branches of the intrahepatic biliary system were not dilated. An endoscopic retrograde cholangiopancreatography was performed, and stones were extracted after a wide sphincterotomy and mechanical lithotripsy for large stones. The procedure was uneventful.

## Discussion

LCH is a poorly understood disorder of immune modulation that results in the proliferation of a subset of histiocytes. It is a challenging disease to diagnose, with a wide clinical spectrum ranging from a spontaneously regressing skin rash to potentially fatal localized disease

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or multifocal disease.<sup>3,4</sup> LCH occurs in all age groups, but its peak incidence is in children between the ages of 1 year and 4 years. The annual pediatric incidence of LCH is estimated to be 2–5 cases per million individuals per year.<sup>5</sup> What causes the histiocytes to proliferate abnormally and infiltrate a variety of organs and sites is unknown. We report a LCH patient with painless, nonprogressive, cholestatic jaundice who incidentally also had choledocholithiasis, which did not manifest with typical biliary colic and cholangitis. The cause of jaundice in a patient with LCH could be multifactorial.

Cholestatic jaundice of parenchymal origin could be due to biliary ductular proliferation secondary to involvement of intrahepatic or extrahepatic bile ducts, resulting in portal triaditis and fibrosis and often terminating in secondary biliary cirrhosis.<sup>6,7</sup> The presence of varices indicates that the patient had progressed to secondary biliary cirrhosis. The prognosis in this patient is poor. Primary sclerosing cholangitis has also been reported in LCH patients.<sup>8</sup> Primary bile duct injury in this patient is probably due to cytokines, such as platelet-derived growth factor, interleukin-1, and tumor necrosis factor, which may contribute to the bile duct injury and portal fibrosis.<sup>9</sup>

A previous report described biliary obstruction in an adult resulting from involvement of the intrahepatic and extrahepatic biliary trees by LCH.<sup>10</sup> Another cause of jaundice in our patient could be the presence of CBD stones. Similar associations have been reported by other authors.<sup>11,12</sup> However, our patient had no obstructive symptoms related to the intraductal CBD stones.

The origin of CBD stones in the setting of LCH is not clear. Hepatomegaly in children is a common and nonspecific clinical finding.<sup>13,14</sup> If hepatomegaly results from enlarged hilar lymph nodes that are causing extrinsic biliary compression and consequent dilatation of the intrahepatic bile ducts, then hepatomegaly is accompanied by jaundice. Hepatomegaly also may occur as an indirect effect of a macrophage activation syndrome accompanying LCH elsewhere in the body. Generalized activation of the cellular immune system may cause Kupffer cell hypertrophy and hyperplasia, with resultant hepatomegaly that is completely reversible with treatment.<sup>5,7</sup> Associated splenomegaly caused by portal hypertension resulting from periportal fibrosis or secondary to direct histiocytic infiltration is another frequent manifestation.<sup>5,15</sup>

One possible explanation for the high incidence of CBD stones in patients with LCH could be the long-term maintenance of these patients on cyclosporine. Experimental work in small animal models has found

that cyclosporine causes cholestasis. These studies showed a significant decrease in bile flow and bile salt secretion in cyclosporine-treated rats and pigs without changes in biliary cholesterol and phospholipids. A proposed mechanism for this effect is perturbation of the hepatocyte membrane by a lipophilic compound such as cyclosporine.<sup>16</sup> LCH patients who are in remission while on cyclosporine treatment should be monitored for CBD stone formation. However, the occurrence of jaundice due to CBD stones in patients with LCH may be an association or concurrence. The nature of this association must remain speculative.

In summary, cholestatic jaundice in patients with LCH could be due to primary intrahepatic biliary ductular injury resulting in secondary biliary cirrhosis and portal hypertension, or jaundice could be secondary to CBD stones, which have been linked to prolonged use of cyclosporine.

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# Review

## Langerhans Cell Histiocytosis and Choledocholithiasis: Is There an Association?

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Langerhans cell histiocytosis (LCH) is a rare disease characterized by clonal proliferation of pathologic cells that have the characteristics of Langerhans cells.<sup>1</sup> Langerhans cells are bone marrow–derived dendritic cells that normally reside in the skin and lymph nodes.<sup>2</sup> The etiology of LCH remains unknown. The clinical presentation of LCH is heterogeneous and can involve single or multiple organs. Patients with LCH have infiltration with abnormal cells, which eventually results in organ dysfunction. Depending on the extent of organ involvement, LCH can range from benign disease to multisystem life-threatening disease.<sup>3</sup>

It remains unknown whether LCH is a reactive disorder or a neoplastic disorder. Clonal histiocytes have been detected in most patients with LCH, which suggests a neoplastic disorder.<sup>4</sup> However, the alternative hypothesis is that LCH is a reaction against an infective agent that results in immune dysregulation.<sup>4</sup> LCH is classified as single-system or multisystem disease. Single-system LCH is characterized by involvement of a single site (unifocal bone, skin, or lymph node) or involvement of multiple sites within the same organ system (multifocal bone or multiple lymph nodes). Multisystem LCH is characterized by involvement of 2 or more organ systems at diagnosis, with or without organ dysfunction.<sup>3</sup> Involvement of the liver, lungs, spleen, or hematopoietic system is often associated with a poor prognosis and a high mortality rate.<sup>3</sup>

Liver involvement is usually seen in the disseminated form of LCH and presents with hepatomegaly related to infiltration of histiocytes into the sinusoids and portal tracts. Biliary involvement secondary to LCH can also occur but only in the disseminated form of the disease; in these cases, the prognosis is uniformly poor.<sup>5,6</sup> Fortunately, biliary involvement, which can present as infiltration of intrahepatic and extrahepatic bile ducts, is a rare occurrence.

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The occurrence of jaundice is considered to be a bad prognostic sign, as biliary involvement is usually progressive. Langerhans cell infiltration of the bile ducts can present with progressive destruction and secondary sclerosing cholangitis, ultimately leading to secondary biliary cirrhosis.<sup>7</sup> In fact, some authors have suggested that some cases of primary sclerosing cholangitis (PSC) are related to biliary involvement in patients with LCH. In advanced cases, differentiating these 2 conditions would be difficult. However, in contrast to patients with PSC, the involvement of extrahepatic ducts is rarely seen in patients with LCH.<sup>7</sup>

The patient reported by Krishnan and coauthors presented with a 1-year history of jaundice with no abdominal pain.<sup>8</sup> He had been diagnosed with LCH and was on maintenance therapy with cyclosporine. An upper endoscopy revealed esophageal varices indicative of portal hypertension. Further evaluation revealed elevations in serum bilirubin, aminotransferases, and serum alkaline phosphatase levels. An ultrasound of the abdomen showed a dilated biliary system (common bile duct of 16 mm) with multiple large calculi, the largest of which was 3.8 cm in diameter and required sphincterotomy, mechanical lithotripsy, and stone removal.

Krishnan and coauthors suggest a possible relationship between LCH and choledocholithiasis.<sup>8</sup> However, their report does not make clear whether there was infiltration of Langerhans cells into the bile ducts nor whether jaundice improved and bilirubin normalized after stone removal. Whether the cholangiogram showed any evidence of secondary sclerosing cholangitis would also be interesting to note.

The question we are facing with this case is whether choledocholithiasis was an incidental finding or related to LCH. One explanation is that, since bile duct stones are common in the general population, it would not be surprising to have cases of bile duct stones coexisting with essentially any other medical condition, including LCH. However, the rarity of bile duct stones in a pediatric patient would make this explanation less likely.

Another explanation, which is also discussed by the authors, is that long-term maintenance treatment with cyclosporine could be responsible for biliary stone formation. Studies in animal models have shown that cyclosporine causes a significant decrease in bile flow and bile salt secretion without changes in biliary cholesterol and phospholipids.<sup>9</sup> These changes alter the composition of bile and predispose patients to stone formation. In addition to the effects of cyclosporine, some reports have suggested a direct relationship between LCH and concomitant biliary sludge or stones. In a case series of 10 children with LCH and biliary involvement, evidence of biliary sludge and/or cholelithiasis was seen in 6 chil-

dren (60%).<sup>10</sup> Similar associations of bile duct stones with LCH have also been reported by other researchers.<sup>11,12</sup>

Yet another explanation for the observed association is that bile duct stones could be related to biliary stasis secondary to the sclerosing cholangitis–like condition seen in LCH patients. Patients with LCH may have cholestatic jaundice due to biliary ductular proliferation secondary to involvement of intrahepatic or extrahepatic bile ducts, potentially resulting in portal triaditis and fibrosis. In an initial study of PSC patients, nearly 50% of patients had common bile duct stones on endoscopic retrograde cholangiography, and these patients were 50% more likely to have ascending cholangitis compared to patients without stones.<sup>13,14</sup> These stones likely contribute to the chronic inflammation, stricturing, cholestasis, and cholangitis seen in PSC patients. Similar to stone formation in PSC patients, LCH patients with secondary sclerosing cholangitis could be predisposed to stone formation, particularly when they are treated with agents such as cyclosporine, which alters the biliary milieu toward a pro-lithogenic state.

To conclude, the report by Krishnan and coauthors suggests an interesting association.<sup>8</sup> We believe that a multitude of coexisting factors can explain their patient's predisposition to biliary stone formation. Biliary stasis secondary to bile duct inflammation, cyclosporine use, and a possible direct relationship between LCH and bile duct stones could have contributed, either alone or in combination, to cholechololithiasis in this patient. Until future studies show the underlying pathophysiologic

mechanism of biliary sludge/stone formation in patients with LCH, a possible relationship between LCH and biliary stones will remain hypothetical.

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