

LANGERHANS' CELL GRANULOMA CONFINED TO THE BILE DUCT

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□ *Langerhans' cell histiocytosis (LCH) of the liver is uncommon. When seen, it is part of multifocal disease and can present as biliary obstruction. We present a case of sclerosing biliary disease with a solitary LCH lesion and no evidence of systemic disease. We postulate that the LCH is a secondary phenomenon, arising against a background of a complex, familial liver disease. This case also raises the possibility that some instances of idiopathic sclerosing cholangitis may follow cryptic LCH of the bile ducts.*

Keywords bile duct, Langerhans' cell histiocytosis, liver, sclerosing cholangitis

Langerhans' cell histiocytosis is a monoclonal proliferation of histiocytes similar in phenotype to dendritic Langerhans' cells [1]. The spectrum of disease varies from single bone involvement (eosinophilic granuloma) to a disseminated and sometimes fatal syndrome. Over the past few years it has become clear that Langerhans' cell histiocytosis (LCH) can affect the liver with a propensity for damage to the major bile ducts that results in sclerosing cholangitis and, eventually, biliary cirrhosis. These patients have all had biliary involvement as part of a multifocal LCH with recorded disease in the skin, lymph nodes, and bone and clinical diabetes insipidus [2–7].

We describe a child who was jaundiced at birth and who, in the absence of documented extrahepatic involvement, had a solitary Langerhans' cell lesion found in the extrahepatic bile duct at $2\frac{1}{2}$ years of age.

CASE REPORT

This $2\frac{1}{2}$ -year-old female was the third offspring, born full term at 3700 g to consanguineous Greek parents. She was jaundiced at birth and was re-

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ported to have developed acholic stools. Radionucleotide imaging and exploratory laparotomy with intraoperative cholangiogram, done in Greece at 40 days of age, were reportedly within normal limits. A wedge biopsy of the liver, reviewed here, showed micronodular cirrhosis and a mild, mixed inflammatory cell infiltrate around portal triads. There was marked canalicular and cholangiolar cholestasis with bile plug formation. Occasional ductules surrounding portal areas and along the fibrous septa had dilated and complex profiles reminiscent of a ductal plate malformation. S-100-reactive histiocytes were not identified when stained retroactively. Over the next 2 years her liver function tests remained elevated with maximal values as follows: alkaline phosphatase, 945 IU/L; aspartate aminotransferase (AST), 328 IU/L; alanine aminotransferase (ALT) 253, IU/L, γ -glutamyltransferase, 1089 IU/L; total bilirubin, 9.8 mg/dL. Urine osmolality was normal. She had no skin lesions or lymphadenopathy. She developed hepatosplenomegaly, ascites, and pruritus and underwent orthotopic liver transplantation at $2\frac{1}{2}$ years of age. The explanted liver weighed 724 g and had a nodular surface. The gallbladder and cystic duct were unremarkable. Microscopic examination showed a micronodular biliary cirrhosis with thick collagenous septa separating parenchymal nodules; cholestasis was minimal. Ductal proliferation was variable but generally quite striking and typically associated with a mild lymphocytic infiltrate; only rarely did the ductules assume a convoluted configuration. Most portal areas were densely sclerotic and had several arteries unaccompanied by bile ducts. Interlobular ducts were surrounded by collagenous or cellular concentric fibrosis. The right hepatic duct was segmentally dilated and had a prominent fibrocollagenous wall. A densely cellular infiltrate invaded the thickened wall, focally destroying the epithelium and obliterating the lumen of the left hepatic duct and its first-order branches (Figure 1a). The majority of cells were histiocytes with grooved and folded nuclei and eosinophilic cytoplasm; Birbeck granules were identified by electron microscopy (Figure 1b and c). Antibodies to S-100 and HLA-DR (LN3) stained the histiocytes intensely. The monoclonal antibody O10, which recognizes a formalin-resistant epitope of CD1a [8], marked the same cells. HLA-DR, in addition, highlighted sinusoidal lining cells and some of the large duct epithelium less intimately associated with histiocytes. Lymphocytes, neutrophils, and numerous eosinophils were associated with the histiocytes. Langerhans' cells were not identified in the parenchyma, peripheral triads, or hilar lymph node. Portal vein branches had signs of hypertension including myxoid changes and eccentric myointimal proliferation. The gallbladder had mild chronic changes. Follow-up of $2\frac{1}{2}$ years has not revealed evidence of other overt LCH lesions.

Her family history is significant. The second child in this sibship was a girl, reported to have died in the neonatal period of "liver failure." A

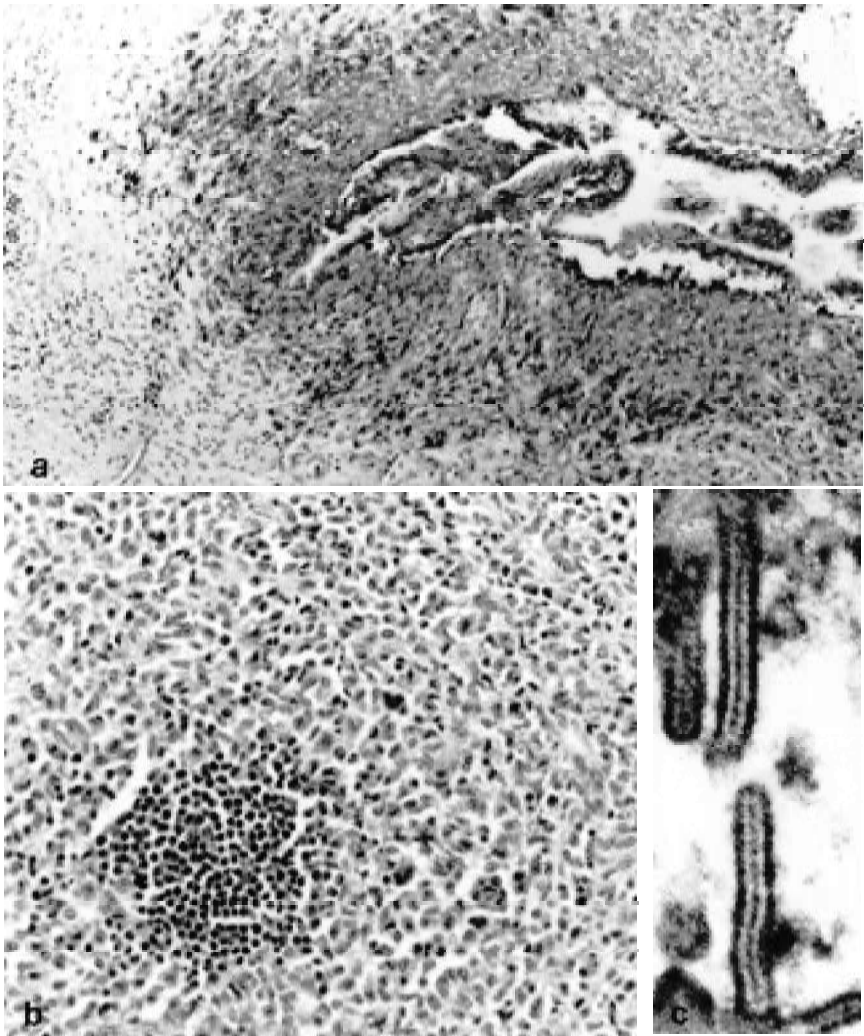


Figure 1. (a) CD1a strongly stains the cellular infiltrate that surrounds the bile duct and destroys epithelium. DAB $\times 100$. (b) The infiltrate has a monomorphous population of cytoplasm-rich histiocytes that have grooved and folded nuclei. A cluster of eosinophils is at the center. H&E, $\times 400$. (c) Ultrastructural examination of the infiltrating cells demonstrates Birbeck granules in the cytoplasm. Electron microscopy, $\times 21,500$.

10-year-old brother, ill from chronic liver failure with portal hypertension and jaundice, had a liver transplant at our institution several months prior to his sister. His native liver weighed 1025 g. It was cirrhotic and bile stained with ectatic hilar portal vein branches. The extrahepatic ducts were dilated and focally collapsed so that their walls formed papillary projections into the lumen. There was diffuse hepatocanalicular cholestasis and marked ductular

proliferation. Many neocholangioles had bile plugs and were surrounded by neutrophils, and occasional ducts had complex, irregular profiles. Most portal triads were sclerotic and without ducts; several had prominent arteries and thick-walled veins. The parenchyma had pseudoglandular transformation, focally prominent Mallory's hyaline, and pigmented Kupffer cells lining sinusoids. A 2.0-cm regenerative nodule was present in the right lobe. The features in his liver were complex and perhaps best classified as Caroli's syndrome, that is, ductal plate malformation of the congenital hepatic fibrosis type with extrahepatic biliary involvement [9]. Langerhans' cells were not evident in the organ or elsewhere in the child, although the clinical data were likewise limited and a wedge biopsy performed during infancy was not available for review.

DISCUSSION

We report a case of LCH in a $2\frac{1}{2}$ -year-old Greek girl who underwent liver transplantation for progressive jaundice and portal hypertension. The explanted liver had biliary cirrhosis with sclerosing cholangitis and a Langerhans' cell lesion confined to the extrahepatic duct. Scattered S-100-positive dendritic cells in the portal triads are not unique to LCH, although sheets and large clusters probably are [10]. Only the demonstration of Birbeck granules or surface CD1a antigen, both demonstrated in this case, fulfills the requirement for a definitive diagnosis of LCH [11].

Single-system disease, other than skin or bone, is unusual in an infant. In fact, hepatic involvement in LCH seems to occur only in patients with multifocal or disseminated disease [12]. The diagnosis of multisystem organ involvement was not actively pursued in this patient after transplantation; a skeletal survey, water deprivation test, and urinary vasopressin levels were not performed. Although signs of diabetes insipidus were not evident, hypothalamic-pituitary involvement cannot be totally excluded [13]. Clinical information prior to admission to our institution was limited. Routine pre- and posttransplantation treatment, however, provided the following data: normal chest and abdominal radiographs, normal abdominal ultrasound examination, no lymphadenopathy, normal urine osmolality. There was no history of skin lesions, pulmonary disease, bone pain, exophthalmos, polyuria, polydypsia, or aural discharge. From the available information, this case appears to represent LCH confined to the extrahepatic bile duct.

When LCH involves the liver, patients may show no dysfunction or present with hepatosplenomegaly, jaundice, portal hypertension, or abnormal liver function tests, particularly hypoalbuminemia. Pathologic features include histiocytic infiltration and proliferation in portal and sinusoidal

regions with variable degrees of cholestasis and ductular proliferation, resulting in triaditis and fibrosis and often terminating as biliary cirrhosis [3, 12, 14, 15]. Circumscribed lesions resembling eosinophilic granuloma are unusual and percutaneous needle biopsies may be nondiagnostic [15]. This may be due in part to the preferential involvement of large-caliber bile ducts that are not represented on a needle biopsy.

Infiltration of large bile ducts by histiocytes is one cause of obstructive biliary cirrhosis in LCH [2, 4, 5, 12]. Cholangiograms in these patients have demonstrated changes of sclerosing cholangitis including irregular duct walls, filling defects, strictures, and dilatations of the extra and intrahepatic biliary tree.

Two and one-half years after transplantation, our patient is without evidence of LCH or sclerosing cholangitis in the allograft. She continues to receive Tacrolimus (FK506) immunosuppression. Orthotopic liver transplantation has been successful treatment for children with severe liver disease complicating LCH [16–22]. Recurrent disease in the allograft has not been reported.

The immunosuppressive agents used after transplantation may be helpful in preventing the return of disease by inhibiting the cellular immune response and cytokine-mediated cellular activation implicated in the pathogenesis of LCH. Cyclosporin A (CSA) has been tried as alternative treatment for LCH [23]. Tacrolimus, with corresponding but more potent action than CSA [24], has been used successfully in the treatment of a variety of autoimmune diseases [25–27] and should have similar immunomodulatory effects on LCH when used in the posttransplantation setting. However, in addition to preventing rejection and hepatic relapse, immunosuppression in this patient (and her brother) may have thwarted other unidentified LCH lesions.

The familial component of the liver disease is enigmatic. Pre- or postmortem examination was not performed on the sister of this patient, who was reported to have died in infancy from “liver failure.” The brother’s liver had features of Caroli’s syndrome, prompting a search for fibrocystic disease in other organs. A renal ultrasound examination identified solitary, 1.0-cm cysts in both the right and left kidneys. Chromosomal linkage analysis for the ARPKD gene [28, 29] was performed in this family and was noninformative.

The relationship of LCH and liver disease in our patient is intriguing and suggests several explanations. First, Langerhans’ cell histiocytosis of the bile duct is etiological, resulting in liver disease that is manifest in these siblings at different stages. Both children presented with jaundice at birth, suggesting a fetal onset. Histopathology of the liver originating with the fetal type of biliary atresia, viewed many years after a successful Kasai procedure, can resemble congenital hepatic fibrosis [30]. The ductal plate malformation is a consequence of damage to an immature biliary tree. These observations

influenced Desmet's [30] suggestion that congenital hepatic fibrosis may represent an "arrested biliary atresia"; when early-onset obstruction is alleviated and the child allowed to grow, a ductal plate malformation, not biliary atresia, results. The livers from both siblings had characteristics of congenital hepatic fibrosis and sclerosing cholangitis. Hypothetically, LCH originated in utero; as the lesions matured (self-limited), Langerhans' cells disappeared and the ensuing fibrosis progressed to cirrhosis.

Second, a Langerhans' cell granuloma in our patient may be an incidental finding and unrelated to the pathogenesis of the as yet undefined and probably familial liver disease. The chance simultaneous occurrence of two unusual entities seems unlikely.

Most plausible is that LCH is "secondary" or "reactive," suggested by the timing and unifocal involvement. The association of LCH with malignant neoplasms is a rare but well-recognized event most frequently reported as concurrent lymphoma or lung carcinoma in the case of solid tumors [31–34]. LCH in these cases differs from "primary" LCH in its clinical presentation and has been considered by various authors as an incidental finding, a localized reactive phenomenon, or, when therapy can be excluded from the association, as part of a generalized immune derangement.

Lymphokines and proinflammatory cytokines acting as autocrine and/or paracrine growth factors have been implicated in the pathogenesis of LCH and may account for the intermingling of two processes. The pattern of cytokines detected in LCH lesions is consistent with local activation of T lymphocytes and other inflammatory leukocytes [35]. A presently unrecognized stimulus, but perhaps a virus, may be responsible for the activation, leading to both cytokine production and aberrant cellular adhesion molecule expression, a recently hypothesized mechanism for the abnormal homing of LCH cells [36]. A similar mechanism may unite our patient's sclerosing cholangitis and LCH.

Sclerosing cholangitis in children is associated with underlying diseases in 75%–80% of the cases; the remainder are considered idiopathic [21, 37]. Various etiologies including inflammatory bowel disease, autoimmune hepatitis, and immunodeficiency states are implicated. Sclerosing cholangitis following liver involvement as part of disseminated LCH accounts for 15%–25% of the cases. Whether the LCH in our patient was primary or secondary, this case uniquely suggests that LCH can affect the extrahepatic bile ducts in isolation. In some instances, idiopathic sclerosing cholangitis may be late, hence undiagnosable, LCH. Early diagnosis is important because the biliary disease is refractory to therapy.

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