

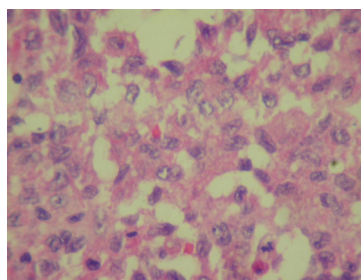
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## Photoclinic

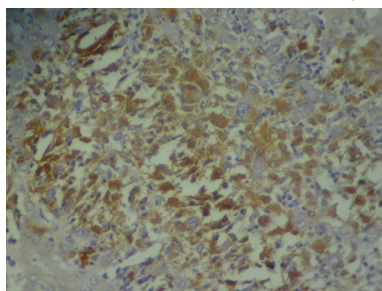
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**Figure 1.** CT scan of the liver with multiple lesions



**Figure 2.** Neoplastic cells with coffee-bean shaped nuclei and a mixture of inflammatory cells, which are predominantly eosinophils (H&E, x400)



**Figure 3.** Tumor cells showed a positive reaction for S-100 protein

A 37-year-old man presented with symptoms presumably related to peptic ulcer disease. Further workup, however, including ultrasonography and CT scan, demonstrated multiple hepatic nodules (Figure 1). His past medical and drug histories were both unremarkable. Most of the routine laboratory tests proved to be normal, except for a WBC count of 14200 cell/ $\mu$ L and a serum alkaline phosphatase level of 760 U/L (normal range in adults: 40 – 140 U/L).

A presumptive diagnosis of multiple liver metastases was made, leading to an exploratory laparotomy in order to better explore the lesions hilar nodes. The liver lobes harbored multiple nodules. Upon closer inspection, the remaining organs were free of any tumor involvement.

Notably, however, the hepatic hilar lymph nodes were enlarged. Consequently two samples,

namely a wedge biopsy from the left liver lobe that had a vaguely nodular appearance on incision as well as two lymph nodes from the hilar region, were taken and sent to the surgical pathology department.

Microscopically the neoplasm contained cells that had a pink cytoplasm, coffee-bean shaped nuclei and indiscernible nucleoli admixed with a number of inflammatory cells, among which eosinophils were conspicuous (Figure 2). The excised lymph nodes also revealed focal involvement by the aforementioned picture. To further confirm the histopathological diagnosis, a panel of immunohistochemical (IHC) markers was requested. Neoplastic cells showed a positive reaction for S-100 protein (Figure 3) and CD1a, but were negative for factor VIII-associated antigen.

After ten days of hospitalization the patient was discharged in good clinical condition. He was then referred to the medical oncologists for chemotherapy.

### What is Your Diagnosis?

See the pages 168 – 169 for the diagnosis

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Langerhans' cells are regarded as a distinct type of immune "accessory" cells that are involved in the capturing of certain antigens and their presentation to lymphoid cells. Contrary to a formerly held belief, these cells are not primarily phagocytic in nature.

The term Letterer-Siwe's disease was used in the past for the systemic form occurring in infants, and Hand-Schüller-Christian's disease for the less widespread and more indolent type seen in older children and adults. A self-healing congenital form is known as Hashimoto-Pritzker's disease.<sup>1</sup>

Langerhans' cell histiocytosis (LCH) primarily affects bones; but lung, skin and lymph node involvement is not uncommon. Hepatic involvement on the other hand, is rare. Kaplan et al. from the AFIP reported nine cases of hepatobiliary LCH, ranging from 7 days to 62 years of age, six of whom were female. Their most common clinical presentations included hepatosplenomegaly, jaundice, liver dysfunction, and ascites. Two of these patients had previously been diagnosed with LCH involving other organ systems. Gross findings include tumor-like masses, visible cysts or even biliary cirrhosis depending on the stage of the disease.<sup>2</sup> The histopathological picture consists of either portal or parenchymal nodules or diffuse infiltration of the sinusoids.<sup>3</sup>

A diagnostic feature is the presence of Langerhans' cells which have an abundant pink cytoplasm, lobulated, coffee-bean shaped or contorted nuclei with a fine chromatin pattern and indiscernible nucleoli. Other types of inflammatory cells and occasional multinucleated giant cells are always seen in the background. Immunostains are useful in confirming the nature of the cells that are decorated by antibodies to the S-100 protein and CD1a.<sup>1</sup> Langerhans' cells are often quite difficult to identify in patients with advanced liver disease. Immunohistochemical staining may aid in their detection.<sup>3</sup>

CD101 is a relatively new marker which can be used in frozen sections. In paraffin sections, both Langerhans' cells and the cells of LCH are reactive for S-100 protein, vimentin, langerin, fascin (a dendritic cell marker), CD1a, CD74, and HLA-DR. in most cases. The most useful of these formalin-resistant epitopes are the S-100 protein and CD1a.<sup>1,4</sup>

By electron microscopy, they contain a highly

characteristic and apparently diagnostic organelle: the Birbeck's or Langerhans' granule. This is an elongated, zipperlike cytoplasmic structure of unknown function which is sometimes continuous with the cell membrane.<sup>1</sup>

Active bile duct injury and destruction is a late finding that gives rise to concentric periductal fibrosis. During childhood the differential diagnosis includes primary sclerosing cholangitis. Therefore, it is recommended that immunostains be performed in pediatric cases diagnosed as primary sclerosing cholangitis in order to exclude LCH.<sup>1,2,5-8</sup> Others believe that Langerhans' cell histiocytosis accounts for 15% to 20% of all sclerosing cholangitis in children and preferentially, but not exclusively, affects the intrahepatic ducts.<sup>3</sup>

Etiologically undetermined, LCH is believed to be a reactive rather than neoplastic disease. William et al., support a clonal proliferative disorder and Kawakubo et al. detected human cytomegalovirus DNA in a number of cases.<sup>6,7</sup>

According to Liberman, patients with LCH have a good overall prognosis.<sup>8</sup> Howarth et al., however, found that 20% of patients with multisystem involvement had a progressive disease course despite treatment. Considerable morbidity and mortality is related to liver involvement by LCH to such an extent that liver transplantation may be considered for advanced cases.<sup>9</sup>

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