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# Solitary Involvement of the Liver: A Rare Manifestation of Langerhans Cell Histiocytosis

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**Patient:** Male, 51-year-old  
**Final Diagnosis:** Langerhans cell histiocytosis  
**Symptoms:** Abdominal pain  
**Medication:** —  
**Clinical Procedure:** —  
**Specialty:** Pathology

**Objective:** Rare disease





**Background:** Langerhans cell histiocytosis (LCH) is a rare condition caused by a neoplastic proliferation of myeloid cells. It can present as a single-system or multi-system disorder. Worse prognosis is associated with the hematopoietic system (spleen, liver, bone marrow), which is routinely observed in multi-system disease. Because of the varied presentation of this disorder, diagnosis can be difficult, and therefore suitable treatment can be delayed.

**Case Report:** We report a case of hepatic LCH in a 51-year-old man who presented with epigastric abdominal pain, with imaging demonstrating a hepatic nodule. A low ejection fraction on hepatobiliary iminodiacetic acid scan suggested chronic cholecystitis. Therefore, the patient underwent a cholecystectomy for biliary dyskinesia, in which liver nodules were noted, and biopsies were taken. The biopsies demonstrated characteristic findings of LCH along with positive immunohistochemical markers and negative BRAF V600E mutation. Radiologic and pathologic findings were consistent with LCH within the liver, associated with bile duct injury and mild biliary obstruction. The patient was placed on a cladribine regimen. His abdominal pain improved.

**Conclusions:** LCH limited to the liver is uncommon and can appear as chronic biliary disease, as was suspected in this case. Despite the poor prognosis of hematopoietic LCH, early recognition can lead to better outcome and chemotherapy susceptibility. This patient was most likely in the first stage of liver LCH, given his presentation, which could have aided his response to chemotherapy. The lack of BRAF V600E mutation could have contributed to a positive prognosis and more possibilities for treatment.

**Keywords:** Abdominal Pain • Biliary Dyskinesia • Histiocytosis, Langerhans-Cell • Liver Neoplasms

**Full-text PDF:** <https://www.amjcaserep.com/abstract/index/idArt/937628>

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## Background

Langerhans cell histiocytosis (LCH) is a rare condition caused by a neoplastic proliferation of myeloid cells [1]. LCH occurs at a rate of 4 to 5 per million in children and 1 to 2 per million in adults [2-4]. It can present as a single-system or multi-system disorder [1]. Involvement of bone or skin is most common [3], but the lungs and central nervous system can also be affected [1]. Worse prognosis is associated with involvement of the hematopoietic system (spleen, liver, and bone marrow), which is routinely observed in multi-system disease [1]. Because of the varied presentation of this disorder, diagnosis can be difficult, and therefore suitable treatment can be delayed. Here, we report a unique case of a 51-year-old man with LCH in the liver, initially misdiagnosed as biliary dyskinesia. To the best of our knowledge, this case may be the fourth adult case of isolated LCH in the liver [5-7].

## Case Report

A 51-year-old man with a past medical history significant for irritable bowel syndrome diagnosed 9 years ago and a history of nephrolithiasis presented to the Emergency Department with colicky, cramping epigastric abdominal pain for the past 3 months. The pain was continuous, and the patient rated it as moderate and severe. It radiated to the right side and to the back, bilaterally. He had lost 13.6 kg during this period. The pain was aggravated by food and activity and was relieved while lying flat and with hydrocodone-acetaminophen tablets.

This acute right upper quadrant abdominal pain appeared to be different and unrelated to his prior history of long-standing irritable bowel syndrome, which had consisted of intermittent constipation and diarrhea. He was then initially treated for peptic ulcer disease; however, the pain did not improve. The patient also used alcohol occasionally and denied tobacco use.

On physical examination, the abdomen was soft, with moderate abdominal tenderness around the epigastric and umbilical areas. There were no palpable masses, abdominal distention, or Murphy's sign. The patient's vital signs were within normal limits.

His laboratory test results were significant for an elevated white blood count of 15.5 K/uL and a platelet count of 452 K/ $\mu$ L, with a hemoglobin level in the reference range, at 14.9 g/dL. His liver enzymes were elevated, with an aspartate aminotransferase level of 40 U/L, alanine transaminase level of 70 U/L, alkaline phosphatase level of 543 U/L, and total bilirubin level of 0.5 mg/dL. The lipase level was within the reference range, at 61 U/L.

The patient underwent colonoscopy and upper endoscopy, which did not demonstrate any abnormalities. Magnetic resonance imaging, right upper quadrant ultrasound, and magnetic resonance cholangiopancreatography (MRCP; **Figure 1**) without contrast all showed hepatic complex cysts. Abdominal computer tomography with contrast demonstrated a nodule in segment 7, measuring 2.3×2.8 cm, with a density of 3 Hounsfield units (**Figure 2**). Nuclear medicine hepatobiliary iminodiacetic

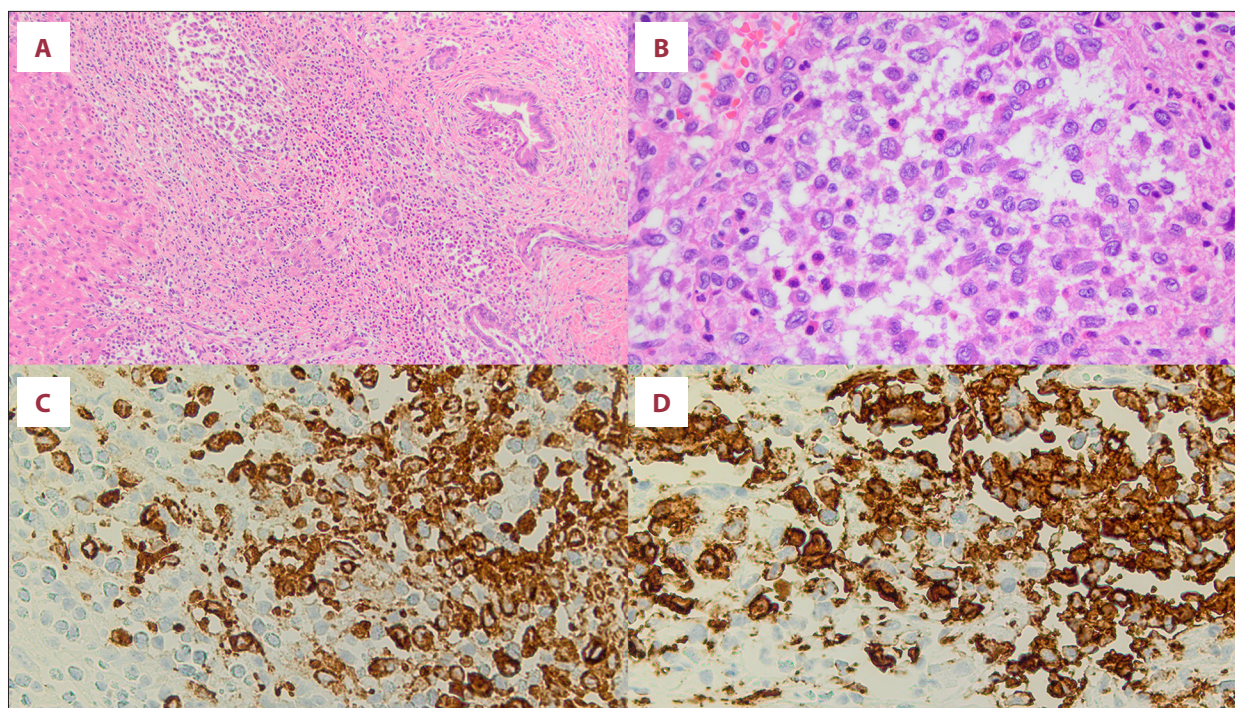


**Figure 1.** Magnetic resonance cholangiopancreatography shows multiple well-defined hepatic T2 hyperintensities, largest in the posterior right hepatic lobe, measuring 2.3 cm (arrow).



**Figure 2.** Abdominal computed tomography shows multiple scattered small liver lesions, with the largest in segment 7, measuring 2.8 cm in greatest diameter (arrow).



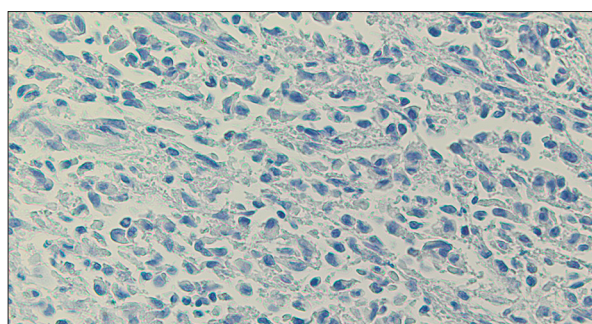


**Figure 3.** (A, 10× magnification; B, 40× magnification) Hematoxylin and eosin-stained slides show portal tract infiltration by a medium-sized cell population of mononuclear cells, characterized by the presence of cleared reniform nuclei, dispersed chromatin, scant, pale eosinophilic cytoplasm, and indistinct nucleoli. A mixed inflammatory cell infiltrate composed of lymphocytes, plasma cells, histiocytes, and numerous eosinophils are present. (C and D, 40× magnification) The lesional cells are positive for CD1a and Langerin immunohistochemical stains, respectively.

acid scan with cholecystokinin was significant for a low ejection fraction of 5%, suggesting chronic cholecystitis.

Given the findings of the hepatobiliary iminodiacetic acid scan, a diagnosis of biliary dyskinesia was given, and the patient was referred to surgery. The patient underwent a cholecystectomy, in which liver nodules were noted, and biopsies were taken. Despite the cholecystectomy, the patient's symptoms continued to worsen, so he was referred to a gastroenterology specialist. The specialist reviewed the recent MRCP and suspected primary sclerosing cholangitis (PSC), owing to segmental dilation of the left hepatic duct. A porphyria workup was negative, including levels of porphobilinogen of 0.2  $\mu\text{mol/L}$  and total plasma porphyrin of  $<0.1 \text{ mcg/dL}$ , which were within the reference range.

The liver biopsy results showed proliferations of oval-shaped cells with grooved (ie, indented) nuclei with a prominent eosinophilic infiltrate (Figure 3). The cells were centered in the interlobular ducts, which is associated with bile duct injury and ductular proliferation. The lesional cells were positive for CD1a and Langerin staining, confirming LCH (Figure 3). The lesion was negative for KIT and CD25. Additional staining included PAS-D, iron, trichrome, rhodanine, and CK7. The PAS-D staining was negative for intracytoplasmic hyaline globules within hepatocytes. The iron staining highlighted a minimal (1+) iron



**Figure 4.** BRAF V600E immunohistochemical stain is negative in the lesional cells. 40× magnification.

deposition in Kupffer cells and portal macrophages. The trichrome staining demonstrated increased fibrosis. The rhodanine stained rare periportal hepatocytes, with equivocal staining for copper accumulation. The CK7 staining revealed mild bile duct proliferation. The BRAF V600E immunostaining was negative (Figure 4). A fluorodeoxyglucose (FDG)-positron emission tomography scan revealed heterogeneous increased FDG uptake throughout the liver, with increased FDG uptake in the periportal lymph nodes. The bone marrow biopsy did not show LCH or another hematopoietic malignancy. The radiologic and pathologic findings were consistent with LCH within the liver, associated with bile duct injury and mild biliary obstruction.

The patient was placed on a cladribine regimen because he had persistent pain after the cholecystectomy. He completed 6 cycles of cladribine 5 mg/m<sup>2</sup>. On imaging, his liver remained stable, with improved adenopathy. His alkaline phosphatase levels normalized soon after his first few doses. His right upper quadrant abdominal pain improved.

## Discussion

LCH is manifested by a clonal neoplastic proliferation of myeloid precursors [1]. Diagnostic cell markers of LCH include CD1a, CD207 (Langerin), and S100 [1]. Microscopically, LCH is characterized by non-branching, round- to oval-shaped nuclei with a nuclear groove that imparts a coffee-bean appearance and a moderate amount of pale cytoplasm [1]. A mixed inflammatory cell infiltrate composed of macrophages, eosinophils, and small lymphocytes is identified [8]. This proliferation develops in small- and medium-sized bile ducts [5]. Birbeck granules can be recognized under electron microscopy, but these are not necessary for diagnosis [1].

LCH has a variable presentation, as it can involve multiple organs [1,9]. Vesicles, pustules, jaundice, hepatomegaly, splenomegaly, and lymphadenopathy are just a few of the many symptoms that can be found [9]. There are 3 clinical versions of LCH [10]. Eosinophilic granuloma is typically present in bones [10]. Hand-Schuller-Christian disease is a chronic, disseminated form of LCH found in children 1 to 5 years old [10], which is characterized by the classic triad of diabetes insipidus, exophthalmos, and bone lesions, typically found in the skull [10]. Letterer-Siwe disease is the acute, disseminated form of LCH, which appears in children less than 2 years old [10].

The hepatic association of LCH specifically constitutes 27% of LCH cases, of which, 87% of cases of LCH with liver findings also have multi-organ involvement [5]. Such examples include those with bone lesions [11,12], diabetes insipidus [11,13], lung nodules and cysts [14,15], and skin rashes [16].

Liver LCH develops in 2 stages: histiocytic infiltration and biliary tree sclerosis [5]. The early stage constitutes hepatomegaly, liver nodules, mild cholestasis, and elevated transaminases and is responsive to treatment [5]. The later stage is predominated by chronic fibrosis surrounding bile ducts, with little to no hepatic histiocytic infiltrates [5]. This latter stage can make it difficult to distinguish LCH from PSC and other chronic biliary diseases that are on the differential diagnosis.

PSC can also be a long-term consequence of LCH, as PSC and LCH present with biliary damage, duct proliferation, fibrosis, and mixed inflammation [17]. MRCP and endoscopic retrograde cholangiopancreatography can demonstrate intrahepatic bile

duct narrowing and strictures as well [17]. Therefore, it is important to keep in mind that the obstructive biliary pattern of PSC can appear like hepatic LCH.

This phenomenon was demonstrated with our patient, who had a reduced biliary ejection fraction, segmental dilation of the left hepatic duct, and an elevated alkaline phosphatase level, which was thought to be due to biliary dyskinesia or PSC. He also had bile duct injury, ductular proliferation, and mixed inflammation, which are the histopathological findings of PSC [17].

Our patient had generalized abdominal symptoms that had been occurring for several months until his diagnosis was known, reinforcing how challenging diagnosis can be. In contrast to other cases of disseminated disease [12,13,18], our patient's hepatic symptoms were limited to right upper quadrant abdominal pain, diarrhea, nausea, fatigue, and anorexia, without jaundice or pruritis. Imaging findings can vary from non-specific features to single-organ or multi-organ involvement of hepatic LCH. For instance, our patient had hypodense liver nodules without biliary duct dilation, as was seen in a case with pulmonary and hepatic LCH [14,15].

Our patient was most likely in the first stage of liver LCH, as this stage presents with liver nodules, mild cholestasis, and elevated liver enzymes [5]. Langerhans cells with prominent eosinophils are indicative of the early stage of liver LCH [12,16] and were also viewed in our patient. Despite liver LCH being associated with poor prognosis [5], the patient's diagnosis of liver LCH in its acute stage could have contributed to his positive response to chemotherapy [5]. Also, although liver LCH in multi-system disease has a reputation of poor prognosis [1], a previous study discovered no difference in the 5-year survival rate between individuals with multi-system disease, with and without lung or liver involvement [19]. This finding indicates that the diagnostic timeline of hepatic LCH can affect prognosis.

A BRAF V600E mutation is a common somatic mutation in the RAS-ERK pathway of LCH [9], which has been associated with permanent neurological damage and increased resistance to the first-line therapy, vinblastine and corticosteroids [20]. Because our patient was negative for a BRAF V600E mutation, he may have had a better prognosis, which is possibly why he was given second-line therapy cladribine [21]. BRAF V600E mutations have also been more prevalent in multi-system LCH [22], which is consistent with our single-organ presentation. Our patient's liver biopsy results revealed a p.N486\_P490del in-frame deletion, with a variant allele frequency of 3.6%. This mutation is commonly located in the  $\beta 3$ - $\alpha C$  loop of the kinase domain of the BRAF gene [23] and is the third most prevalent mutation of the MAPK pathway in LCH [24]. The effects of this mutation on kinase activity have yet to be



investigated, but it may act akin to BRAF V600E, which leads to continuous activation of BRAF [23].

The utilization of cladribine may also be useful for the treatment of unifocal gastrointestinal LCH, since vinblastine-prednisone has improved survival in multi-system LCH and high-risk organ involvement [25]. Cladribine has been prescribed in a case of isolated extrahepatic bile duct LCH [26] and in a patient with LCH misdiagnosed as Crohn's disease [21]. The patients in these cases had mild cholestasis and biliary strictures [21], as well as bile duct proliferation and periductal fibrosis [26], leading to a suspicion of PSC. However, their biopsies were immunohistochemically diagnosed to be consistent with LCH, the same as with our patient.

There are currently no standard therapies for adult LCH [23]. Cladribine may also have been used in our patient because BRAF in-frame deletions have been shown to be resistant to BRAF inhibitors, such as vemurafenib [24]. Current studies are looking at whether RAF plus MEK inhibition should be the first treatment [27]. Future studies need to explore these inhibitors in combination with standard chemotherapy [1]. For non-BRAF V600E mutations, clinical trials are still needed to look at MEK inhibition [27]. Further research on other mutations associated with LCH may help elucidate prognosis and treatment regimen specificity.

Because our patient's case was detected during the acute stage of hepatic LCH, follow-up with his treatment and course of disease would contribute to the medical literature by showing how early diagnosis and treatment of isolated hepatic LCH may prevent further progression to sclerosis and multi-system LCH originating in a high-risk organ.

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## Conclusions

LCH limited to the liver is an uncommon entity, as LCH is commonly associated with multi-organ disease. LCH can appear as a chronic biliary disease, but diagnosis is confirmed histologically along with immunohistochemistry. Despite the poor prognosis of hematopoietic LCH, early recognition and diagnosis of LCH in the liver may lead to a better outcome and chemotherapy susceptibility. The lack of a BRAF V600E mutation may contribute to a positive prognosis and more possibilities for treatment. Because there is variability in curing LCH, additional studies should investigate how patients with LCH fare with traditional chemotherapy compared with newer targeted therapies and which mutations these patients have that may cause their response, or lack of response, to the given regimen.

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## Department and Institution Where Work Was Performed

The patient in this case was treated at Altru Health System in Grand Forks, North Dakota, USA.

## Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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