



# Hepatobiliary and Gastrointestinal Involvement in Langerhans Cell Histiocytosis—Spectrum of Three Cases

Thara Pratap<sup>1</sup> Muhammed Jasim Abdul Jalal<sup>2</sup> Rashmi R.<sup>3</sup> Anupama Gopalakrishnabhakthan<sup>4</sup> Vishnu A.K.<sup>1</sup>

<sup>1</sup> Department of Radiology, VPS Lakeshore Hospital, Kochi, Kerala, India

<sup>2</sup> Department of Internal Medicine and Rheumatology, VPS Lakeshore Hospital, Kochi, Kerala, India

<sup>3</sup> Department of Pathology, VPS Lakeshore Hospital, Kochi, Kerala, India

<sup>4</sup> Department of Medical Oncology, VPS Lakeshore Hospital, Kochi, Kerala, India

Address for correspondence Muhammed Jasim Abdul Jalal, MBBS, DNB (Family Medicine), MNAMS, MRCP (UK), MRCP (UK), Department of Internal Medicine and Rheumatology, VPS Lakeshore Hospital, Nettoor. P.O., Maradu, NH 47 Bypass, 682040 Kochi, Kerala, India (e-mail: jasimabduljalal@yahoo.com).

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## Abstract

### Keywords

- ▶ histiocytosis
- ▶ Langerhans cell
- ▶ nodular
- ▶ gastrointestinal
- ▶ alanine aminotransferase

Langerhans cell histiocytosis (LCH) is a rare group of disorder, due to clonal neoplastic proliferation of dendritic cells in the bone marrow expressing a Langerhans cell phenotype.<sup>1</sup> This disease particularly affects the pediatric age group and young adults and often presents with skin rashes, lung infiltrates, and bone lesions. It can also manifest with endocrine dysfunction and hematopoietic disorders. Involvement of gastrointestinal tract is very rare. Herein, we present a spectrum of three cases with gastrointestinal involvement.

## Introduction

The classic Letterer-Siwe, Hand-Schuller-Christian disease and eosinophilic granuloma are no longer recommended. These terminologies were integrated into a single entity Langerhans cell histiocytosis (LCH) by the landmark Research of Lichtenstein in 1953.

LCH is the most common histiocytic disorder. Erdheim-Chester disease and juvenile xanthogranuloma due to dendritic cell proliferation are other rare histiocytosis. Macrophage related and malignant histiocytoses are also described.

LCH is rare with an annual incidence of approximately 2 to 5 per million per year with a peak incidence at 1 to 4 years of

age. It may manifest at any age, with males being affected more frequently than females.<sup>1</sup> In adults, LCH presents at an average age of 32 years.<sup>2</sup>

LCH can involve single or multiple organ systems. Clinical manifestation can range from self-limiting disease to those with fatal outcome. The age at diagnosis and extent of organ involvement are found to have a statistically significant effect on the overall survival rates.

LCH could be of three forms and is classified based on the number of organ systems involved and the extent of lesions in these organs.

1. Unifocal, localized in 70% in the age group of 5 to 15 years.
2. Multifocal, single system in 20% in the age group of 1 to 5 years.

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3. Multifocal, multisystem in 10% mostly below 2 years of age. This is often of the fulminant type.

Single system disease (predominantly bony involvement) accounts for 73% of cases of histiocytosis and 27% had multisystem disease. Liver involvement occurs in 16 to 36% of multi-system LCH in the pediatric population and has been reported rarely in adult.

Multifocal forms of LCH may involve any organ in the body –bone, skin, lungs, posterior pituitary, and lymph nodes and are more frequently involved among children over 5 years and adult patients. Among children younger than 5 years old, the hematopoietic system is more frequently involved; this includes the spleen, lymph nodes, bone marrow, and the liver.<sup>3,4</sup>

Multisystem disease is further subdivided into low-risk and high-risk groups. Low-risk group (approximately 20%) is characterized by the absence of risk organs (liver, lungs, spleen, and hematopoietic system) involvement and they have good prognosis. “High-risk” patients (80%) have at least one risk, organ involved and a high mortality rate. Frequency of liver involvement is known to be high (19–60%) in children and bears a poor prognosis.

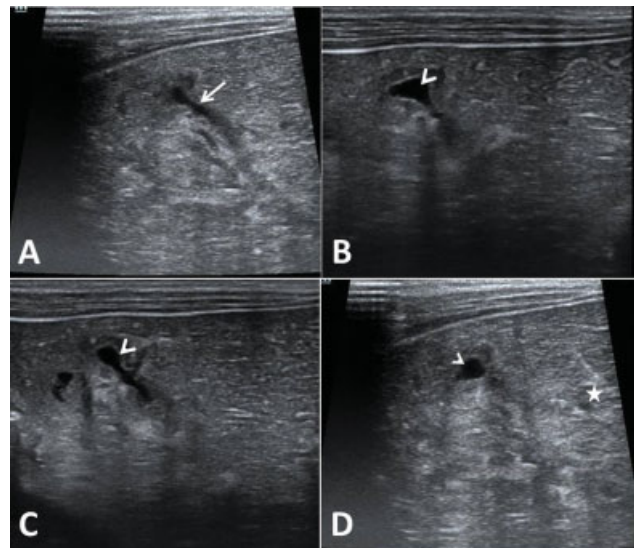
In adults, bone is the most commonly involved organ (80% of cases). Extrasosseous sites most commonly involved are the hypothalamic-pituitary-axis, the skin in 50% of patients and lymph nodes in 10% of patients. Lung involvement is frequent in multisystem disease, however, seen in only 5% of all patients while the liver and spleen involvement are seen in 1% of the patients.<sup>2</sup> Liver involvement is usually seen in the later stage of the disease or is associated with a more fulminant disease process.<sup>5</sup>

### Case 1

A 2-year-old male child was evaluated with abdominal pain of a few weeks duration. There was no associated fever. Liver function tests were altered. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were 253 and 345, respectively (normal value <40 IU/L); serum alkaline phosphatase (SAP) was 1,365 (normal range 44–147 IU/L) and lactate dehydrogenase (LDH) was 443 (normal range 135–210 U/L).

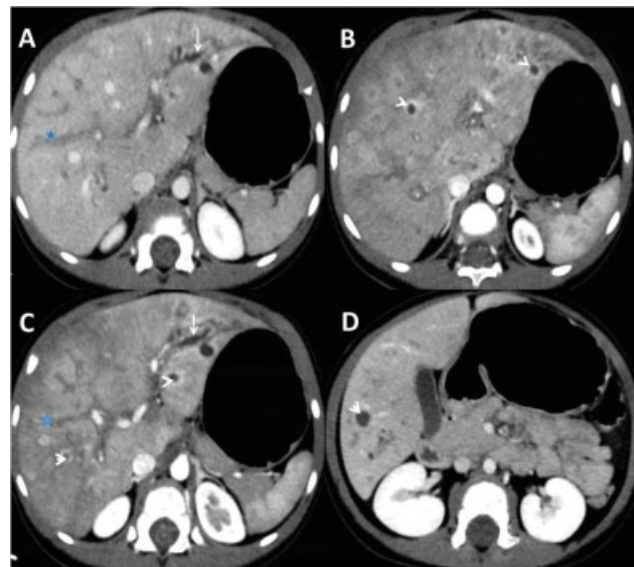
Ultrasound scan of abdomen (►**Fig. 1**) showed hepatomegaly with periportal linear hypoechoic bands with other rounded small hypoechoic areas close to bile ducts. Contrast-enhanced CT abdomen (►**Fig. 2**) showed hepatomegaly, mild IHBRD (arrow) with small scattered cystic lesions (arrowhead) with peripheral enhancement involving both lobes of liver, periportal low density areas (blue asterisk), and altered attenuation of liver parenchyma. This is the early phase of hepatic histiocytosis, proliferative and granulomatous stage with periportal infiltrates and granulomas with cystic changes. Periportal infiltrates were seen at the level of portal vein as linear hypodensities (blue asterisk) along the portal vein with scattered cystic areas (arrowhead). Arrow indicates dilated gall bladder. Below the level of portal vein (D) showing scattered cystic areas (arrowhead). CECT, contrast-enhanced computed tomography; IHBRD, intrahepatic biliary radicle dilatation.

With a provisional diagnosis of multiple intrahepatic abscess MRI liver (►**Fig. 3**) and MRCP was done, which

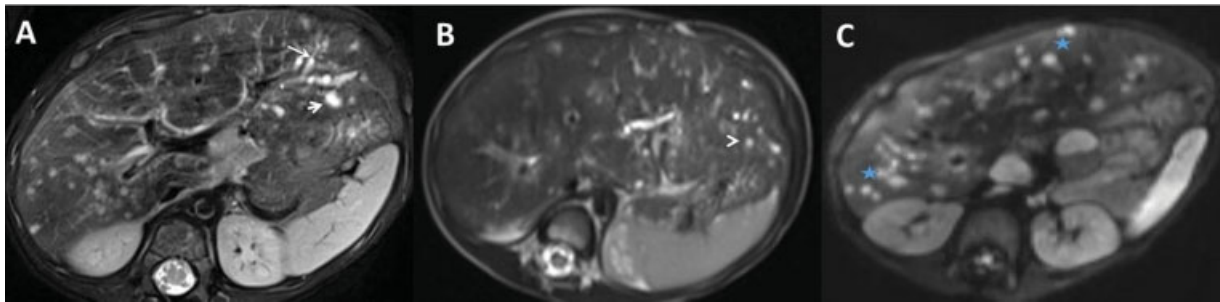


**Fig. 1** High resolution ultrasound of liver: (A) shows diffusely altered echotexture with segmental bile duct wall dilatation with thickening (arrow). Panels (B, C) show segmental bile duct dilatation (arrowhead). Panel (D) shows scattered nodular (star) and cystic areas (arrowhead) in the liver parenchyma with altered parenchymal echotexture.

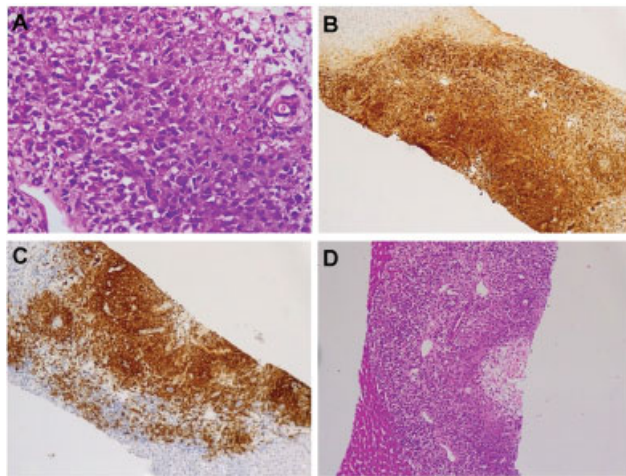
showed enlarged liver, T2 hyperintense, multiple small hypointense lesions with mild peripheral enhancement scattered in the hepatic parenchyma, close to the bile ducts. Some of these lesions show mild diffusion restriction. There



**Fig. 2** CECT abdomen. Axial sections (A, B) showing hepatomegaly, mild IHBRD (arrow) with small scattered cystic lesions (arrowhead) with peripheral enhancement involving both lobes of liver, periportal low density areas (blue asterisk), and altered attenuation of liver parenchyma. This is the early phase of hepatic histiocytosis, proliferative and granulomatous stage with periportal infiltrates and granulomas with cystic areas. At the level of portal vein panel (C) showing periportal infiltrates seen as linear hypodensities (blue asterisk) along the portal vein with scattered cystic areas (arrowhead). Arrow indicates dilated gall bladder. Below the level of portal vein (D) showing scattered cystic areas (arrowhead). CECT, contrast-enhanced computed tomography; IHBRD, intrahepatic biliary radicle dilatation.



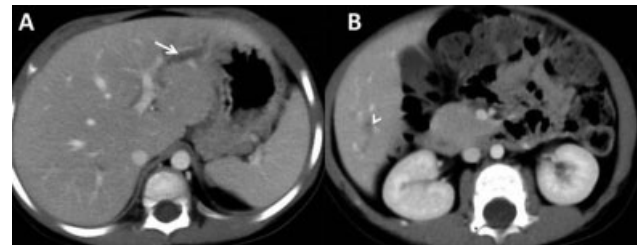
**Fig. 3** MRI T2-weighted fat-sat sequences (A, B) showing segmental biliary dilatation (arrows) with parenchymal nodular and cystic areas (short arrows and arrowhead). Diffusion-weighted sequence (C) showing multiple hyperintense areas (blue star) involving both lobes of liver.



**Fig. 4** (A) H&E stain of liver parenchyma. The histiocytes have ill-defined cytoplasmic borders and elongated nuclei some showing nuclear grooving. Numerous eosinophils were seen admixed with these along with lymphocytes and plasma cells. (B) IHC. The nodular histiocytic aggregates show diffuse strong positivity for s100. (C) IHC. The nodular histiocytic aggregates show diffuse strong positivity for CD1a. (D) H&E. The large histiocytic aggregate showed central edematous stroma admixed with eosinophilic fibrinous material and neutrophils. IHC, immunohistochemistry.

was mild intrahepatic biliary dilatation in both lobes of liver with duct narrowing and intervening nondilated segments giving a beaded appearance. Enlarged periportal nodes were also seen. A diagnosis of infiltrative hepatic disease was considered and trucut biopsy of liver was done.

Microscopy showed single linear core of adequate liver biopsy and large portal tract with large nodular histiocytic aggregates. The largest histiocytic aggregate showed central edematous stroma admixed with eosinophilic fibrinous material and neutrophils (►Fig. 4D). The histiocytes had ill-defined cytoplasmic borders and elongated nuclei some showing nuclear grooving (►Fig. 4A). Numerous eosinophils were seen admixed with these along with lymphocytes and plasma cells. Few other portal tracts also showed small histiocytic aggregates. Hepatocytes were unremarkable. Special stains PAS & PASD were negative for organisms. Reticulin, Trichrome highlighted portal fibrosis with occasional foci of bridging fibrosis. Immunohistochemistry



**Fig. 5** Post treatment CECT shows marked resolution of findings with a few ill-defined residual lesions. Panel (A) shows marked resolution of findings with mild residual biliary dilatation left lobe (arrow). Panel (B) shows an ill-defined area (arrowhead) in segment VI. CECT, contrast-enhanced computed tomography.

showed the nodular histiocytic aggregates positive for CD 1a, S 100 and CD68 confirming LCH (►Fig. 4B and C). Ki 67 index was 30 to 40%.

Bone marrow biopsy was normal. The child was started on induction therapy with vinblastine and steroids. On follow-up, there was good response, with improvement in AST and ALT values of 41 and 31, respectively, with SAP level of 327.

Follow-up CT scan (►Fig. 5) showed reduction in the size and number of hepatic lesions. However, the liver enzymes are slightly altered with persisting periportal fibrosis on follow-up.

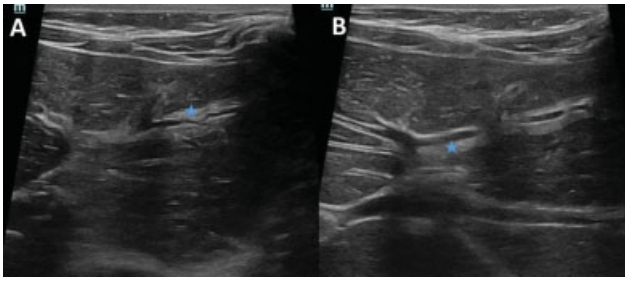
On further follow-up, US abdomen (►Fig. 6) showed coarse echotexture of the liver with hyperechoic periportal bands suggesting fibrosis. The disease progressed to the fibrotic stage following treatment.

## Case 2

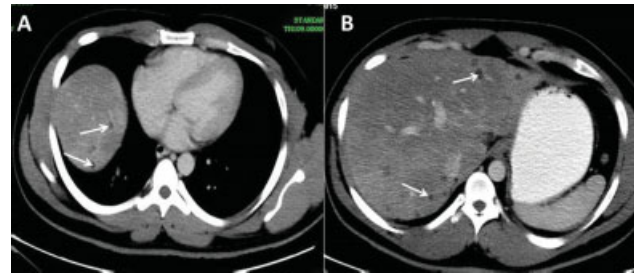
A 2-year-old male child presented with scalp swelling and seborrheic dermatitis with nail involvement. Liver function tests were altered. ALT and AST were 215 and 225, respectively (normal value <40 IU/L); SAP was 1,265 (normal range 44–147 IU/L) and LDH was 285 (normal range 135–210 U/L).

Skeletal survey showed extensive bone disease with involvement of skull, femur, and pelvis. Biopsy from the scalp swelling was suggestive of LCH. His symptoms progressed while on induction treatment and he was started on second line therapy with mercaptopurine and cladribine. He was found to have hyperbilirubinemia, hepatomegaly, and high alkaline phosphatase (1424 IU/L) after





**Fig. 6** On further follow-up, USS (A, B) shows coarse echotexture of the liver with hyperechoic periportal bands suggesting fibrosis (blue star). The disease has progressed to the fibrotic stage in spite of treatment. USS, ultrasound screening.



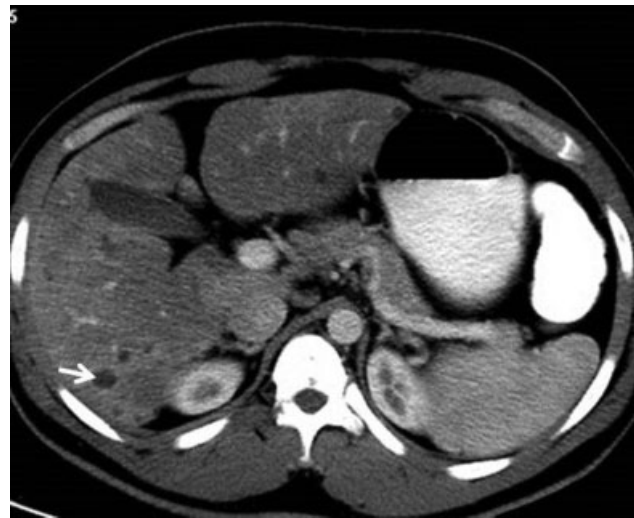
**Fig. 8** CECT shows multiple small hypodense lesions (arrow) in the liver parenchyma involving both lobes (A, B). CECT, contrast-enhanced computed tomography.

6 months of mercaptopurine. Hence, mercaptopurine was stopped considering drug-induced cholestasis and a liver biopsy was planned to differentiate between drug-induced cholestasis and hepatic histiocytosis. Liver biopsy was in favor of drug-induced hepatitis. His liver enzymes continued to be mildly altered and is on follow-up. Ultrasound abdomen (►Fig. 7) showed sclerosing cholangitis with periportal band like echogenicities due to periductal fibrosis along with coarse echotexture of liver and lobulated margins. These imaging findings are indistinguishable from sclerosing cholangitis.

### Case 3

A 29-year-old male presented with abdominal discomfort. Liver function tests were altered. ALT and AST were 219 and 376, respectively (normal value < 40 IU/L); SAP was 1,164 (normal range 44–147 IU/L) LDH was 482 (normal range 135–210 U/L).

Ultrasound abdomen showed multiple liver nodules suggesting possible diagnosis of granulomatous disease or metastasis. CT scan (►Figs. 8 and 9) showed few scattered hypodense lesions of varying sizes in both lobes of liver. The lesions were small and less than 1 cm in size. Evaluation of lung (►Fig. 10) showed few irregular cystic areas in both lower lobes. Trucut biopsy and IHC confirmed the diagnosis of hepatic LCH. The nodule of large/medium cells was positive for CD 20 with admixture by CD 3 positive T cells and showed a  $K_i$  67 proliferation index of



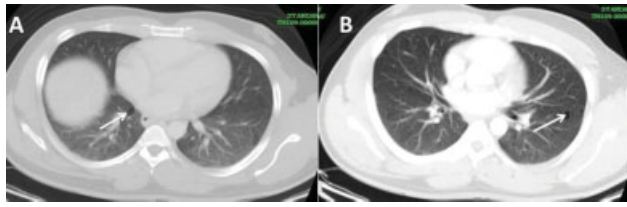
**Fig. 9** Axial CECT at the level of gall bladder showing a few hypodense lesions in segment 6 of liver (arrow). CECT, contrast-enhanced computed tomography.

less than 5%. The cells were negative for CD 68, S 100, and CD 1a. Skeletal survey, bone scan, and bone marrow biopsy were normal. He was started on induction with vinblastine and steroids.

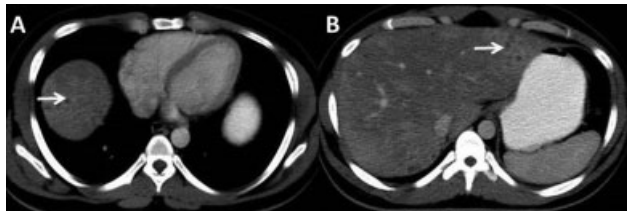
He was stable and follow-up CT scan (►Fig. 11) showed moderate resolution of hepatic nodular lesions initially. On further follow-up with CT scan (►Fig. 12), there was mild to moderate increase in the size and number of hepatic nodular lesions. His liver functions were mildly deranged with ALT of



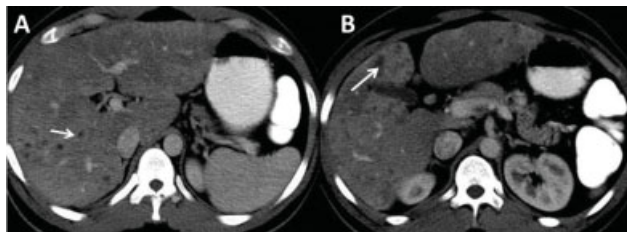
**Fig. 7** Ultrasound shows altered coarse echotexture of liver with architectural distortion, lobulated contour (A) (arrow) with periportal hyperechoic bands (A, B, C) (arrowhead).



**Fig. 10** (A, B) Sections through the lower chest show tiny scattered cystic areas (arrow) both lower lobes involving the lung parenchyma.

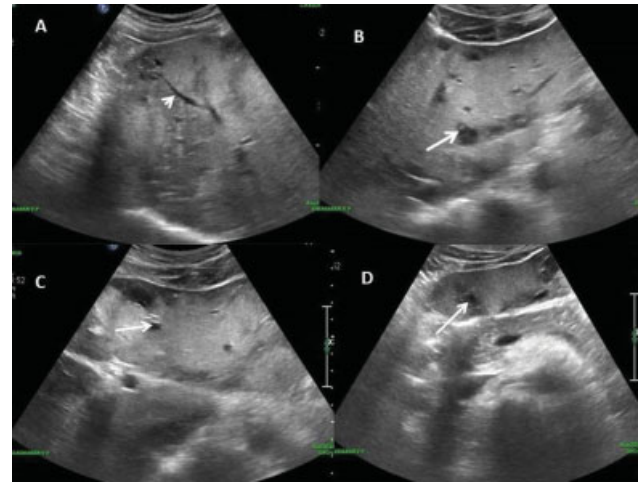


**Fig. 11** Post chemotherapy CECT showing increase in size and number of lesions. The hypodense lesions are marked (arrow) (A, B). CECT, contrast-enhanced computed tomography.



**Fig. 12** Post chemotherapy CECT at the level of left portal vein and gall bladder shows multiple scattered hypodense lesions in both lobes (arrows) (A, B). CECT, contrast-enhanced computed tomography.

103 and AST of 39. Hence, he was started on second line chemotherapy with six mercaptopurine. Ultrasound evaluation on follow-up (→Figs. 13 and 14) showed periportal fibrosis and altered morphology of liver with lobulated con-



**Fig. 14** Follow-up ultrasound 1 month later shows mild increase in the extent of biliary dilatation (arrowhead) (A) with increase in the size of cystic lesions in both lobes as indicated by arrows (B, C, D).

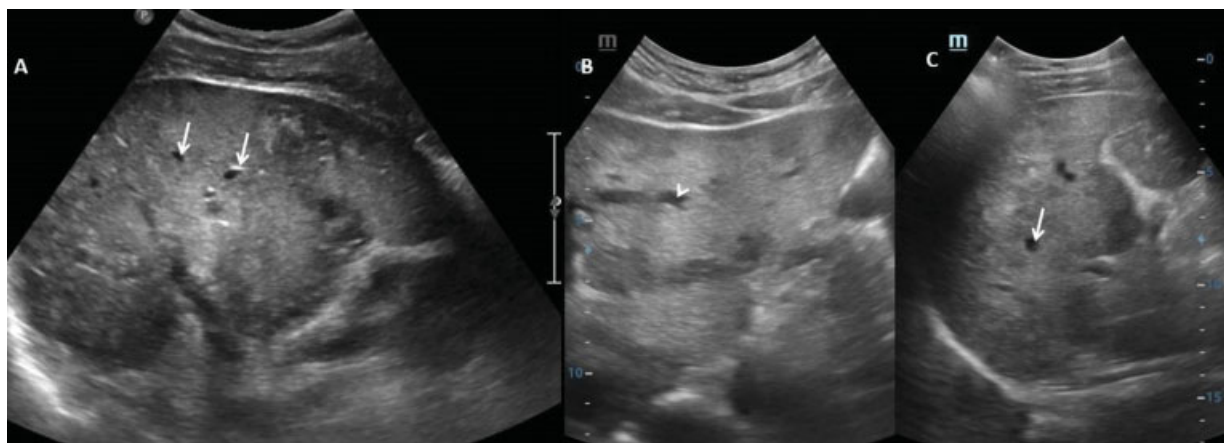
tour along with tree appearance of periportal nodular lesions indicating progression.

### Discussion

In LCH, clonal proliferation and accumulation of dendritic cells occur in various organs. The clinical course and outcome of LCH depend on the patient's age, the distribution, and extension of the lesions, and the degree of organ dysfunction present at the time of initial diagnosis. Gastrointestinal (GI) tract involvement is rare in LCH.

Liver involvement is usually part of multiorgan LCH or can be localized where liver is the sole site of involvement. At times, it could be the first manifestation of LCH as in our first case. The diagnosis may be missed or delayed when liver is the only site of involvement. Liver involvement in LCH drastically changes a patient's prognosis and treatment.

Etiology is thought to be due to immune response to an unknown antigenic stimulation. The cell of origin is closer to



**Fig. 13** Follow-up ultrasound showed altered coarse echotexture of liver with few scattered cysts (arrows) and mild biliary dilatation (arrowhead) (A, B, C).

a myeloid dendritic cell than to an epidermal LCH.<sup>6</sup> Langerhans cells function as antigen presenting cells; they take up soluble antigen, which is then processed into immunogenic peptides that are presented to T lymphocytes so that an immune response may be elicited. In LCH, the classic pathological feature is the inappropriate proliferation of Langerhans cells, which then infiltrate and accumulate in various tissues. Another theory for the disease is neoplastic etiology due to clonal proliferation of Langerhans cells in histology.<sup>7,8</sup>

Patients with hepatic LCH may present with fatigue, pruritus, and jaundice. Hepatomegaly (enlargement of liver 3 cm below costal margin in the midclavicular line), hepatic dysfunction with altered LFT, hypo-proteinemia, hypo-albuminemia not as a result of other causes, imaging findings, or histopathological findings help in diagnosis.<sup>9,10</sup>

Hepatomegaly occurs either due to the direct infiltration of LCH or Kupffer cell hypertrophy and hyperplasia secondary to a generalized immune reaction.<sup>11</sup> Periportal involvement may be seen on imaging sometimes with little or no liver function abnormality.

Liver injury in LCH can be caused by histiocytic infiltration itself predominantly in the periportal region but also due to extrinsic compression of common bile duct by hilar adenopathy, histiocytic infiltration of extrahepatic bile ducts, or rarely by an adverse effect of chemotherapeutic agents used to control the disease.<sup>12</sup>

Histiocytosis can involve the liver either in the early stages or as a late manifestation. Pattern of hepatic involvement varies in histopathology and radiology depending on the stage of disease. In the early stages there is infiltration by histiocytes and in late stages there is periportal hepatic sclerosis.

Engelbreth-Holm et al described the existence of four histological phases of LCH<sup>13</sup>:

1. Proliferative
2. Granulomatous
3. Xanthomatous
4. Fibrous

The first three stages are characterized by infiltration of LC and other inflammatory cells causing periportal proliferative and granulomatous lesions appearing as band-like or nodular areas. The typical clinical pattern of this acute stage is associated with hepatomegaly, liver nodules, minor cholestasis, and raised transaminases.

The fibrous stage is characterized by progression to periductal fibrosis and micronodular biliary cirrhosis resembling sclerosing cholangitis. There will be little, or no liver histiocytic infiltrates and typical clinical picture would be severe cholestasis and liver failure.<sup>13</sup>

On histopathology, diagnostic LCH cells are oval and measure approximately 10 to 15  $\mu$ m. They are recognized by grooved, folded, indented, or lobed nuclei, as well as fine chromatin, inconspicuous nucleoli, and thin nuclear membranes. Nuclear atypia is minimal, but mitotic activity is variable, and can be high without atypical forms. The cytoplasm is moderately abundant, slightly eosinophilic, and devoid of dendritic processes. The characteristic milieu

includes variable number of eosinophils, histiocytes (both multinucleated LCH-type and osteoclastic type cells, especially in bone), neutrophils, and small lymphocytes. Plasma cells are usually sparse. The ultrastructural hallmark is the cytoplasmic Bierbeck granule, which is 200- to 400-nm long and 33-nm wide with a tennis-racket shape and a zipper-like appearance. In immunohistochemistry, LCH cells express CD1a, S-100, langerin (CD207), CD68, and HLA-DR.

LCH cells predominate in early lesions. In late lesions they are decreased in number, with increased foamy macrophages and fibrosis. Due to its patchy distribution, there may be little or no CD1a +, langerin (CD207) + histiocytes in the biopsy. If the liver biopsy is done at a late stage of the disease, the biopsy may show fibrosis only with little or no LC.

In the latter scenario, it would be very difficult to differentiate secondary sclerosing cholangitis associated with LCH from primary sclerosing cholangitis. A "beaded" appearance of extrahepatic biliary tree by imaging may be helpful for the diagnosis of primary sclerosing cholangitis.

It is also difficult to differentiate hepatic Langerhans cell clusters from primary biliary cirrhosis (PBC)-associated granulomas in a small liver biopsy. Lack of usual histological features of PBC, such as dense portal lymphocytic infiltrate and mild degree of interface activity, and AMA negativity might be a clue. In addition, recognizing nuclear grooves of Langerhans cells might be helpful for the diagnosis along with immunohistochemistry.<sup>8</sup>

There can be confusion between Crohn's granuloma and LCH in gastrointestinal tract biopsies. In those cases, immunohistochemistry for LC (S100, CD1a, Langerin) is the clue to diagnosis.

Imaging findings in USS and cross-sectional imaging depend on the stage of the disease and reflect the findings seen on histopathology. In the early stages, US of the liver shows hepatomegaly, periportal hypo-echogenicity seen as band like thickening along the periportal region, with or without multiple hypoechoic nodules (solid or cystic) within the liver parenchyma adjacent to biliary radicles some of which with a target-like appearance. Well-defined hypoechoic periportal lesions are seen in the proliferative and granulomatous phases whereas they evolve to hyperechoic lesions in the xanthomatous phase due to fat. Periportal fibrosis resembling sclerosing cholangitis occur in late stages due to fibrosis with altered hepatic architecture on USS.

Cross-sectional imaging findings can be summarized as hepatomegaly, periportal hypo-attenuation with hypodense nodules, and cystic changes on CT and as nodules with moderate to high signal at T2W1 in early stages on MRI. The nodule of varying sizes can be seen, some show ring enhancement resembling granuloma or metastasis.<sup>14</sup> Periportal contrast enhancement reflects portal triad with active infiltrates.

In xanthomatous phase, lesions are hypodense on CT, hyperintense on T1-weighted images and hypointense on T2-weighted images on MRI. This characteristic feature is due to lipid laden Langerhans cell in xanthomatous phase.<sup>3</sup>

In fibrous phase, CT and MR show features of periductal fibrosis and micronodular biliary cirrhosis which results from



sclerosing cholangitis. Dilation and beading of the biliary ducts, consistent with sclerosing cholangitis, can be seen with conventional cholangiography and MR cholangiopancreatography.

Studies show that liver involvement in LCH in children may be higher than expected. Unexplained hepatomegaly or liver dysfunction causing impaired laboratory parameters may give the initial clue. Hence, clinicians should consider ultrasound screening (USS) for liver involvement in patients with newly diagnosed LCH especially if there is multisystem involvement, significant hepatomegaly or altered liver function tests, so that patients can be treated with systemic chemotherapy earlier to avoid biliary cirrhosis. If the findings are indeterminate on USS, cross sectional imaging can be done as the different imaging modalities would be complementary and yield more diagnostic information.<sup>14</sup> The ideal treatment of liver LCH remains controversial and in advanced cases liver transplantation has been reported as a treatment for end-stage hepatic involvement predominantly in children.<sup>8</sup>

LCH involvement of the gastrointestinal tract—small and large bowel is very rare, and it occurs in approximately 2% of systemic LCH.<sup>10</sup>

It is more common in children and males compared with adults and female. It peaks under the age of 2 years. The presentation and severity of gastrointestinal LCH are greatly different in pediatric and adult age groups.

LCH in the pediatric population classically presents with symptoms including diarrhea or bloody stools, failure to thrive, abdominal pain, protein losing enteropathy, and vomiting whereas in adults it presents as an incidental polyp found on colonoscopy in asymptomatic individuals or patients being evaluated for other reasons. Up to 50% of adult patients are asymptomatic, and usually without multisystem involvement.<sup>15,16</sup> According to Geissmann et al, GI involvement is always associated with multisystem disease together with mucosal and cutaneous LCH.<sup>17</sup> In 85% of patients, GI symptoms are preceded by skin rash. Few cases of isolated GI disease have been reported and these cases are more common in adults.

In the GI tract, usually the colorectum and small intestine are involved and in some cases stomach is also involved. Isolated polyp or erosions are the usual finding in stomach. In small bowel LCH affects most commonly the terminal ileum causing malabsorption and protein losing enteropathy. In some patients, disease may be limited to colon.<sup>18</sup> Endoscopy and biopsy are the gold standard for diagnosis.

The radiological findings are usually nonspecific with minimal bowel wall thickening due to histiocytic infiltration and erosions and is generally indistinguishable from inflammatory, infectious, or ischemic bowel diseases.

On small bowel contrast study, LCH involvement is characterized by the loss of typical mucosal pattern, cobblestone appearance segmental luminal narrowing generally indistinguishable from nonspecific enteropathies, and inflammatory bowel diseases. On intravenous contrast-enhanced CT, diffuse marked circumferential wall thickening of the small bowel or colonic segments with mucosal contrast enhance-

ment, mural stratification, and surrounding fat stranding can be demonstrated. Enlarged mesenteric or other lymph nodes are not a particular association.

After initiating induction treatment, monitoring of the disease can be done with CT, MRI, or positron emission tomography-computed tomography (PET-CT). PET-CT is able to detect the foci of metabolically active LCH (especially in lung, skull, extremities) to instruct therapy and to predict prognosis.

Following treatment clinical improvement equates with gradual reappearance of normal mucosal pattern. Although GI involvement is not a criterion for poor prognosis, reports show that more than half of the patients die within 1.5 years of diagnosis.<sup>19</sup> Gastrointestinal tract involvement has dismal prognosis and should be aggressively treated.

Treatment strategy for LCH varies depending on the degree of organ involvement and clinical course. Induction is usually with vinblastine and steroids. In cases of treatment failure cytarabine, cladribine, or 6 mercaptopurine is started followed by maintenance dose. Radiotherapy is reserved for single or limited bony lesion which is either inoperable or requires extensive surgery. The prognosis of patients with hepatic LCH is worse than those with non-hepatic LCH, with a fatality rate of 30 versus 10%. Early-stage disease with either nodules or hepatomegaly due to histiocytic infiltration responds well to chemotherapy. However, late-stage disease with sclerosing cholangitis like features is difficult to treat. In patients with advanced liver involvement, liver transplantation is a curative option.<sup>20</sup>

## Conclusion

LCH is a rare group of disease with wide spectrum of imaging features and clinical manifestation and hepatic involvement is a poor prognostic factor. LCH lacks pathognomonic, clinical, or radiographic characteristics. A definitive diagnosis should be based on a histological and immunohistochemical examination of biopsy specimens.

Recognition of liver involvement is important for early diagnosis and is crucial for patient management and such patients should be treated with systemic chemotherapy earlier<sup>14</sup> to prevent periductal fibrosis and biliary cirrhosis.

Radiology plays an important role in diagnosis and follow-up. Familiarity with the imaging appearance of hepatic LCH will facilitate the inclusion of this rare entity in the differential diagnosis.

Among children with LCH especially in those with multisystem disease, liver involvement is relatively frequent, even though it is often overlooked. Hence clinical and biochemical liver evaluation and abdominal imaging must be performed regularly to screen every LCH patient from the time of the initial diagnosis.

The ideal treatment of liver LCH remains controversial and in advanced cases liver transplantation is the sole option.

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None.

**Conflict of Interest**

None declared.

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