Outcomes of Liver transplantation in children with Langerhans Cell Histiocytosis: Experience from a quaternary care centre and an algorithmic approach

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Abstract

Objective : Spectrum of hepatic presentation in Langerhans cell histiocytosis (LCH) varies from asymptomatic hepatomegaly to secondary sclerosing cholangitis leading to cirrhosis with or without decompensation. Conventional chemotherapy may be counterproductive in a patient with LCH and hepatic decompensation. We analysed the outcomes of our patients with hepatic presentation of LCH, including their post liver transplant (LT) follow up. Methods: A retrospective analysis was performed on patients with hepatic presentation of LCH referred to our unit. Their clinical profile, chemotherapy protocol, details of LT and survival were analysed. A management algorithm based on the outcomes was proposed. Results: Five of 8 patients were male. Median age of diagnosis was 25(9-48) months. 8(100%) patients had portal hypertension with 4(50%) having decompensated cirrhosis. 6 (75%) patients underwent LT of which 2 had acute decompensation and 4 had sclerosing cholangitis with portal hypertension. Of the two remaining patients, 1 did not tolerate chemotherapy and succumbed, whereas 1 patient after first cycle of chemotherapy was lost to follow up. As their liver disease was worsening during chemotherapy (after 8 & 20 weeks of chemotherapy), two patients underwent urgent LT followed by continuation of chemotherapy. After median follow-up of 30.5 (10.5-50) months, all patients were alive with stable graft function and no disease recurrence. Conclusion: As shown in our series, an algorithmic approach to patient and treatment selection for LCH patients with liver involvement combined with newer chemotherapeutic agents and an optimized immunosuppression can result in excellent outcomes for a hitherto unfamiliar disease.

Introduction

Langerhans cell histiocytosis (LCH) is characterised by florid proliferation of histiocytes causing tissue destruction. Commonly described in children of age group 1-5 years, this disease also affects infants and adults.[1,2] The spectrum of hepatic involvement in LCH include hepatomegaly with elevated transaminases, acute liver failure, secondary sclerosing cholangitis from burnt out disease, biliary cirrhosis and end stage liver disease.[3-5] Moreover, liver involvement portends a poorer survival and is classified as high risk disease.[6] Among a large French cohort of 348 patients with LCH, liver involvement was seen in 14.5% children and their 3-year survival was 52% when compared to 97% in those without liver involvement.[7]

Later, an update from the French cohort involving 1478 children with LCH, have reported increased survival of these patients, especially those with risk organ involvement, in the post 1998 era when compared to pre 1998.[8] This improvement is due introduction of newer chemotherapeutic regimen in cases where the conventional drugs were showing poor response.[8]

Precise role of liver transplantation (LT) in the management algorithm of LCH remains unclear as the literature is sparse. LCH associated end stage liver disease is one of the clearer indications for LT.[9] However, the need and outcome of LT for other hepatic manifestations especially in the presence of active disease remains ambiguous. We also present our management algorithm of LCH patients with hepatic manifestations, emphasising the importance of a modified chemotherapeutic protocol and LT in this subset.

Methods

A review of a prospectively collected database of all paediatric liver disease (age less than 18 years) managed for LCH at our unit between January 2014 and December 2020 was performed. Each patient would be discussed in multidisciplinary meet consisting of paediatric hepatologist and paediatric oncologist, prior to initiation of therapy. These patients would be jointly managed by both the teams until completion of treatment. Eight patients were identified with a diagnosis of LCH and hepatic involvement, of whom six subsequently underwent LT. Data with regards to their baseline demography, age of presentation of LCH and diagnosis, type of hepatic involvement, Pediatric end stage liver disease (PELD)score, sites of extrahepatic involvement, modality of diagnosis, chemotherapy protocols, disease remission and survival were analysed. In patients who underwent LT, interval from diagnosis of LCH to LT, the type of LT (living donor or deceased donor), type of liver graft, intra operative or post-operative complications, duration of hospital stay, post LT chemotherapy regimen, immunosuppression protocol and long term survival were analysed. Institute ethical board approval was obtained for performing the current analysis.

Definitions:

LCH was confirmed in all cases with histology by the demonstration of CD1a and / or CD207 immunostaining along with supportive evidence of histiocytic infiltration.[10] Site of LCH involvement were described clinically as skin rash, seborrhoea like lesions of the scalp, chronic otitis for middle ear, nails infiltrates etc. All patients underwent Fluorodeoxyglucose-positron emission tomography(FDG-PET) scans and involvement of various organs (bone, spleen, lung, brain, lymph nodes) were noted by significant uptake of FDG.

Hepatic involvement is defined as per the European Consortium for Histiocytosis as palpable liver 3 cm below the coastal margin confirmed by ultrasound and liver dysfunction is defined by hyperbilirubinemia (at least 3 times the upper limit of normal) hypoalbuminemia (<30g/dl) , alanine transaminase (ALT) and / or aspartate transaminase (AST) (more than 3 times the upper limit of normal), gamma glutamyl transpeptidase (GGT) > 2times normal, ascites, edema, or intra hepatic nodular mass.[10]

Sclerosing cholangitis in LCH was defined either by involvement of extrahepatic/intrahepatic biliary tree with strictures, dilatation, pruning detected on imaging (CT scan or MRI) and / or on liver biopsy with or without elevated gamma glutamyl transpeptidase.[11,12] Portal hypertension was defined as the presence of varices on esophagoduodenoscopy or splenomegaly. An active uptake in FDG-PET scan was used as a marker of disease activity in the extrahepatic sites, whereas an absent uptake would indicate disease remission (passive or burnt out disease).[13]

Management Algorithm:

Patients with LCH and hepatic involvement were divided into 2 categories based on the severity of liver involvement.

Category 1: Patients with clinical, radiological or histological evidence of chronic liver disease or cirrhosis with bilirubin <3 and no signs of decompensation i.e absence of ascites, hepatic encephalopathy (HE), or gastrointestinal bleed.

Category 2: Patients with decompensated liver disease; i.e with ascites, variceal bleed or encephalopathy and bilirubin > 3mg/dl, and /or acute on chronic liver failure ; ACLF (bilirubin > 5 mg/dl with INR >1.5 along with onset of ascites and / or HE within 4 weeks of onset of jaundice).[14,15.]

Category 1 patients were treated with standard chemotherapy regimen for high-risk LCH. whereas category 2 patients who might not tolerate standard chemotherapy regimen were started on modified chemotherapy

regimen (Details provided below). [16,17]

Chemotherapy:

Standard chemotherapy regimen for high-risk LCH as per the LCH IV protocol

Induction phase consists of six weeks with Vinblastine (6mg/m^2) once a week for 6 weeks and Prednisolone (40mg/m^2/day) daily for 4 weeks taper over the next 2 weeks. At the end of 6 weeks FDG-PET scan is done to look for remission. If FDG-PET negative (remission)patient would be started on maintenance therapy. Non-responders would receive another 6 week cycle of the same medication. If still remission not achievable, second-line chemotherapeutic agents were used.

The maintenance phase consists of Vinblastine (6mg/m^2) given once in three weeks along with prednisolone 40mg/m^2/day for 5 days in the same week for one year period.

Modified low dose induction regimen

Modified induction regimen of low dose Cytarabine (100mg/m^2) every 3 weeks along with Prednisolone (40mg/m^2/day) daily for 4 weeks tapered over the next 2 weeks (one cycle consists of 6 weeks).

Maintenance chemotherapy includes continuation of Cytarabine (100mg/m^2) every 3 weeks and prednisolone 40mg/m^2/day for 5 days in the same week for 1 year was instituted if FDG-PET at 6 weeks showed disease remission.

Liver Transplantation: A FDG-PET documented disease remission was always mandatory prior to a LT. LT was offered for acute decompensation or patients with compensated cirrhosis and sclerosing cholangitis with portal hypertension. Patients who did not tolerate the full course of chemotherapy were also considered for a LT during mid-cycle. Where possible, LT was planned to coincide with the completion of chemotherapy. To avoid the systemic effects of chemotherapy, a 2-week weaning off period was given between the last cycle of chemotherapy and LT. Post-LT, chemotherapy was recommenced after 3 weeks.

Immunosuppression: Post LT, all patients were started on steroid and tacrolimus-based immunosuppression targeting a trough levels of 8-10 ng/dL in the first 3-4 weeks post-LT. The levels are then adjusted to target a trough level of 5-6ng/dL once chemotherapy is restarted (usually 3 weeks post-LT). Trough levels at 3-4ng/dL were maintained after an year of transplant. Low dose steroids (1mg for children under 4 years and 2mg for those over 4 years) were continued as per the institute protocol.

Follow up :

A PET scan was done

1) At the end of chemotherapy to confirm disease remission.

2) On follow-up if there is clinical or biochemical suspicion of disease recurrence.

Periodic monitoring of tacrolimus trough levels and of graft function (with LFT and hepatic doppler)was done in the follow up period.

Results :

Of the 8 patients with a diagnosis of LCH, active disease was present in 6, and 2 patients were referred after completion of chemotherapy with cirrhosis and portal hypertension. (Table 1). The median age of onset of symptoms of LCH was 13.5 months (3 to 26 months). The median age of diagnosis was 25 months and the median interval between the onset of symptoms of LCH and its diagnosis was 10 months (1 to 15 months).

The common clinical presentations of LCH included hepatomegaly (100%), scaly lesions of the scalp (75%), skin rash (75%), splenomegaly (75%) and lytic bone lesions (50%). Liver biopsy revealed features of large duct obstructive cholangiopathy with portal fibrous expansion, and bile ductular proliferation without active infiltration by Langerhans cells One patient had Langerhans cells which were positive for CD1a . The median PELD score of patients with active disease was 21 (4 – 31.4) and those with burnt-out disease was 2.2.

The flow of patients is depicted in Figure1. 4 patients each were fitting into Category 1(Patients 1,2,3 and 4) and Category 2 (Patients 5,6,7 and 8) (Table 1) as per the previously mentioned classification. In category 1, patient 1 and 2 who had completed chemotherapy 95 and 183 months prior, presented with compensated cirrhosis and portal hypertension. They underwent FDG-PET screening to make sure there is no active disease and were offered LT. Patient 3 and 4 with active LCH and compensated cirrhosis were started on standard Vinblastine based chemotherapy. They tolerated the chemotherapy and underwent LT after completion course of drug regimen.

All patients in Category 2, i.e Patients 5,6,7 and 8 had active disease. Patient 5 was started on standard Vinblastine based protocol and child had deterioration of his liver function and died of gram negative sepsis. We changed our policy to use low dose Cytarabine instead of Vinblastine, which is less hepatotoxic for category 2 patients. The modified regimen was subsequently started in 3 patients.[18] Of the three patients, one (patient 8) defaulted therapy and was lost to followup. Patient number 6 achieved remission after 1 cycle of induction and patient number 7 achieved remission after 3 cycles of induction therapy. Both underwent liver LT and then completed one year maintenance phase of chemotherapy (Table 1). Hence 2 out of 6 patients underwent chemotherapy in the post LT period.

The median time of LT from time of diagnosis was 28 months (2 – 195 months) for the whole cohort. Median Duration of ICU stay and hospital stay were 4 & 12 days respectively. There were no episodes of vascular, biliary or immunological complications.

The liver explants showed greenish discolouration macroscopically (Figure 3E, 3F) Light microscopy revealed biliary pattern cirrhosis with ulceration in large ducts, biliary sludge and duct loss (Figure 3G, 3H). No significant CD1a or CD 207 positive Langerhans cells were identified in the explants – indicating LCH in remission

Post-LT patient and graft survival was 100% at a median follow-up of 36 months (18 to 80 months). None of the patients had recurrence of LCH in the graft or extrahepatic sites.

Discussion:

Hepatic involvement in LCH is divided into two phases based on histology. The early hepatitis phase is characterised by the active infiltration of hepatic parenchyma by the Langerhans cells, predominantly damaging hepatocytes and initiating fibrosis. The damage is mediated by release of various proinflammatory cytokines released by these cells leading to apoptosis and/or necrosis of hepatocytes.[4] The biopsy shows diffuse infiltration with cells which are CD 207 and CD1a positive. The second phase which may occur despite chemotherapy is a more chronic involvement, occurring as a cholangiolar burnt-out disease.[4] It is characterised by hepatic parenchymal loss with progressive destruction of biliary tree leading to sclerosing cholangitis.[12]This phase has minimal presence of histiocytes and is also observed post-chemotherapy phase. In a large series from Argentina, sclerosing cholangitis was seen in 18% patients with multisystem LCH.[18]LT in LCH is mainly indicated for cirrhosis with decompensation or portal hypertension due to LCH related secondary sclerosing cholangitis. [18, 19]

Among our cohort of 6 patients with LCH who underwent LT, the overall graft and patient survival was 100% after a median follow up of 3 years. In a previous series on LCH related liver disease, 6 patients had underwent LT, with a survival of 67% after a median period of 5.8 years.[19] Two-thirds of their patients suffered from post-transplant lymphoproliferative disorder (PTLD), and 50% required a re-transplantation for acute refractory rejection within 3 months post LT.

In a report from King's College London on LCH, Of the 2 patients who underwent LT with active disease, both had recurrence of LCH in the allograft liver, 5 and 60 months after LT respectively despite post-transplant chemotherapy using vinblastine, etoposide and steroids.[20] In a recent population based analysis of 60 patients undergoing LT for LCH, the overall 1-year survival was 79.4%.[9] Also it was noted that more than 50% patients had active extrahepatic disease at the time of LT and 8% had disease recurrence in the graft over a mean follow up period of 2 years.[9] 50% of the patients had acute rejection and 10% had Post

transplant lymphoproliferative disorder (PTLD). Similar conclusions were drawn by the Whitington group, where 6 post-LT patients had a 5-year survival of 67%, with 33% disease recurrence and PTLD.[19]

None of our patients had recurrence of LCH or PTLD or T/B cell mediated rejections in the post LT period. We start these patients on tacrolimus based immunosupression, with periodic monitoring of trough levels as mentioned before.

Vinblastine which is part of the first line regimen of the LCH IV chemotherapy guidelines may worsen liver dysfunction.[21,22] It is also known to cause increased systemic toxicity including peripheral neuropathy and bone marrow suppression.[23] Thus, in the category 2 subset of patients, choosing the chemotherapeutic agents involves finding a fine balance between disease remission and hepatotoxicity. We used a modified chemotherapeutic protocol where vinblastine was replaced with cytarabine.[17] Two of our patients with decompensated cirrhosis tolerated the drug well and completed the induction course. There is also accumulating literature evidence in this regard. The Japanese LCH 96 guidelines recommend cytarabine along with vincristine and the group from Texas children hospital use a cytarabine based chemotherapy (NCT02670707).[24] Nonetheless, it is noteworthy that there is no unified protocol for treating LCH with liver disease. Many centres treat patients on case-to-case basis. In a recent series from China, of 5 patients who underwent LT the pre-LT chemotherapy regimen was different for each patient.[25]

The timing of LT in patients with LCH has been always a matter of scientific debate. An LT done for a rapidly worsening liver without achieving remission may lead to persistence of the disease post LT or a disease recurrence. In patients with active disease and cirrhosis with decompensation, a delay in LT may result in progressive liver failure.[20] The current available scientific evidence is meagre to recommend a LT during active extrahepatic disease in patients with LCH, and it is a general recommendation that active extrahepatic malignancy is a contraindication for performing a LT. A prior analysis has shown a good outcome when a LT is done following disease remission in patients with LCH.[25] Therefore, it is imperative to confirm remission before offering LT. Two of our patients who presented with active LCH and decompensated cirrhosis underwent LT after successful induction chemotherapy cycles (after 1 and 3 cycles respectively) as the hepatic dysfunction was rapidly progressing. Both these patients were confirmed to have disease remission before undergoing LT.

The major limitation of our study is the small sample size. However, this study throws light on the role and timing of LT in LCH. More evidence is needed in suggesting specific agents like BRAF inhibitors for the inducing remission of LCH in presence of an advanced liver disease, whose disease is refractory to conventional and modified chemotherapy.[26] Based on our experience, we propose a treatment algorithm for LCH patients with liver involvement (Figure 2). Close monitoring by a multidisciplinary team though out the care with timely interventions when needed could be the reasons for the excellent results demonstrated in our series.

Conflicts of interests : Nil

Financial disclosures : Nil

Author contributions :

JM: Wrote the paper, designed & performed research, analysed data

NS : Performed research, analysed data, did the proof reading

JV : Analysed data, did the proof reading

MV : Reported the histopathology, analysed data, did the proof reading

VK : Analysed data, did the proof reading

DM : Analysed data, did the proof reading

ARH :Analysed data, did the proof reading

AR :Analysed data, did the proof reading

MR :Analysed data, did the proof reading & gave final approval for publishing the paper

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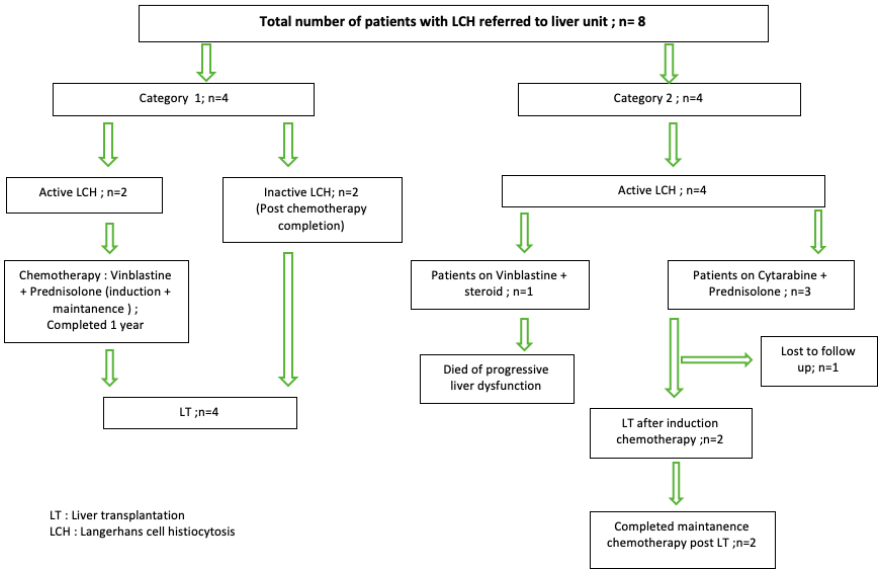
Figure legends :

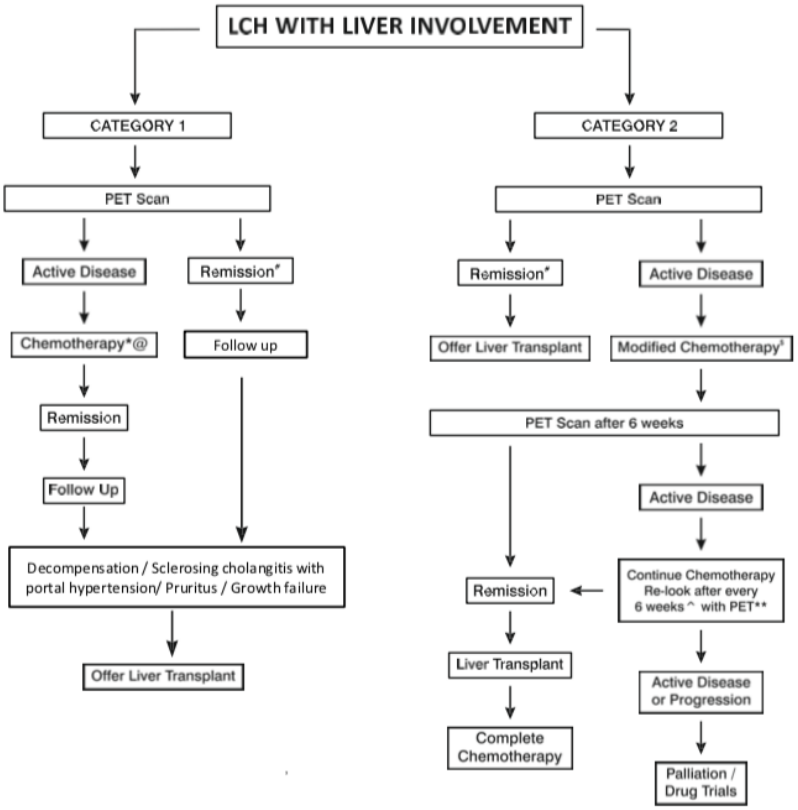
Figure 1: Flow diagram of patients with hepatic presentations of LCH

Figure 2: Algorithm to approach a patient with LCH associated chronic liver disease based on stage of liver disease (category 1 and category 2)

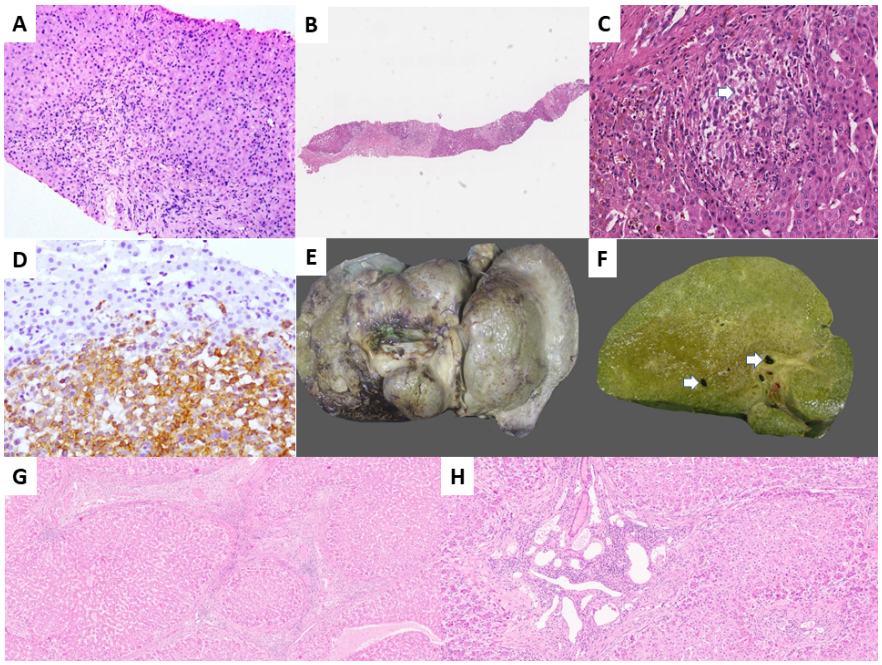
Figure 3: **:** Liver biopsies demonstrating features of large duct obstructive cholangiopathy with portal fibrous expansion and bile ductular proliferation (A & B, H&E). Liver biopsy with cluster of Langerhans cells (arrow, C, H&E). CD1a immunostaining of Langerhans cells (D). External surface of an explant liver with greenish discolouration and micronodularity (E). Cut surface of an explant liver with marked greenish discolouration and multiple bile ducts with biliary sludge (arrow, F). Light microscopy image displaying cirrhosis (H&E, G). Ductopenia in an explant liver (H&E, H)

Figure 1 : Flow diagram of patients with hepatic involvement with LCH





* If no remission after 2 cycles of induction, need to change the chemotherapy regimen
@ If the patient shows signs of decompensation between chemotherapy, (ascites, variceal bleed encephalopathy) ,the regimen needs to be changed (to modified chemotherapy)
** If the PET scan shows disease remission, liver transplant can be offered, and this should be followed by completion of chemotherapy
$ Cytarabine plus prednisolone based therapy
# Patients who had completed the chemotherapy
^ At present there is no consensus on how many cycles we could offer, as the patient could succumb to liver failure or whether to transplant a patient with active disease and then offer intensive chemotherapy



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