

Hepatobiliary Involvement of Hematolymphoid Malignancies in Children: From a Pediatric Gastroenterologists Perspective

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ABSTRACT

Aim: To describe hepatobiliary involvement in pediatric hematolymphoid malignancies and their approach in clinical practice.

Background: Pediatric hematolymphoid malignancies primarily consist of leukemias, lymphomas, and Langerhans cell histiocytosis (LCH). Although they involve the hepatobiliary system frequently, they are often misdiagnosed as infectious or inflammatory diseases.

Also, consolidated literature on their presentation and approach is scarce in children.

Review results: Hepatobiliary involvement is seen in up to 60% of acute leukemias and LCH and up to 40% of lymphomas in children. Clinical features result from infiltration, compression, overwhelmed immune system, and chemotherapy-related hepatotoxicity. Hepatobiliary involvement in hematolymphoid malignancies is diverse, ranging from subtle asymptomatic hepatomegaly, raised transaminases, and biliary obstruction to fulminant presentations like liver failure and decompensated biliary cirrhosis due to sclerosing cholangitis. The majority of the chemotherapeutic drugs have the potential for hepatic impairment, necessitating pharmacovigilance.

Conclusion: Hepatobiliary involvement in children can present with a wide range of manifestations, from asymptomatic hepatomegaly to fulminant liver failure. Pivotal for favorable outcomes is to arrive at an early diagnosis of malignancy by differentiating it from inflammatory and infectious diseases. Hepatotoxicity can be reduced or even prevented by practicing pharmacovigilance.

Clinical significance: Liver involvement in hematolymphoid malignancies often overlaps with common infectious and inflammatory diseases requiring a high index of suspicion. It is essential to improve cross-referrals between a hemato-oncologist and a pediatric gastroenterologist for optimal outcomes.

Keywords: Hepatobiliary, Langerhans cell histiocytosis, Leukemia, Lymphoma.

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INTRODUCTION

Leukemias, lymphomas, and LCH constitute the common hematolymphoid malignancies in children. The reticuloendothelial system includes the liver, which is frequently involved either at the time of presentation or during the disease course. The mechanisms causing various hepatobiliary manifestations are a multitude, including infiltration, drug toxicity, immunodeficiency, etc. (Table 1). They may be subtle in the form of asymptomatic hepatomegaly and/or mildly elevated transaminases to a fulminant presentation like liver failure, often posing a challenge to pediatric gastroenterologists/hepatologists. Their presentation frequently overlaps with chronic infectious and inflammatory conditions causing a delay in diagnosis and impacting survival. In this review, we briefly discuss the aspects of hepatic involvement, focusing on their presentation and approach in clinical practice.

Leukemias in Children

Among the pediatric malignancies seen in the <15 years of age-group, one-third are constituted by acute leukemias.¹ Acute leukemias often infiltrate the lymphoreticular organs, like the lymph nodes, liver, and spleen.

Hepatobiliary Involvement in Acute Lymphoblastic Leukemia (ALL)

Disease-related: At initial presentation, asymptomatic hepatomegaly is the most common manifestation seen in up to two-thirds of children with ALL.¹ Abnormal liver biochemistry

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may be seen at initial contact or during the treatment course. Leukemic cells can infiltrate the hepatic sinusoids and portal tracts in the liver. Infiltration can lead to hepatocellular necrosis and elevated transaminases. In a pediatric study of 147 patients with ALL, elevated transaminases were reported in 34% at presentation.² Along with abnormal liver enzymes, 3.4% had associated conjugated hyperbilirubinemia. Comparing patients who had normal vs elevated transaminases, there was no significant difference in the overall outcome indicating that

Table 1: Overview of hepatobiliary manifestations in childhood hematolymphoid malignancies

<i>Pathophysiology</i>	<i>Manifestations</i>
Infiltration	Hepatomegaly; jaundice (biliary wall infiltration); acute liver failure; vanishing bile duct syndrome; portal hypertension.
Immunodeficiency	Hepatitis B and C reactivation; opportunistic infections including CMV, hepatic candidiasis, etc.
Drug toxicity	Hepatotoxicity including liver failure.
Compression	Cholestasis, cholangitis due to biliary obstruction; secondary Budd–Chiari syndrome.
Others	Secondary hemophagocytic lymphohistiocytosis.

hepatitis at presentation does not alter the prognosis or the induction chemotherapy success in ALL.² Hepatitis usually resolves with treatment with liver biopsy to be performed in children with elevated transaminases either refractory to induction chemotherapy or have persistent elevation with normal imaging and viral tests. Liver failure is a known but rare presentation of ALL, usually seen with T-cell ALL. The prognosis is poor despite intensive chemotherapy or transplantation. Success, although short-term, was documented in a few case reports after liver transplantation.³ Ischemic liver injury may occur in the setting of hypovolemia. Unscreened blood product transfusion may result in hepatitis B and/or hepatitis C infection. An overall immunocompromised state increases the risk of opportunistic infections like fungal, bacterial, viral, or parasitic infections.

Chemotherapy-related: Using steroids prior to induction chemotherapy has shown to normalize elevated transaminases in ALL children with hepatitis (without liver failure). This allows the administration of full chemotherapy as per the recommended protocol. Although it usually reflects hepatotoxicity, any rise in transaminases while on chemotherapy merits a thorough workup. Hepatotoxicity is commonly secondary to L-asparaginase, methotrexate, 6-mercaptopurine (6-MP), vincristine, and daunorubicin. It is necessary to evaluate thiopurine methyltransferase activity in children with a rise in liver enzymes after 6-MP exposure.⁴ Either a dose reduction or withholding of the chemotherapeutic agent is advised in those with significant liver dysfunction. In a predisposed child with underlying hepatic impairment L-asparaginase, anthracyclines, and high-dose methotrexate can cause liver failure. Hepatitis B virus (HBV) reactivation is a serious and well-known complication that may be subclinical or lead to uncontrolled flare, liver failure, and even death.⁵ Similarly, steroids impair cellular immunity against cytomegalovirus (CMV), often causing hepatic reactivations, particularly in countries with high CMV seroprevalence.

Hepatobiliary Involvement in Acute Myeloid Leukemia (AML)

Disease-related: Clinically, hepatomegaly is reported though less commonly in AML compared to ALL; however, autopsy studies have documented up to 75% liver involvement.⁶ Myeloid cell infiltration can cause acute hepatitis, and conjugated hyperbilirubinemia can result from granulocytic sarcoma obstructing bile flow. Fulminant hepatitis is rare with childhood AML. AML-M3 variant can cause coagulopathy and bleeding manifestations in the absence of liver failure.

Chemotherapy-related: Chemotherapeutic agents used for AML, such as cytarabine, mitoxantrone, and daunorubicin can cause hepatitis, cholestasis, and/or biliary stricture.⁷ Additionally, arsenic trioxide and tretinoin are hepatotoxic, potentially requiring dose modifications in AML-M3.

Hepatobiliary Involvement in Infantile Leukemias

An aggressive presentation with infiltration of extramedullary organs, central nervous system involvement, and high white blood cell characterizes infantile leukemias. In infantile leukemias, unlike in older children, the incidence of AML is the same as ALL. Massive hepatosplenomegaly is frequently seen, and they show mixed-lineage leukemia gene rearrangements. They can manifest as infantile cholestasis with elevated liver enzymes, and liver failure may ensue if untreated. Bone marrow biopsy is often unyielding because of marrow fibrosis, and the diagnosis can be clinched by liver biopsy. Outcomes are usually poor. Around 15% of neonates with Down syndrome with GATA-1 gene mutation have transient abnormal myelopoiesis (TAM). TAM has a wide range of presentations from an asymptomatic state to widespread leukemic infiltration seen in 10–20% of neonates presenting with jaundice (70%), hepatitis (25%), hepatosplenomegaly (30–40%), and coagulation disturbances (10–25%).⁸ Leukemic infiltration, iron deposition, or idiopathic progressive fibrosis can result in liver failure. For asymptomatic cases, observation is recommended. Chemotherapy is indicated when there is organomegaly causing respiratory compromise, total blast count higher than 100,000/ μ L, life-threatening hepatic dysfunction, ascites, hepatitis, hyperbilirubinemia, disseminated intravascular coagulation, significant anemia resulting in cardiac failure, and hydrops fetalis. Spontaneous regression occurs within 3 months in the majority. Acute megakaryoblastic leukemia may develop over 1–3 years in 20–30% of TAM.⁸

Hepatobiliary Involvement in Chronic Leukemias

Chronic leukemias commonly reported in children are chronic myelogenous leukemia (CML) and juvenile myelomonocytic leukemia (JMML). Although liver dysfunction is uncommon, the majority (~85%) of childhood CML and JMML have hepatomegaly.

Clinical Impact of Leukemias for a Pediatric Gastroenterologist/Hepatologist

It is important to differentiate acute leukemias from other infectious and immunological causes, especially when presenting as febrile hepatitis. Before the diagnosis is ascertained, a substantial proportion of children undergo extensive workup and multiple failed antimicrobial therapy. Chemotherapy-related hepatic impairment is a major problem resulting in alterations of the routine protocol affecting the prognosis. Screening for hepatitis B should be done by HBsAg, anti-HBs, and total anti-HBc testing, and those who are negative for all three should be vaccinated against HBV as soon as possible before starting chemotherapy. Depending on the risk of reactivation, appropriate antiviral prophylaxis should be started.

Lymphomas in Children

In the pediatric age-group, combined Hodgkin's disease (HD) and non-Hodgkin lymphomas (NHL) constitute the third most common malignancy.⁹

Hepatobiliary Involvement in HD

Around 5% of HD children have liver involvement at presentation, usually as hepatomegaly.¹⁰ However, despite infiltration, liver size may be normal. Rather than large masses, smaller lesions are usually seen in the liver. A notable observation is that liver involvement is invariably associated with splenic involvement. The chance of liver involvement is high when the splenic involvement is extensive. Initial presentation as jaundice is seen in 3–13% of HD.¹¹ Diagnosis can be established by performing a biopsy of the enlarged lymph nodes and/or imaging-guided biopsy [ultrasound or computed tomography (CT)] of the affected areas. Hepatic involvement rarely causes fulminant hepatitis, commonly by ischemia resulting from infiltration of the hepatic sinusoids or malignant cells replacing the liver parenchyma. HD can cause cholestasis due to biliary obstruction, viral hepatitis, infiltration, chemotherapy-induced hepatotoxicity, and rarely vanishing bile duct syndrome.

Hepatobiliary Involvement in NHL

Biliary obstruction and lymphomatous infiltration are seen more commonly with NHL than HD. Around 16–43% of patients with NHL have liver involvement.¹² Acute liver failure, as well as cholestasis, can occur due to the same mechanisms as described earlier with HD. Ghosh et al. in a retrospective analysis, described nine children (11.2% of all NHL) with NHL who presented with jaundice.¹³ In seven out of nine patients, jaundice was due to biliary obstruction caused by compression due to periportal, periampullary, subhepatic, or gastroduodenal masses. The other two children had jaundice due to hepatic infiltration. Resolution of jaundice with chemotherapy alone was achieved in seven patients in this study, with biliary drainage performed in one patient.¹³

Published small case series have used biliary drainage, steroids, cytotoxic agents, and surgery in different combinations and sequences. Delaying chemotherapy in want of normalization of bilirubin postbiliary drainage or treating with only steroids can adversely affect the outcome. Complications in the form of biliary leak and peritonitis have been reported with the institution of chemotherapy after biliary drainage.

Chemotherapy-related Toxicities in Lymphoma

For jaundiced patients, dose reductions are necessary. Recommendations suggest a dose reduction of 50% for etoposide when total serum bilirubin is 1.5–3 mg/dL and stopping or avoiding when bilirubin is >3 mg/dL. However, there is no strong data to suggest modifications for ifosfamide and cytarabine.¹⁴ In children with prior hepatic impairment, methotrexate can cause further insult and hence is withheld or its dose reduced. However, some clinicians have used higher doses safely without any hepatic dysfunction or mortality.¹³

Imaging Patterns of Liver Involvement in Lymphomas

Hodgkin's disease more often manifests as small miliary-like lesions (<1 cm in diameter) than large masses.

In NHL, CT may show either discrete lesions or increased uptake (diffuse or focal) in the liver, with or without focal or diffuse nodules. Liver biopsy from suspicious areas accurately ascertains hepatic involvement. Fluorodeoxyglucose positron emission tomography (FDG-PET) with CT is currently the gold standard for both staging and follow-up of HD and NHL. It is not required to perform a bone marrow in HD once FDG-PET is obtained. Bone marrow is necessary when discordance occurs with positive histology and negative PET scan in diffuse large B-cell lymphoma (DLBCL) type of NHL.⁴

Clinical Impact of Lymphomas for a Pediatric Gastroenterologist/Hepatologist

Liver (in case of hepatic infiltration) or lymph nodal (in case of biliary obstruction) biopsy is required for diagnosis in patients presenting with cholestasis. A percutaneous plugged liver biopsy (transhepatic or transjugular) is often needed, along with platelet transfusions in the setting of severe thrombocytopenia. Liver biopsy showing granulomas may mislead the physician about tuberculosis and unwarranted antitubercular therapy in countries with a high prevalence of the infection. Prognosis is invariably poor in the presence of vanishing bile duct syndrome. In the case of challenging biopsies like periportal, peribiliary, or peripancreatic nodes performing CT-guided biopsies may be risky, especially with the overlapping bowel and vasculature. In such situations, the use of endosonography-guided procedures in specialized centers is rewarding. Similarly, deep mesenteric or perivascular nodes are not amenable to endosonography and usually require laparoscopy-guided sampling. Biliary drainage by therapeutic endoscopic cholangiography and stent placement is challenging in children.

Primary Lymphomas in Children

When the tumor bulk is limited to the organ of genesis after complete staging without any blood (peripheral blood smear or bone marrow) or distant lymph node involvement, then the diagnosis of primary lymphoma is considered. Based on the primary organ of involvement, they are classified into primary hepatic lymphoma (PHL) involving the liver, primary splenic lymphoma involving the spleen, primary gastrointestinal (GI) lymphoma involving the GI tract, and hepatosplenic T-cell lymphoma (HSTCL) involving both liver and spleen.

Primary Hepatic Lymphoma

Primary hepatic lymphoma, although more common in the 5th–6th decade, has been reported in children. Abdominal pain due to hepatomegaly is the most common presentation. B-symptoms, including, fever, weight loss, and/or night sweats, are seen in about one-third of the patients. Citak et al. studied 10 children with PHL and reported male predisposition with hepatomegaly, anorexia, fatigue, and abdominal pain being the common presenting symptom.¹⁵ DLBCL is the most common type of PHL seen in 80–90% of cases. Imaging shows solitary masses in the liver in >50% of PHL patients, with multiple masses and diffuse involvement also being reported. Radiological differentials for nodular PHL in children include hepatoblastoma, hepatocellular carcinoma, metastatic neuroblastoma, embryonal sarcoma, hepatic rhabdomyosarcoma, and Ewing sarcoma. Prompt anthracycline-based combination chemotherapy has shown promise with prolonged remissions in PHL patients. Off late, there has been a change in approach from primary surgery to current chemotherapy-based management, circumventing extensive hepatic lobectomies.

Hepatosplenic T-cell Lymphoma

Hepatic and splenic sinusoidal infiltration with an aggressive course is typical of HSTCL. Isochromosome 7q and trisomy 8 are the common cytogenetic anomalies seen with HSTCL.¹⁶ Young males <35 years with inflammatory bowel disease who have a history of long-term (>2 years) use of combined thiopurines and biologicals have a high risk of HSTCL. Thiopurines are known to induce apoptosis in immunodeficient states with resultant loss of tumor surveillance. Biologicals also affect T-cells causing increased

apoptosis and complement-mediated lysis, contributing to the development of malignancy. Patients commonly present with fever, anorexia, weight loss, hepatosplenomegaly, no lymphadenopathy, abnormal liver function tests (LFTs), and pancytopenia. Invariably all patients have bone marrow involvement with its biopsy, and immunophenotyping clinches the diagnosis.

Post-transplant Lymphoproliferative Disorder (PTLD)

Epstein-Barr virus infection is a primary driver of PTLD in most cases. PTLD can occur post-solid organ as well as hematopoietic stem cell transplantation. In that order, its highest risk is heart-lung, followed by the small intestine and liver transplantation.^{17,18} Liver and splenic involvement is seen in around 16% of patients over 2 decades of follow-up.¹⁹ PTLD affecting the liver can present with intrahepatic cholestasis as well as extrahepatic cholestasis due to bulky lymphadenopathy around the porta hepatis.

Clinical Impact of Primary Lymphomas for Pediatric Gastroenterologist/Hepatologist

As they are initially confined to the organ of origin, they usually present as organomegaly. PHL usually mimics other hepatic tumors and congestive states. When performed in HSTCL, liver biopsy has similarities with autoimmune hepatitis delaying the diagnosis. Especially considering the poor outcomes in HSTCL, recommendations suggest withdrawal of thiopurines from the prescribed combination therapy. This is advised in both ulcerative colitis (after 6 months) and Crohn's disease (after 6–12 months) once the trough levels of antitumor necrosis factor agents are adequate and therapy targets are achieved.^{20,21}

Langerhans Cell Histiocytosis in Children

Langerhan cell-like dendritic cells can proliferate involving one or more systems. LCH is confirmed on biopsy by the presence of cluster of differentiation 1a (CD1a), CD207 (langerin), or by electron microscopy showing Birbeck granules. Nearly 60% of the diagnosed LCH children carry the oncogenic BRAF V600E variant. LCH can involve any organ, and the most commonly affected is the bone in 80%.²² Up to 50% of the affected children with localized disease progress to multisystemic involvement. Infiltration of the liver, spleen, bone marrow, and lungs defines clinical risk organ involvement, with the former three constituting organs with high risk.²³

Hepatobiliary Involvement in LCH

Involvement of the liver is seen in 15–60% of LCH children and portends a poor prognosis. One or more of the following should be fulfilled to define liver involvement in LCH: hepatomegaly (with >3 cm palpable in mid clavicular line), hepatic dysfunction (hypoproteinemia <5.5 mg/dL, hypoalbuminemia <2.5 mg/dL, hyperbilirubinemia >1.5 mg/dL, edema, or ascites, not due to other causes) or biopsy findings of active disease.²² Liver involvement commonly presents as hepatomegaly secondary to Kupffer cell hyperplasia or infiltration by Langerhans cells. Lesions are proliferative or locally destructive early on; however, they become more fibrotic in later stages. The characteristic involvement of the biliary tree is sclerosing cholangitis (intrahepatic and/or extrahepatic) which is seen in ~15% of patients with LCH.²⁴ LFT typically shows elevated serum gamma-glutamyl transferase. Sclerosing cholangitis can cause cholestasis, cholangitis, portal hypertension, and secondary biliary cirrhosis. Liver biopsy shows

periductal fibrosis and bile duct proliferation typical of sclerosing cholangitis. In an otherwise proven case of LCH, liver biopsy helps to assess activity and evaluation of other secondary causes. Inactive (no LC/CD1a positivity) and burnt-out parenchyma does not respond well to chemotherapy and has a poor prognosis. Magnetic resonance cholangiopancreatography shows bile duct beading and dilatation. Response to chemotherapy is seen in around 25% of LCH with sclerosing cholangitis, as usually, the disease is inactive and advanced with fibrosis.²⁴ Recommendations suggest using vinblastine/prednisolone for 1 year and adding 6-MP for high-risk LCH. Monoclonal antibodies to BRAF V600E, like vemurafenib, have been successfully used in mutation-positive, refractory pediatric LCH.

Clinical Impact of LCH for a Pediatric Gastroenterologist/Hepatologist

In the natural history of isolated hepatobiliary involvement, usually, the disease is mismanaged as the primary type of sclerosing cholangitis until it progresses into a multisystemic disease. Hence guidelines recommend ruling out LCH effectively in sclerosing cholangitis. Liver involvement as sclerosing cholangitis is usually a burnt-out phenomenon; hence wait-listing for liver transplantation is required despite chemotherapy. Non-pharmacological interventions like therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for biliary drainage are often needed (Table 2).

The approach to common hepatobiliary manifestations with recommendations is presented in Table 3.

CONCLUSION

The horizon of hepatobiliary manifestations in childhood hematolymphoid malignancies is vast. Involvement may be subtle such as asymptomatic hepatomegaly to fulminant liver failure. It is crucial to differentiate malignancy from other inflammatory and infectious diseases, which is a pivotal part of the management. Cross-referrals between a pediatric gastroenterologist and pediatric

Table 2: Non-pharmacological interventions for hepatobiliary involvement in pediatric hematolymphoid malignancies

Intervention	Clinical relevance
Endoscopy	<ul style="list-style-type: none"> Biliary stenting by ERCP for cholangitis due to biliary obstruction in lymphoma. Endoscopic balloon dilatation for dominant strictures in sclerosing cholangitis (for the control of cholangitis and intractable pruritus affecting quality of life). Endoscopic variceal band ligation or endoscopic sclerotherapy in portal hypertension with variceal bleed or with high-risk varices.
Radiological	<ul style="list-style-type: none"> Percutaneous transhepatic biliary drainage for strictures proximal to the hilum or after a failed ERCP.
Liver assist devices	<ul style="list-style-type: none"> Like Prometheus and molecular adsorbent recirculation system acting as a bridge for liver transplantation.
Others	<ul style="list-style-type: none"> Optimizing nutrition, psychosocial support, and the judicious use of blood products can help in early recovery.

Table 3: Common hepatobiliary manifestations in pediatric hematolymphoid malignancies with their clinical possibilities and recommendations for practice⁴

Hepatobiliary manifestation	Likely reasons at the time of diagnosis and recommendations	Likely reasons during therapy and recommendations
Jaundice	<ul style="list-style-type: none"> Obstruction of biliary system by enlarged lymph nodes. <p>Recommendation: (a) biliary drainage along with initiation of chemotherapy.</p> <ul style="list-style-type: none"> Tumor infiltration and necrosis of hepatocytes. Transfusion-related viral hepatitis. <p>Recommendations: (a) safe transfusion practices; (b) test for hepatotropic viruses like HBV, HCV. Initiation of antiviral prophylaxis prior to the start of chemotherapy for HBV and HCV infection as appropriate based on the standard guidelines.</p> <ul style="list-style-type: none"> Consider the possibility of HLH as an atypical presentation of hematolymphoid malignancies. <p>Recommendation: (a) prioritize chemotherapy initiation for underlying malignancy rather than waiting for resolution of HLH with HLH treatment protocol.</p> <ul style="list-style-type: none"> Sclerosing cholangitis in a case of LCH. <p>Recommendations: (a) initiate chemotherapy; (b) ERCP for dominant strictures; (c) wait listing for liver transplantation.</p>	<ul style="list-style-type: none"> Chemotherapy-induced hepatotoxicity (e.g., 6-MP and methotrexate). <p>Recommendations: (a) practice pharmacovigilance—chemotherapeutic drug dose modifications with underlying hepatic impairment, therapeutic drug monitoring, for example, methotrexate; (b) screen for genetic polymorphisms (e.g., TPMT and NUDT15 genotype for 6-MP) as appropriate.</p> <ul style="list-style-type: none"> Reactivation of viral infections (e.g., HBV, HCV, CMV, etc.) <p>Recommendations: (a) Screen for HBV, HCV infections before starting chemotherapy. Initiation of antivirals prior to the start of chemotherapy for hepatitis B, hepatitis C infection as appropriate based on the standard guidelines; (b) anticipatory close monitoring for possible flare/reactivation during chemotherapy in case of occult HBV infection apart from appropriate antiviral prophylaxis; (a) to test for and treat reactivation with antivirals as per standard guidelines.</p>
Liver failure	<ul style="list-style-type: none"> Peculiar presentation with T-ALL, AML. <p>Recommendation: (a) early steroid initiation at presentation for preventing further liver cell necrosis in a case of ALL.</p> <ul style="list-style-type: none"> TAM of the newborn. <p>Recommendation: (a) consider chemotherapy for TAM.</p> <ul style="list-style-type: none"> Overwhelming sepsis at baseline due to poor immune reserve. <p>Recommendations: (a) blood product transfusions with FFP plasma and cryoprecipitate for hemostasis; (b) antibiotics with or without antifungals.</p>	<ul style="list-style-type: none"> Peculiar toxicity with L-asparaginase, high dose methotrexate, and anthracyclines in predisposed individuals. <p>Recommendation: (a) practice pharmacovigilance—chemotherapeutic drug dose modifications with underlying hepatic impairment, therapeutic drug monitoring, for example, methotrexate.</p> <ul style="list-style-type: none"> Viral hepatitis especially hepatitis B reactivation. <p>Recommendation: (a) screen for hepatotropic viral markers and initiate appropriate antiviral therapy as indicated.</p>
Ascites (portal-hypertensive related)	<ul style="list-style-type: none"> Secondary biliary cirrhosis due to sclerosing cholangitis in LCH. <p>Recommendations: (a) initiate chemotherapy; (b) salt restriction, diuretics, and evaluate for spontaneous bacterial peritonitis; (c) ERCP for dominant strictures; (d) waitlisting for liver transplantation.</p> <ul style="list-style-type: none"> Secondary BCS due to Burkitt’s lymphoma (rarely reported). 	<ul style="list-style-type: none"> Drug-induced liver failure (e.g., anthracyclines at toxic dose, L-asparaginase). <p>Recommendation: (a) exercise pharmacovigilance.</p>

hemato-oncologist should be improvised for better outcomes. To avoid hepatic impairment, strict pharmacovigilance is needed.

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