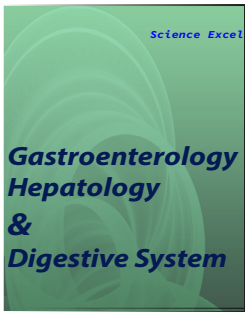
Gastroenterology Hepatology and Digestive System

Case Series



Primary Hepatic Lymphoma –An Enigmatic Diagnosis: A Case series

Kakodkar Pramath[1], Shekari Nooshin[2], Zhang Dan[1], Kanthan Selliah[3], and Kanthan Rani[1*]

[1]*Department of Pathology and Laboratory Medicine, College of Medicine, University of Saskatchewan, Canada*
[2]*Department of Anatomic, Physiology, and Pharmacology, University of Saskatchewan, Saskatoon, SK, Canada.*
[3]*Department of Surgery, College of Medicine, University of Saskatchewan, Saskatoon, SK, Canada*

Correspondence

Rani Kanthan

Professor, Pathology and Lab Medicine, Royal University Hospital, 103 Hospital Dr, Saskatoon, SK S7N 0W8, Canada

Phone: (306) 655-2158

Fax: (306) 655- 2223

- Received Date: 22 Dec 2025
- Accepted Date: 29 Dec 2025
- Publication Date: 01 Jan 2026

Keywords

Autoimmmune Hepatitis; Burkitt lymphoma; diffuse large B-cell lymphoma; marginal zone lymphoma; Primary Liver Lymphoma,

Abstract

Background: Primary hepatic lymphoma (PHL) is a rare presentation of a common hematological disease and is defined as lymphoma confined to the liver without extrahepatic involvement. PHL can mimic carcinoma, inflammatory or infectious conditions, posing a diagnostic challenge across clinical, radiological and pathological domains. Lab investigations and radiology often lack specificity, and early suspicion is limited. This case series highlights the importance of timely recognition and accurate diagnosis through a review of seven patients with PHL.

Methods: An index case of PHL identified on a routine medical liver biopsy prompted a retrospective search of our laboratory information system for the diagnosis of 'hepatic lymphomas' since 2010 [14 years]. Inclusion criteria included identification of cases with absent lymphadenopathy, bone marrow involvement or peripheral compartment lymphoma at the time of the liver biopsy. Histopathological features were independently reviewed, and relevant clinical data, imaging and management parameter were compiled from the electronic medical records. All cases were deidentified.

Results: Seven cases of PHL were included from a pathology caseload of 586,813 cases (prevalence: 1.2 per 100,000). Median age at diagnosis was 54 ± 12.3 years with a slight female predilection (F:M=1.3:1). Presentation ranged from acute liver dysfunction (14.2%, n=1) to nonspecific abdominal pain (85.7%, n=6). Radiology ranged from normal (14.3%, n=1), to solitary hepatic lesions (14.3%, n=1), multifocal perfusion abnormalities without discrete masses (14.3%, n=1), or heterogeneous, multiple, ill-defined hypodense liver lesions (57.1%, n=4). Diffuse large B-cell lymphoma (71.4%, n=5) was the predominant subtype, followed by Burkitt lymphoma (14.3%, n=1), and marginal zone lymphoma (14.2%, n=1). Remission was achieved in 57.1% of cases, whereas 42.8% died within 2 months of diagnosis, reflecting underlying biological heterogeneity.

Conclusions: PHL is rare, and histopathology along with ancillary tests remains the gold standard for accurate diagnosis. Clinician awareness and early liver biopsy are essential for appropriate patient management.

Introduction

Primary hepatic lymphoma (PHL) is a rare form of extranodal non-Hodgkin lymphoma that arises within the liver and is confined to the hepatic compartment, without evidence of extrahepatic disease (bone marrow, lymphadenopathy, or splenic infiltration) at diagnosis [1]. PHL is extremely rare, accounting for 0.4% of all extranodal lymphomas, 0.1% of hepatic malignancies, and approximately 0.016% of all cases of non-Hodgkin lymphoma [2,3]. The markedly reduced incidence of PHL translates to reduced exposure during clinical training and service, making it a challenging diagnostic entity for both clinicians and pathologists. In contrast, secondary hepatic involvement by systemic lymphoma is relatively common and can often be detected by ancillary investigations, including bone marrow examination and peripheral blood flow cytometry.

The clinical presentation for PHL can be ambiguous and mimic a wide range of hepatic pathologies. These patients may present with abdominal pain, hepatomegaly, jaundice, acute liver dysfunction, and constitutional symptoms [1,4]. Notably, some patients can remain asymptomatic with incidental radiologic findings [5]. Radiologic imaging, including computer tomography (CT) and magnetic resonance imaging (MRI), frequently identifies solitary (homogeneous or heterogeneous) or multiple hypodense hepatic lesions [6]. These clinical and radiological features overlap considerably with granulomatous disease, hepatocellular carcinoma, metastatic disease, and inflammatory pseudotumour [6]. As a result, timely categorical diagnosis of PHL based solely on imaging is often challenging, and definitive identification depends on accurate histopathological diagnosis.

Citation: Kakodkar P, Shekari N, Zhang D, Kanthan S, Kanthan R. Primary Hepatic Lymphoma –An Enigmatic Diagnosis: A Case series. Gastroenterol Hepatol Dig Sys. 2026;3(1):2601.

According to the Surveillance, Epidemiology, and End Results (SEER) PHL registries (1983-2015), the majority of PHLs are histologically B-cell origin (85.7%), with diffuse large B-cell lymphoma (DLBCL) representing the predominant subtype (62.3%), followed by Burkitt lymphoma (3.4%) and marginal zone lymphoma (3.7%) [7]. Importantly, immunohistochemistry (IHC) is indispensable not only for establishing the cell lineage but also for confirming monoclonality in PHL, thereby excluding its predominant histological mimics, autoimmune hepatitis, small round blue cell tumors, and melanoma [8,9]. Ancillary tests, including flow cytometry and molecular studies, may further confirm clonality and refine the lymphoma subtype.

The pathogenesis of PHL remains unclear, but several etiological risk factors have been seen associated, such as cirrhosis, systemic lupus erythematosus, transplant patients on immunosuppressive therapy, and chronic hepatitis particularly, hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and Epstein–Barr virus (EBV) [4,10–14]. Notably, many patients present without identifiable predisposing factors, further complicating our understanding of the exact disease pathogenesis.

Given its rarity and diagnostic challenges, awareness of PHL is essential for clinicians, radiologists, and pathologists. Early liver biopsy and prioritizing PHL in the histopathological workup can lead to timely diagnosis and the initiation of life-saving therapy [15,16]. In this study, we present a retrospective case series of seven patients with PHL diagnosed at our institution over 14 years. We highlight their clinicopathological features, histopathological findings, management, and outcomes.

Case Series

We report a series of 7 patients with primary hepatic lymphoma (PHL), diagnosed between 2010–2024 at our tertiary care center, with no evidence of palpable lymphadenopathy, bone marrow involvement, or systemic lymphoma.

Clinical features

The mean age for this cohort was 54 ± 12.3 years and showed a slight female predilection (F:M ratio = 1.3:1). Abdominal pain was the most frequent presenting symptom (85.7%, n= 6), followed by acute liver dysfunction (28.6%, n=2), while others presented with sepsis, upper gastrointestinal bleeding, or nonspecific abdominal symptoms leading to imaging investigations. Comorbidities were frequent and diverse, ranging from cirrhosis with non-alcoholic fatty liver disease to synchronous non-lymphoid malignancies such as pancreatic adenosquamous carcinoma and metastatic colorectal carcinoma. Viral associations were prominent; HIV (42.8%, n=3), hepatitis C (28.6%, n=2), and Epstein-Barr virus (14.3%, n=1). Detailed clinical and demographic parameters are presented in Table 1.

Table 1. *Baseline clinical, demographical features, and viral exposure status of patients with suspected primary hepatic lymphoma (n=7).*

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (Sex)	56 (F)	47 (M)	36 (M)	65 (F)	40 (M)	63 (F)	71 (F)
Clinical Presentation	Abdominal pain with acute liver failure	Abdominal pain with liver lesions on imaging	Abdominal pain with liver lesions on imaging	Sepsis and liver lesions on imaging	Abdominal pain with upper GI bleed	Abdominal pain with acute liver failure	Abdominal pain with liver lesions on imaging
Co-morbidity	HIV, Miliary MTB, influenza A, Acute pancreatitis	Pancreatic adenosquamous carcinoma, HSV1, esophageal atresia, migraines	HIV	Reactive axillary lymphadenopathy, MDS Hypertriglyceridemia, T2DM, Renal disease	HIV, Hep C, cirrhosis, NAFLD	TIA, RA, COPD	Metastatic colorectal carcinoma, Macrovesicular steatosis
ALP	Elevated	Elevated	Elevated	Elevated	Elevated	Elevated	Normal
GGT	Elevated	Elevated	Elevated	Elevated	Elevated	Elevated	Normal
AST	Elevated	Elevated	Normal	Elevated	Elevated	Elevated	Normal
ALT	Normal	Elevated	Normal	Elevated	Elevated	Elevated	Normal
T. Bili	Normal	Elevated	Normal	Elevated	Elevated	Elevated	Normal
LDH	Elevated	Elevated	Elevated	Elevated	Elevated	Elevated	Not performed
CEA	Not performed	Not elevated	Not elevated	Elevated	Not elevated	Not performed	Not elevated
AFP	Not performed	Not elevated	Not performed	Not performed	Elevated	Not performed	Not performed
HBV	No acute infection, Non-immune	No acute infection, Non-immune	Immune	No acute infection, Non-immune	Immune	No acute infection, Non-immune	Immune
HCV	Negative	Positive	Negative	Negative	Positive	Negative	Negative
HIV	Positive	Negative	Positive	Negative	Positive	Negative	Negative
EBV	Acute Infection	Past Infection	Past Infection	NA	Past Infection	NA	NA

Abbreviation: Male (M), Female (F), gastrointestinal (GI), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human immunodeficiency virus (HIV), Ebstein barr virus (EBV), Mycobacterium tuberculosis (MTB), Herpes simplex virus 1 (HSV1), Lymph node (LN), myelodysplastic syndrome (MDS), Non-Alcoholic Fatty Liver Disease (NAFLD), Transient ischemic attack (TIA), Rheumatoid arthritis (RA), chronic obstructive pulmonary disease (COPD), type 2 diabetes mellitus (T2DM), Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma-Glutamyl Transferase (GGT), Total Bilirubin (T. Bili), Lactate Dehydrogenase (LDH), Carcinoembryonic Antigen (CEA), alpha-fetoprotein (AFP).

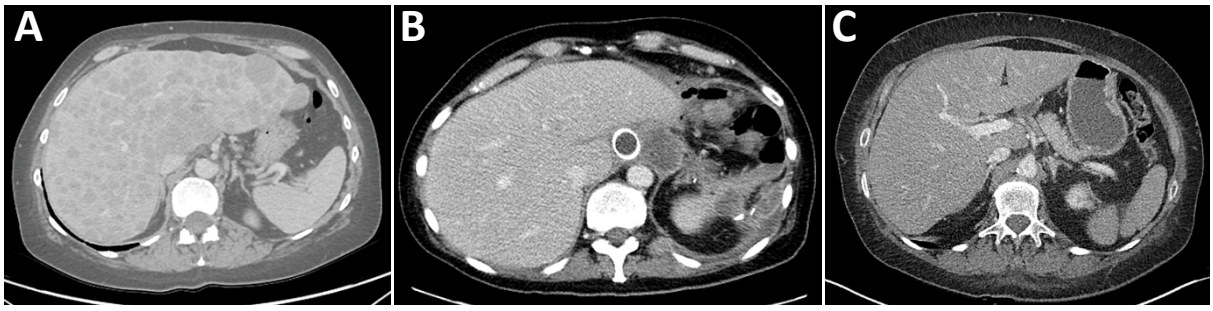


Figure 1. *Contrast enhanced computer tomography images of the abdomen, demonstrating varied radiological findings in patients with primary hepatic lymphoma (PHL). (A) Case 1 showing heterogeneous multiple ill-defined hypodense liver lesions. (B) Case 2 demonstrating multifocal perfusion abnormalities without discrete masses. (C) Case 6 appearing unremarkable with no intrahepatic or extrahepatic biliary duct dilatation.*

Throughout the group, abnormal liver biochemistry was frequently observed. 57.1% (n=4) of cases had increased ALT and total bilirubin, and the hepatocellular pattern of AST levels, when available, were elevated. Particularly, in patients with underlying hepatic comorbidities like cirrhosis or NAFLD, cholestatic indicators, such as ALP and GGT, were inconsistently raised. In contrast, LDH's function as a sensitive biomarker of systemic involvement in this disease entity is supported by the fact that it was consistently increased in all examined patients (100%, n=6). Tumor markers, on the other hand, stayed within normal ranges: AFP was normal in every measured case, and CEA was not increased in 83.3% (n=5/6 examined), indicating that these laboratory abnormalities are more likely to be the result of inflammatory and infiltrative processes than basic hepatic or stem cell malignancy.

Radiological features

CT-based radiological evaluation across the seven cases revealed a nonspecific differential list for hepatic abnormalities. Radiological imaging for Cases 1, 2, and 6 are depicted below in Figure 1. Data for available CT reports showed that the most frequent finding was heterogeneous, multiple, ill-defined hypodense liver lesions (57.1%, n=4; cases 1, 3, 4, and 5). Case 2 demonstrated multifocal perfusion abnormalities without discrete masses, case 6 showed no abnormality, and case 7 showed a solitary lesion. Across all cases, the radiological differential diagnosis spanned disseminated *Mycobacterium tuberculosis* (case 1), benign transient hepatic perfusion abnormalities (case 2), regenerative nodules (case 5), metastases (cases 1, 3, and 4), and hepatocellular carcinoma (cases 3, 4, 5, and 7). Collectively, these observations highlight the tendency

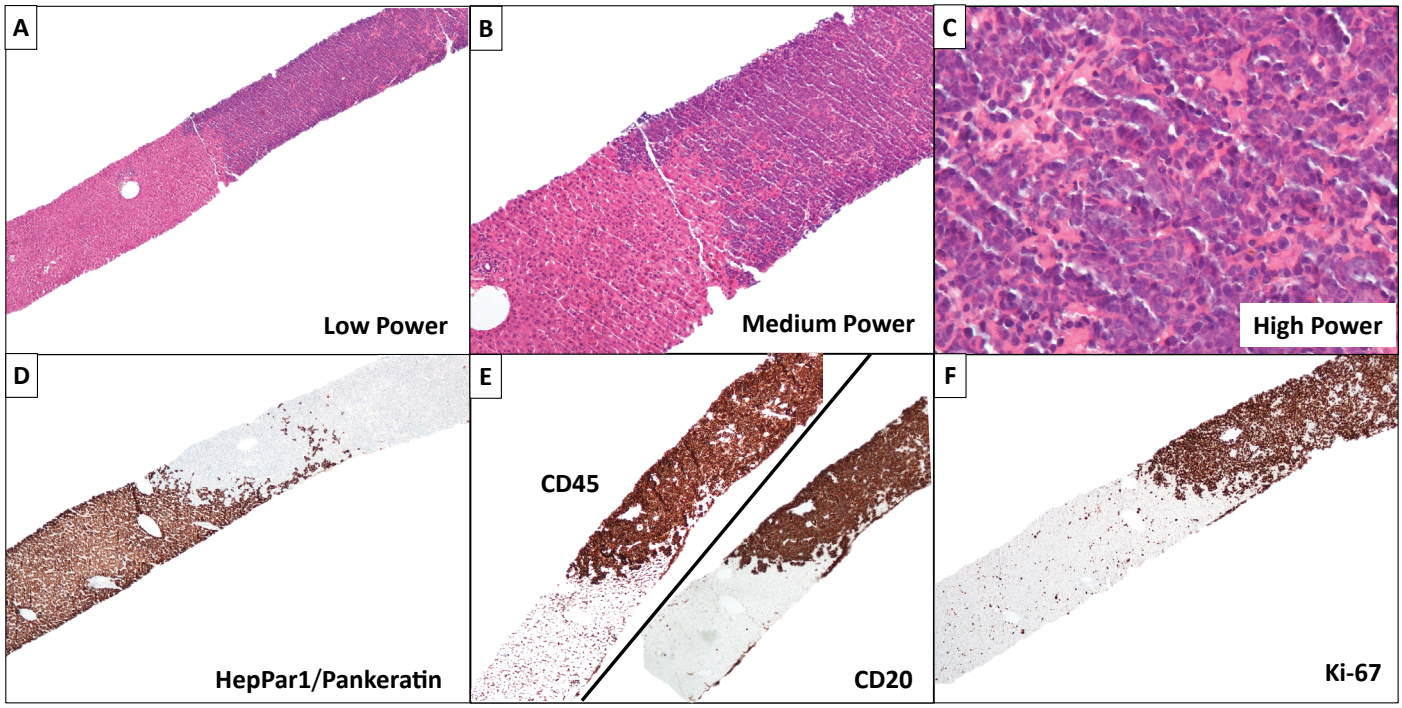


Figure 2. *Nodular infiltration pattern in Primary Hepatic Lymphoma (Case 2, Burkitt lymphoma). (A) and (B) Combined low- and medium-power H&E image demonstrating well-circumscribed nodular aggregates of lymphoma replacing hepatic lobules. The nodular pattern is characterized by sharply demarcated expansile foci of malignant lymphoid cells set against otherwise preserved hepatic parenchyma. (C) High-power view highlights classic Burkitt cytology with medium-sized cells, basophilic cytoplasm, and frequent mitoses/apoptotic bodies. (D) Hepar-1/pancytokeratin immunostaining highlights residual hepatocytes and confirms complete architectural effacement within the involved nodules. (E) The infiltrate shows diffuse CD45 and strong CD20 positivity. (F) Ki-67 proliferation index approaches 100%, supporting a high-grade B-cell neoplasm.*

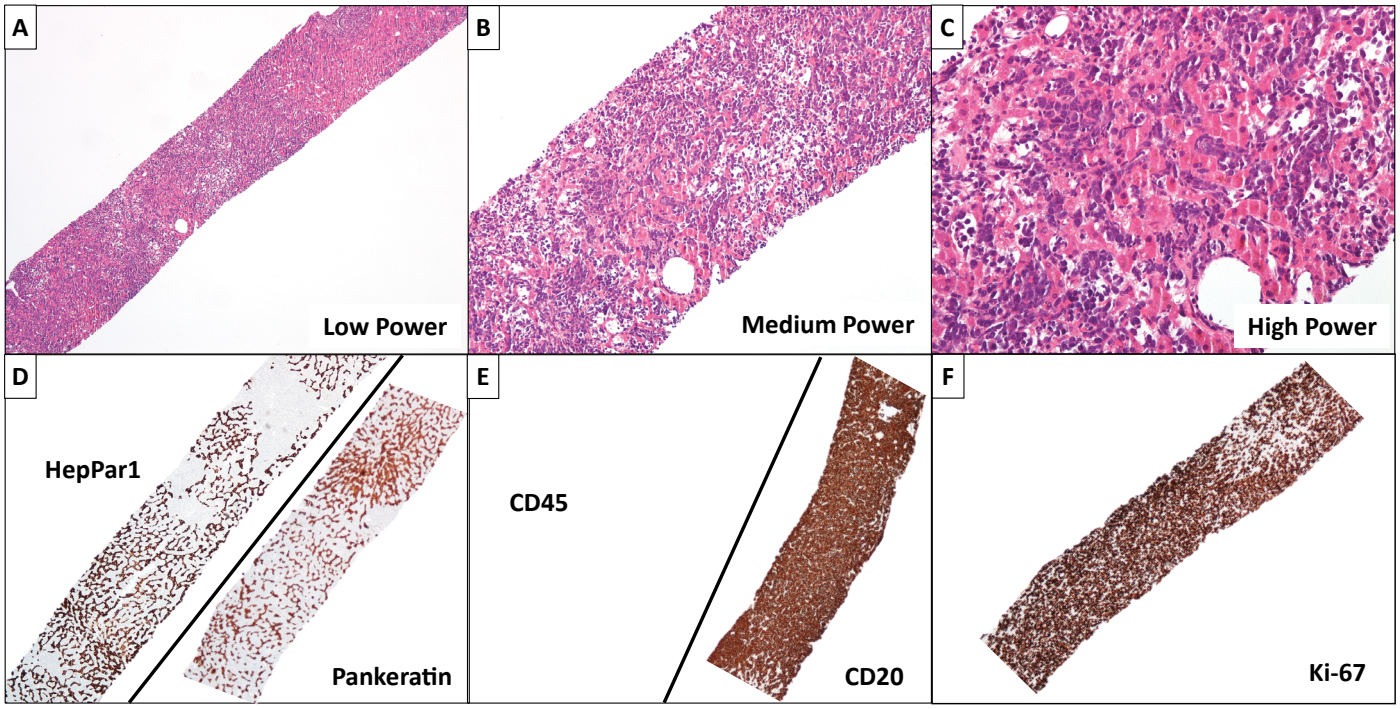


Figure 3: *Sinusoidal infiltration pattern in Primary Hepatic Lymphoma (Case 6, Double-Hit DLBCL). (A) and (B) Combined low- and medium-power H&E image showing a diffuse sinusoidal infiltration pattern, with atypical large lymphoid cells distending hepatic sinusoids and disrupting the lobular architecture. (C) High-power view highlights pleomorphic cytology with prominent nucleoli and abundant apoptosis/necrosis. (D) Hepar-1 and pancytokeratin staining outline the residual hepatocytes and accentuate near-complete sinusoidal replacement by the infiltrate. (D) CD45 and CD20 demonstrate diffuse B-cell lineage involvement. (E) Ki-67 shows a markedly elevated proliferation index.*

of primary hepatic lymphoma to present radiologically as heterogeneous liver lesions without distinctive features, underscoring that imaging alone is insufficient for diagnosis. Furthermore, PHL can present as hypoattenuated areas on CT mimicking focal fatty infiltration and devoid of any mass-effect.

Histopathological Features

Final diagnoses were confirmed on core needle liver biopsies for all 7 cases. The pattern of infiltration ranged from diffuse sheet-like replacement of hepatic parenchyma (n=5) to focal or clustered aggregates of atypical lymphoid cells (n=2). Histologically, the most common subtype was diffuse large B-cell lymphoma (DLBCL; 71.4%, n=5). The DLBCL subtypes in this cohort included germinal center type (n=2), MYC-rearranged (n=1), EBV-positisve (n=1), and double-hit (n=1). In the non-DLBCL group, one patient was diagnosed with Burkitt lymphoma (14.3%), and another with marginal zone lymphoma (14.3%).

Figure 2 shows the histopathological features in Case 2, with a predominantly nodular pattern of hepatic infiltration and sharply demarcated aggregates of atypical lymphoid cells replacing the liver parenchyma. The cells displayed classic Burkitt cytomorphology and a Ki-67 index near 100%. Findings were diagnostic of Burkitt lymphoma.

Figure 3 demonstrates the histological and IHC findings in Case 6. The histomorphology in this case demonstrated a diffuse sinusoidal pattern of infiltration, with large atypical lymphoid cells permeating hepatic sinusoids and effacing the native architecture. The biopsy was submitted under the clinical suspicion of florid autoimmune hepatitis and was therefore processed as a medical liver biopsy, with reflex staining for PAS, PAS-D, reticulin, trichrome, and iron stains that were performed before the malignant infiltrate was recognized. Reclassification as a surgical/oncologic specimen and subsequent expansion to a full immunohistochemical panel resulted in a diagnostic delay, after which the findings confirmed double-hit DLBCL, correlating with the patient's fulminant hepatic failure.

Immunohistochemistry Profile

Immunohistochemistry supported B-cell lineage in all cases. All patients demonstrated CD20 positivity (100%, n=7/7). PAX5 was positive in all cases assessed (100%, n=6/6); PAX5 was not performed in one case. Additional B-cell markers were present in subsets, including CD79a and CD10. EBER in situ hybridization was positive in the EBV-associated DLBCL. Non-lymphoid lineage markers were negative where tested, helping exclude mimics: hepatocellular (Hepar-1), epithelial (CK7/CK20), neuroendocrine (synaptophysin/INSM1/chromogranin), and melanocytic (HMB45/Melan-A) panels were negative in multiple cases. Additional immunophenotypic patterns were consistent with the expected biology of each lymphoma subtype. By the Hans classification, three DLBCL cases (Cases 1, 3, and 5) demonstrated a germinal-center B-cell (GCB) phenotype. Cases 3 and 5 were CD10-positive, while Case 1 showed a CD10-negative but BCL6-positive/MUM1-negative profile, including strong BCL6 expression, all supportive of a GC derivation. The EBV-associated DLBCL demonstrated a non-germinal center/ABC phenotype

Pt.	Diagnosis	CD45	CD20	PAX5	MUM1	BCL2	CD30	CD10	BCL6	c-MYC	CD21	CD23	Cyclin D1	EBER	ALK1	Ki67 %
1	● DLBCL (GC)															90
3	● DLBCL (MYC)	NA														100
4	DLBCL (EBV)									NA						90
5	● DLBCL (GC)			NA							NA	NA		NA	NA	100
6	DLBCL (double hit)														NA	100
2	Burkitt Lymphoma						NA					NA			NA	100
7	Marginal zone Lymphoma									NA	NA	NA	NA		NA	80

Figure 4: *Immunohistochemical heatmap of hepatic lymphomas in this case series. Strong, weak, and absent expression are represented by green, orange, and red tiles, respectively. Black circles beside DLBCL diagnoses denote cases classified as germinal-center B-cell (GCB) phenotype by the Hans algorithm. "NA" indicates markers that were not assessed in a given case.*

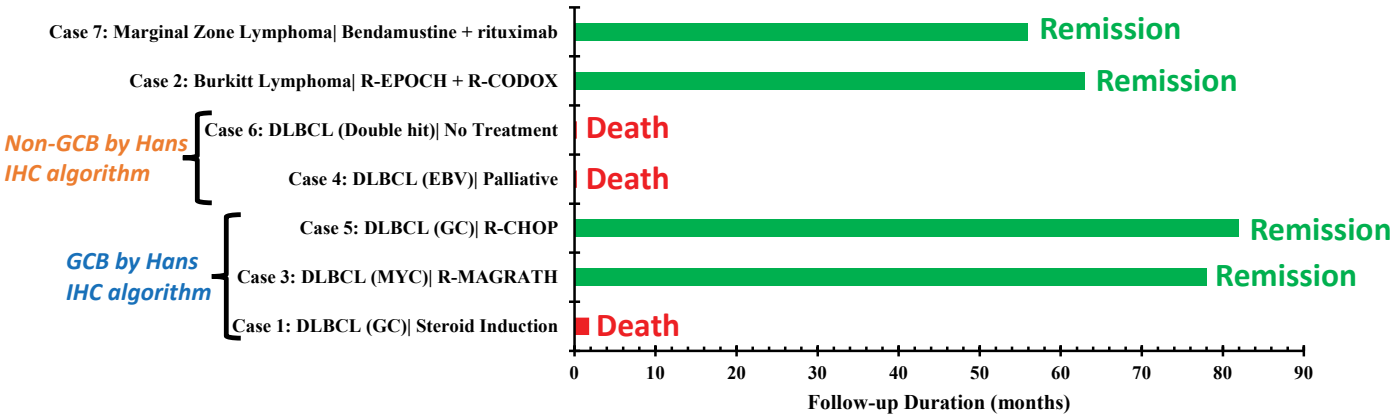


Figure 5: *Swimmer plot summarizing treatment, cell-of-origin (Hans classifier), outcomes, and follow-up duration in the primary hepatic lymphoma cohort. Abbreviations: DLBCL – diffuse large B-cell lymphoma; GCB – germinal center B-cell phenotype; Non-GCB – non–germinal center B-cell phenotype; EBV – Epstein–Barr virus; IHC – immunohistochemistry; R-CHOP – rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-MAGRATH – rituximab-Magrath regimen (cyclophosphamide, doxorubicin, vincristine, methotrexate, leucovorin, cytarabine, intrathecal therapy); R-EPOCH – rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; R-CODOX – rituximab-CODOX-M regimen (cyclophosphamide, vincristine, doxorubicin, methotrexate).*

(CD10–/BCL6–/MUM1+) with strong CD30 expression, consistent with its immunoblastic morphology and EBV-driven differentiation. The Burkitt lymphoma case showed the classic COO (Cell Of Origin) signature of CD10 and BCL6 co-expression with BCL2 negativity and an almost 100% Ki-67 index. The marginal zone lymphoma retained a low-grade B-cell phenotype (CD20+/PAX5+) and was negative for CD10, BCL6, Cyclin D1, and CD30. One MYC-rearranged DLBCL (Case 3) demonstrated BCL2 negativity on our institutional assay (clone 124) but positivity at an external reference center using the more sensitive E17 clone; because double-expressor classification is assay-specific and clone-dependent, this case was categorized as MYC-rearranged only. Across the cohort, proliferation indices were uniformly high (80–100%), reflecting the aggressive biological behavior of these B-cell lymphoproliferative disorders.

Treatment and prognosis

Across the seven-case cohort, clinical outcomes varied substantially by lymphoma subtype, cell-of-origin phenotype, and initial presentation (Figure 5). Among the GCB-type DLBCLs, two patients (Cases 3 and 5) achieved durable remissions following R-MAGRATH (rituximab, cyclophosphamide, doxorubicin, vincristine, methotrexate, leucovorin, cytarabine, intrathecal therapy) and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), with follow-up of 78 and 82 months, respectively. In contrast, fulminant hepatic presentations were associated with inferior outcomes: Case 1 (GCB-DLBCL) survived 1.8 months despite steroid induction; Case 4 (EBV-positive DLBCL, non-GCB by Hans) died within 0.3 months from multiorgan failure; and Case 6 (double-hit DLBCL, non-GCB by Hans) died within days (0.2 months) from acute liver

failure prior to receiving treatment. The Burkitt lymphoma (Case 2) demonstrated an aggressive course despite intensive chemotherapy (R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) followed by R-CODOX (rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate)), with death at 63 months due to progression of an unrelated pancreatic adenosquamous carcinoma while the lymphoma remained in remission. The marginal zone lymphoma (Case 7) responded well to bendamustine-rituximab and remains in ongoing remission at 56 months. Taken together, these findings illustrate the heterogeneity of PHL and underscore that cell-of-origin (GCB vs non-GCB), molecular high-grade features (MYC/BCL2), and pattern of liver involvement strongly influence clinical trajectory and survivorship.

Discussion

PHL is a hepatic lymphoproliferative disorder confined to the hepatic compartment with no clinical, radiological, or pathological evidence of extrahepatic disease at the time of diagnosis [1]. PHL represents a rare extranodal form of non-Hodgkin lymphoma (NHL), accounting for approximately 0.4% of all extranodal NHL and only 0.016% of total non-Hodgkin's lymphoma cases [2,3]. Overall PHL spans about 0.1% of all primary hepatic malignancies [2]. The rarity of PHL can be attributed due to the relative paucity of native lymphoid tissue within the hepatic parenchyma. Furthermore, the host microenvironment creates a generally unfavourable environment for the propagation of malignant lymphoid clones.

In keeping with the western literature, all cases in our series were B-cell lymphomas, reflecting the predominance of diffuse large B-cell lymphoma (DLBCL) and other mature B-cell neoplasms in North America and Europe. One large (n=1372) study based on the US population showed that the top four high-incidence subtypes of PHL were DLBCL (78.8%, n=856), T/NK-cell lymphoma (4.7%, n=51), marginal zone lymphoma (4.5%, n=49), and follicular lymphoma (3.1%, n=34) [17]. In contrast, series from East Asia report a proportionally higher incidence of T/NK-cell lymphoma type PHL [18–22]. These geographic differences emphasizes the importance of regional epidemiology when interpreting hepatic lymphoid infiltrates and reporting of cases in the literature.

In our series, patients had a background history of HIV (n=3), chronic hepatitis C (n=2), and acute (n=1) or past (n=3) EBV infections, which are well-documented risk factors for PHL [17,23–26]. The viral interplay in the pathogenesis of PHL may result from chronic immune activation, persistent antigenic stimulation at the gut–liver interface, and impaired T-cell surveillance. EBV could similarly prime the hepatic microenvironment and lead to B-cell transformation. Moreover, comorbidities such as miliary tuberculosis, HSV1, autoimmune disease, or MDS, as seen in our case series, can further exacerbate this chronic inflammatory state and subsequent immune dysregulation, which favours hepatic recruitment and retention of mature clonal B cells. These epidemiological factors reinforce the notion that PHL arises not from hepatic hematopoietic progenitors (CD34+) but from mature B cells that home to the liver in the context of immunologic dysregulation. Early hepatic confinement in PHL reflects the unique hepatic microenvironment. Sinusoidal endothelial cells and Kupffer cells express adhesion molecules and chemokines that promote lymphocyte retention [27]. We propose that it may be that these PHL downregulate lymph-node homing receptors while upregulating liver-tropic receptors, resulting in a survival advantage within the hepatic compartment and thus preventing early dissemination to lymph nodes or bone marrow. Thus, PHL we believe is predominantly associated with hepatic-recruited mature B cells.

Radiologic assessment for PHL remains nonspecific. Depending on the histological pattern of infiltration, such as nodular, diffuse sinusoidal, or portal-based, the resultant imaging findings may resemble a broad spectrum of hepatic diseases, such as metastases, abscess, autoimmune hepatitis, or fulminant hepatocellular injury. In our series, even within the DLBCL group itself, four patients (cases 1,3,4,5) had multiple hepatic lesions, and one patient (case 6) remained non-diagnostic on imaging. These observations reinforce the notion that imaging cannot reliably distinguish PHL from more common hepatocellular disease, and that histopathology remains essential for diagnosis. Outside of routine lymphoma staging protocols and assessment response to treatment, there may be a role for [18F]FDG-PET as a non-invasive imaging modality to confirm that the lymphoma is confined to the liver compartment, thereby increasing the pretest probability for PHL [28–30]. Due to the rarity of PHL, more studies are needed to establish the utility of PET in increasing the pretest probability of PHL. Historically, the presence of radiologic lymphadenopathy has been used to exclude PHL and assign a diagnosis of secondary hepatic lymphoma (SHL). It is important to note that reliance on imaging alone can lead to misclassification between PHL and SHL. Case 4 in our series showed the presence of axillary lymphadenopathy (LAD) during the clinical workup, which raised the leading differential diagnosis to SHL. However, the subsequent axillary lymph node biopsy revealed reactive hyperplasia. This highlights a critical distinction that radiology-based LAD should not automatically exclude PHL and requires biopsy-proven nodal lymphoma involvement to differentiate PHL from SHL.

A recurring systems-level pathological challenge in diagnosing hepatic lymphoma occurs at the preanalytical stage, due to the tissue's triage status. Most liver biopsies are obtained based on clinical suspicion to investigate autoimmune, infectious, or metabolic disease and are therefore appropriately processed within the 'medical-liver biopsy' workflow. This reflexes special stains such as PAS, PAS-D, reticulin, trichrome, and Perls Prussian Blue, which are essential in evaluating the broad differential diagnosis for hepatocellular pathology. However, these medical liver biopsies can masquerade the underlying process as an occult lymphoma; therefore, this sequential exclusion-based approach delays the early recognition and pathology targeted work-up for lymphoma. In Case 6, the liver biopsy was triaged as a medical liver case based on clinical suspicion for autoimmune hepatitis, and only after the evaluation of the initial panel of stains was the case reclassified as suspicious for lymphoma and worked up as such. These delays reflect workflow design rather than shortcomings of any individual diagnostic service, highlighting the diagnostic complexity of lymphomas whose clinical presentations closely mimic acute liver injury or hepatitis. Hepatic dysfunction caused by hematological malignancies usually occurs late in the course of the disease, and liver involvement as the predominant primary

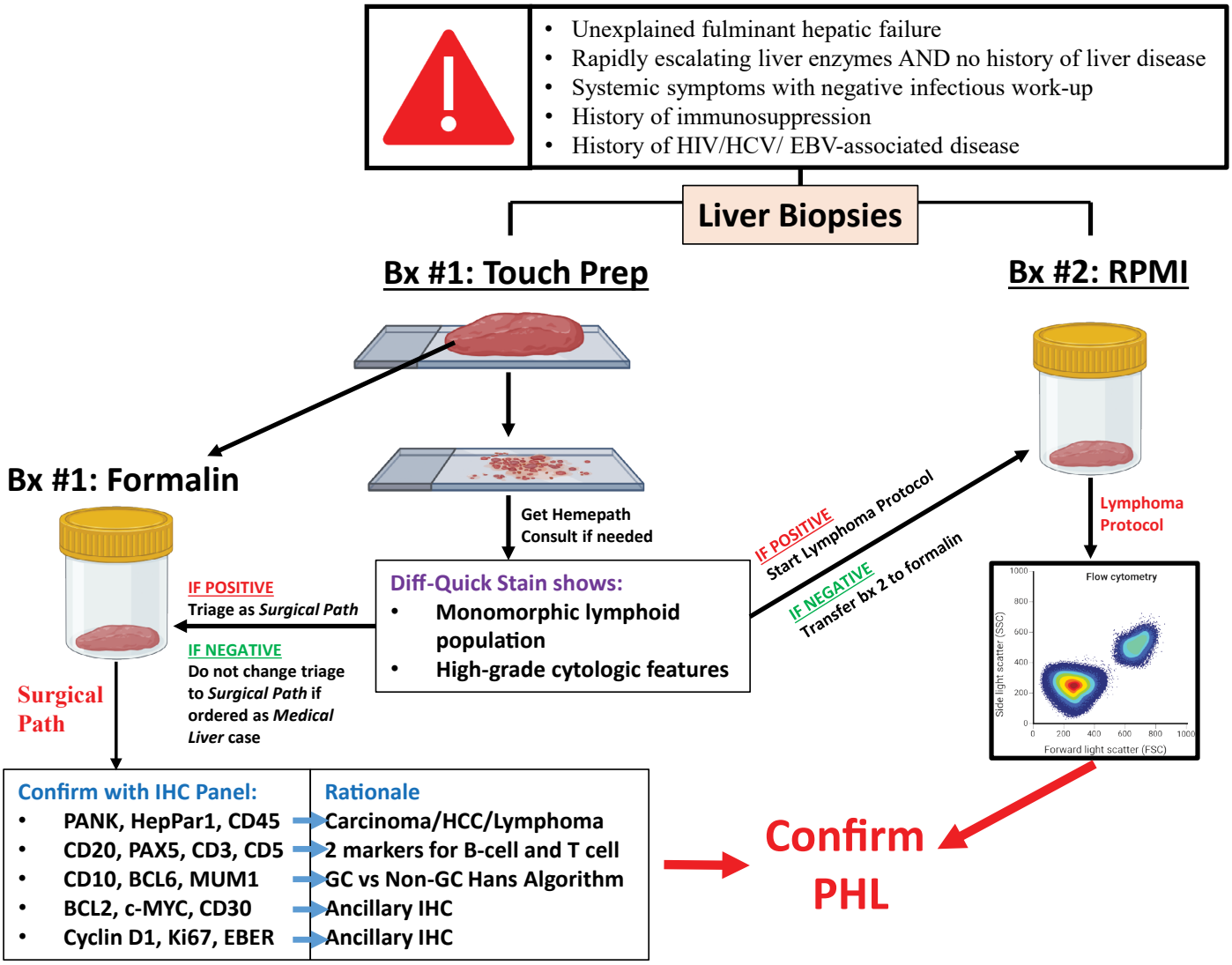


Figure 6: *Proposed ideal Triage Algorithm for Suspected Primary Hepatic Lymphoma (PHL).*
Abbreviations: Human immunodeficiency virus (HIV), Hepatitis C virus (HCV), Epstein–Barr virus (EBV), Roswell Park Memorial Institute medium (RPMI), Immunohistochemistry (IHC), Pan-cytokeratin (PANK), Hepatocellular carcinoma (HCC), germinal center (GC), primary hepatic lymphoma (PHL)

presentation remains relatively rare [11,12]. PHL can manifest as progressive hepatitis and acute hepatic failure. The presence of constitutional symptoms, hematological abnormalities and altered acute phase reactants can complicate diagnostic evaluation. From an epidemiological perspective, the most common causal factors of acute liver failure (ALF) include viral infection, medications, drug use, toxins, metabolic disorders, and vascular disorders such as hepatic vein thrombosis. Invasion of tumors can also cause ALF. Hepatic infiltration by hematological malignancies is observed in 15–22% of cases, and it can be the underlying etiology of ALF [10].

It is crucial to identify PHL as the underlying cause of ALF at the earliest possible, as early intervention with chemotherapy could potentially improve the patient's outcome. However, 'proving' the hepatic involvement of DLBCL is difficult if liver dysfunction is the primary presentation. Hence, lymphoma should be suspected in any patient whose course is atypical for hepatitis and who present with ALF, hepatomegaly, lactic acidosis, and/or a markedly elevated lactate dehydrogenase even in the absence of lymphadenopathy. Accurate diagnosis of lymphoma-induced ALF and prompt introduction of chemotherapy are crucial for improved outcomes as these lesions are exquisitely chemosensitive.

Improving the early diagnosis of PHL requires heightened clinical suspicion, which justifies earlier interdisciplinary review and early intervention with a liver biopsy in clinical scenarios such as unexplained fulminant hepatic failure, rapidly escalating liver enzymes devoid of prerequisite liver disease, systemic symptoms with negative infectious work-up, or a history of immunosuppression or HIV/HCV/ EBV-associated disease. In such scenarios, several adjunctive techniques may expedite the diagnosis of PHL. A pathway outlined in Figure 6 commences with touch imprints, which can provide immediate cytologic clues for lymphoma, such

as monomorphic lymphoid infiltrates or high-grade cytology. A complementary core biopsy can be placed in Roswell Park Memorial Institute medium (RPMI) for flow cytometry to expedite evaluation of B-cell or T-cell monoclonal populations. Subsequently, these cases can then be classified as surgical biopsies from the outset, avoiding the stepwise medical-liver work-up that may postpone definitive diagnosis. These strategies are not intended for all liver biopsies but can be selectively employed when clinical concern for PHL is suspected. However, due to the rare occurrence of this disease, added retrieval of onsite cytology for all liver biopsies is not cost effective and remains unattainable in our current clinical workflow protocols.

The overall outcomes in our seven series cohort mirrored the known heterogeneity of hepatic lymphomas. GCB-type DLBCLs treated with R-CHOP or R-MAGRATH achieved long-term remission lasting more than 6 years, whereas marginal zone lymphoma displayed an indolent course with sustained remission. In contrast, fulminant hepatic presentations, notably the EBV-positive DLBCL and double-hit DLBCL, are associated with survival measured in days, consistent with the published literature, linking diffuse sinusoidal infiltration to catastrophic hepatic failure. The Burkitt lymphoma responded to intensive therapy but ultimately succumbed to an unrelated malignancy rather than lymphoma progression.

Conclusion

PHL represents a rare subtype of otherwise common diffuse large B-cell lymphoma (DLBCL) accounting for less than 1% of all DLBCL cases. Due to the very nonspecific clinical manifestation, PHL diagnosis becomes challenging clinically, radiologically and pathologically. Moreover, the rarity and atypical presentation of PHL makes it is often clinically indistinguishable from a broad spectrum of other common hepatic diseases such as malaria, hydatid cyst, viral and autoimmune hepatitis, hepatocellular carcinoma, hepatic adenoma, and metastatic malignancy. Although hepatic dysfunction with acute liver failure as a presenting feature is uncommon, its occurrence requires a high index of clinical suspicion particularly in patients with underlying viral infections (HIV, HCV, EBV) to prompt early intervention of liver biopsy for a timely diagnosis. Ultimately, the final diagnosis of PHL is made by the histology and immunohistochemistry examination of a liver biopsy which remains the gold standard for establishing the diagnosis

Though the clinical course of PHL is aggressive, yet it remains highly chemosensitive which makes early recognition crucial and clinically impactful. Thus, early liver biopsy and the judicious utilization of rapid ancillary techniques, coupled with appropriate triage and multidisciplinary involvement ensures that the timely diagnosis of PHL is is likely to influence clinical decision-making. Given these challenges, the development and adoption of universal, consensus-based diagnostic criteria are essential for improving diagnostic standardization and for expanding our knowledge of this rare but clinical important entity.

Disclosures

The authors declare no conflicts of interest.

This was presented in part as an oral presentation at the XXXVth International Association of Pathology Congress, 27-31 October 2024, Cancun, Mexico.

Financial Support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Anthony PP, Sarsfield P, Clarke T. Primary lymphoma of the liver: clinical and pathological features of 10 patients. J Clin Pathol. 1990;43(12):1007–13.
2. Padhan RK, Das P. Primary hepatic lymphoma. Trop Gastroenterol. 2015;36(1):14–20.
3. Lohana AK, Tariq MA, Abid S. Hepatic Lymphoma. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
4. Ugurluer G, Miller RC, Li Y, et al. Primary Hepatic Lymphoma: A Retrospective, Multicenter Rare Cancer Network Study. Rare Tumors. 2016;8(3):6502.
5. Bohlok A, De Grez T, Bouazza F, et al. Primary Hepatic Lymphoma Mimicking a Hepatocellular Carcinoma in a Cirrhotic Patient: Case Report and Systematic Review of the Literature. Case Rep Surg. 2018;2018:9183717.
6. Alves AMA, Torres US, Velloni FG, Ribeiro BJ, Tiferes DA, D'Ippolito G. The many faces of primary and secondary hepatic lymphoma: imaging manifestations and diagnostic approach. Radiol Bras. 2019;52(5):325–30.
7. Zhang SL, Chen C, Rao QW, et al. Incidence, Prognostic Factors and Survival Outcome in Patients With Primary Hepatic Lymphoma. Front Oncol. 2020;10:750.
8. Harris AC, Ben-Ezra JM, Contos MJ, Kornstein MJ. Malignant lymphoma can present as hepatobiliary disease. Cancer. 1996;78(9):2011–9.
9. Harris AC, Kornstein MJ. Malignant lymphoma imitating hepatitis. Cancer. 1993;71(8):2639–46.
10. Lisker-Melman M, Pittaluga S, Pluda JM, et al. Primary lymphoma of the liver in a patient with acquired immune deficiency syndrome and chronic hepatitis B. Am J Gastroenterol. 1989;84(11):1445–8.
11. Mohamed M, Fernando R. Diagnostic and therapeutic quandaries in a patient with primary hepatic lymphoma and concurrent hepatitis C infection. Indian J Hematol Blood Transfus Off J Indian Soc Hematol Blood Transfus. 2014;30(Suppl 1):394–7.
12. Kikuma K, Watanabe J, Oshiro Y, et al. Etiological factors in primary hepatic B-cell lymphoma. Virchows Arch Int J Pathol. 2012;460(4):379–87.
13. Sutton E, Malatjalian D, Hayne OA, Hanly JG. Liver lymphoma in systemic lupus erythematosus. J Rheumatol. 1989;16(12):1584–8.
14. Rostaing L, Suc B, Fourtanier G, Baron E, Lloveras JJ, Durand D. Liver B cell lymphoma after liver transplantation. Transplant Proc. 1995;27(2):1781–2.
15. Weigand K, Weigand K. Percutaneous liver biopsy: retrospective study over 15 years comparing 287 inpatients with 428 outpatients. J Gastroenterol Hepatol. 2009;24(5):792–9.
16. Swadley MJ, Deliu M, Mosunjac MB, Gunthel CJ, Nguyen MLT, Hanley KZ. Primary and secondary hepatic lymphomas diagnosed by image-guided fine-needle aspiration: a retrospective study of clinical

and cytomorphologic findings. Am J Clin Pathol. 2014;141(1):119–27.

17. Qiu MJ, Fang XF, Huang ZZ, et al. Prognosis of primary hepatic lymphoma: A US population-based analysis. Transl Oncol. 2021;14(1):100931.
18. Mishra S, Shukla A, Tripathi AK, Kumar A. Primary T-cell lymphoma of liver. BMJ Case Rep. 2013;2013.
19. Stancu M, Jones D, Vega F, Medeiros LJ. Peripheral T-cell lymphoma arising in the liver. Am J Clin Pathol. 2002;118(4):574–81.
20. Miyashita K, Tomita N, Oshiro H, et al. Primary hepatic peripheral T-cell lymphoma treated with corticosteroid. Intern Med Tokyo Jpn. 2011;50(6):617–20.
21. Higuchi T, Nomoto K, Mori H, et al. Case report: primary hepatic lymphoma associated with chronic liver disease. J Gastroenterol Hepatol. 1997;12(3):237–42.
22. Eom DW, Huh JR, Kang YK, Lee YS, Yu E. Clinicopathological features of eight Korean cases of primary hepatic lymphoma. Pathol Int. 2004;54(11):830–6.
23. Aozasa K, Mishima K, Ohsawa M. Primary malignant lymphoma of the liver. Leuk Lymphoma. 1993;10(4–5):353–7.
24. Nasr Ben Ammar C, Chaari N, Kochbati L, Besbes M, Maalej M. Primary non-Hodgkin lymphoma of the liver: case report and review of the literature. Cancer Radiother J Soc Francaise Radiother Oncol. 2006;10(8):595–601.
25. Santos ES, Raez LE, Salvatierra J, Morgensztern D, Shanmugan N, Neff GW. Primary hepatic non-Hodgkin's lymphomas: case report and review of the literature. Am J Gastroenterol. 2003;98(12):2789–93.
26. El-Sharkawi D, Ramsay A, Cwynarski K, et al. Clinico-pathologic characteristics of patients with hepatic lymphoma diagnosed using image-guided liver biopsy techniques. Leuk Lymphoma. 2011;52(11):2130–4.
27. Wang Q, Wu K, Zhang X, et al. Primary hepatopancreatobiliary lymphoma: Pathogenesis, diagnosis, and management. Front Oncol. 2022;12:951062.
28. Isasi CR, Lu P, Blaufox MD. A metaanalysis of 18F-2-deoxy-2-fluoro-D-glucose positron emission tomography in the staging and restaging of patients with lymphoma. Cancer. 2005;104(5):1066–74.
29. Seshadri N, Ananthasivan R, Kavindran R, Srikanth G, Chandra S. Primary hepatic (extranodal) lymphoma: utility of [(18)F]fluorodeoxyglucose-PET/CT. Cancer Imaging Off Publ Int Cancer Imaging Soc. 2010;10(1):194–7.
30. Pan B, Wang CS, Han JK, Zhan LF, Ni M, Xu SC. 18F-fluorodeoxyglucose PET/CT findings of a solitary primary hepatic lymphoma: a case report. World J Gastroenterol. 2012;18(48):7409–12.