Hepatic Lymphoma Diagnosis

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KEYWORDS

• Aggressive NK-cell leukemia • B-lymphoblastic leukemia/lymphoma • Burkitt lymphoma
• Chronic lymphocytic leukemia/small lymphocytic lymphoma • Classic Hodgkin lymphoma
• Diffuse large B-cell lymphoma • Follicular lymphoma • Hairy cell leukemia

Key points

- Although hepatic involvement by systemic lymphoma is common, rare cases of primary hepatic lymphoma (PHL) may be first encountered on liver biopsy.
- Epstein-Barr virus (EBV) typically infects B-cells through the EBV receptor (CD21). In EBV hepatitis, a liver biopsy most commonly shows a mild sinusoidal lymphohistiocytic infiltrate with only rare EBV-positive B-cells, which are best demonstrated by comparing a Pax-5 immunostain with an EBV *in situ* hybridization stain.
- Diffuse large B-cell lymphoma and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue are the most common PHLs.
- T-cell or natural killer (NK)-cell lymphomas are less commonly diagnosed on liver biopsy; specific considerations include peripheral T-cell lymphoma, not otherwise specified; hepatosplenic T-cell lymphoma; and aggressive NK-cell leukemia.
- Classic Hodgkin lymphoma (CHL) and nodular lymphocyte–predominant Hodgkin lymphoma can rarely involve the liver; ductopenia may be associated with CHL.

ABSTRACT

Systemic hematopoietic disorders may present on liver biopsy, and rare cases of primary hepatic lymphoma (PHL) may be encountered. Hepatopathologists must be familiar with the full spectrum of hematopoietic disorders involving the liver and be prepared to exclude benign mimics. PHL, which is confined to the liver without extrahepatic involvement, can present as solitary or multiple nodules, raising consideration for carcinoma on imaging, or may mimic benign inflammatory conditions, posing a diagnostic challenge. This article describes clinical, morphologic, and immunophenotypic features of some of the most common hematopoietic neoplasms involving the liver, along with differential diagnosis and recommended ancillary testing.

OVERVIEW

Although systemic hematopoietic neoplasms commonly involve the liver, hepatopathologists may encounter rare cases of primary hepatic lymphoma (PHL), which can often mimic benign conditions. PHL is defined as a liver-confined lymphoma without extrahepatic involvement,[1,2] and it constitutes approximately 0.4% of all primary extranodal non-Hodgkin lymphomas (NHLs).[3–5] It most commonly affects middle-aged men, with a mean age of 50 years to 62 years

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(range: 21–86 years), who present with nonspecific symptoms (fever, night sweats, and/or weight loss) and elevated lactate dehydrogenase in the setting of normal levels of α-fetoprotein and carcinoembryonic antigen.[4–8] The exact etiology of PHL is unknown, but chronic viral infection (ie, hepatitis B virus [HBV], hepatitis C virus [HCV], HIV, or Epstein-Barr virus [EBV]) and/or immune dysfunction (ie, autoimmune diseases or immunosuppression) may play a role in pathogenesis.[5,8,9] Although initially considered an aggressive disease,[2] recent studies indicate that PHL patients may have a more favorable prognosis than previously believed, with a reported 5-year survival rate of 77% to 83%.[4,5,8]

A majority of PHLs are B-cell lymphomas with diffuse large B-cell lymphoma (DLBCL) the most common subtype.[4,5,8] Although many cases of PHL efface the hepatic parenchyma and form solitary or multiple nodules, some cases may have more subtle morphologic findings in which neoplastic cells are small or intermediate in size with predominant portal and/or sinusoidal involvement.[4,5,8] For this reason, hepatopathologists must be familiar with clinical (ie, lactate dehydrogenase elevation, viral infection status, and transplant history), morphologic (ie, architectural pattern and atypical cytologic features [**Box 1**]), and immunophenotypic features of lymphoma on liver biopsies to distinguish between reactive and neoplastic lymphoid infiltrates. Assessment of an overall architectural pattern of injury (ie, portal/effacing vs sinusoidal) and cell size can be helpful in narrowing the differential diagnosis (**Fig. 1**, **Table 1**). Immunophenotyping is always required for classification of lymphoma, and an initial panel of B-cell and T-cell markers (including CD20, Pax-5, CD3, and CD5 immunohistochemical stains as well as Epstein-Barr encoding region [EBER] *in situ* hybridization [ISH] stain) is indicated when lymphoma is a consideration. A second round of stains targeted to a more

Box 1
Atypical cytologic features of a hepatic lymphoid infiltrate that suggest a need for further work-up

- Large cells
- Piling up in the sinusoids
- Increased or atypical mitotic figures
- Prominent nucleoli
- Hemophagocytosis
- Ductopenia
- Extramedullary hematopoiesis
- Geographic necrosis
- Granulomas
- Marked portal expansion/parenchymal effacement

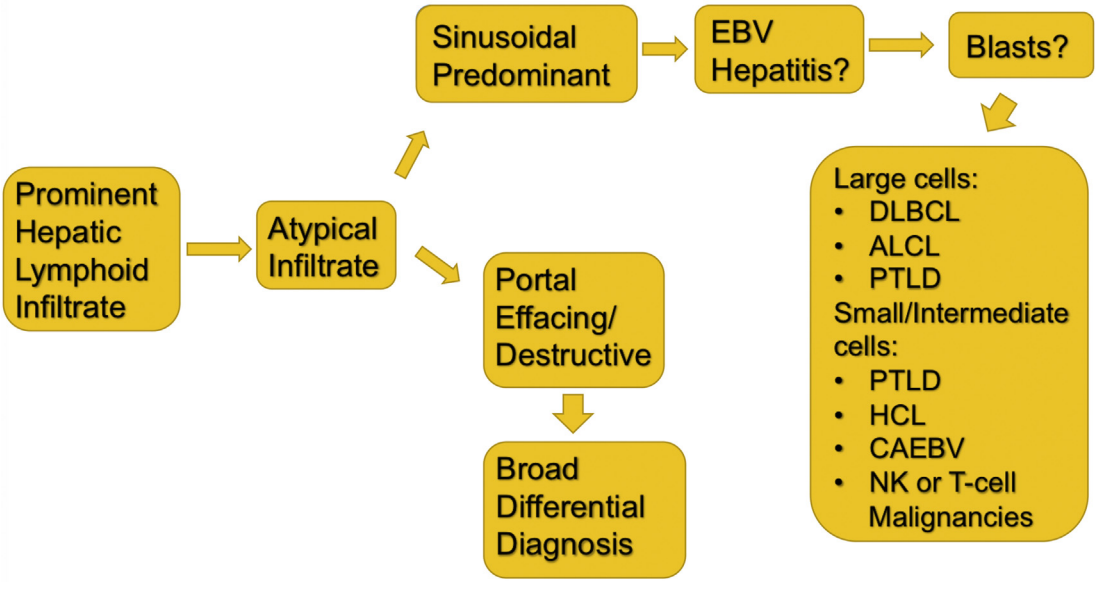

Fig. 1. Differential diagnosis of an atypical hepatic lymphoid infiltrate by architecture. CAEBV, chronic active EBV.