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Original contribution

Hepatic involvement by T-cell neoplasms: a clinicopathologic study of 40 cases☆

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Summary Hepatic involvement by a T-cell neoplasm is rare and often challenging to diagnose in liver biopsies. We collected 40 cases of T-cell neoplasms diagnosed in the liver from five large academic institutions to assess the clinicopathologic features. The patients included 11 women and 29 men, with a median age of 54 (range: 2−75) years and a high mortality rate (31/37, 83.8%). Fourteen (35%) patients were diagnosed with hepatosplenic T-cell lymphoma (HSTCL), 13 (32.5%) peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), and 13 (32.5%) other types of T-cell neoplasms. Patients with HSTCL were much younger and had worse survival than PTCL-NOS and other T-cell neoplasms ($P < 0.05$). On imaging studies, 20 cases (50%) showed abnormalities, including 10 with mass lesions that correlated with normal or cholestatic pattern enzyme elevation. Histomorphological analysis revealed four main patterns; with the exception of mass forming lesions (pattern 4; n = 8), cases with sinusoidal predominant (pattern 1; n = 12), portal predominant with sinusoidal infiltrates (pattern 2; n = 13) or lobular aggregates (pattern 3; n = 5) demonstrated small to medium lymphocytes resembling a reactive/inflammatory process. In addition, we described two cases of T-cell large granular lymphocytic leukemia that mimicked HSTCL, and a case of aggressive post-transplant lymphoproliferative disorder that developed after chronic Epstein-barr virus (EBV) infection, suggesting the importance of EBV testing in some lymphoma cases. As the largest cohort of T-cell neoplasms in liver, our study provides critical data on disease frequency, distribution, and clinicopathologic features that are

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essential for accurate diagnosis.

1. Introduction

The liver is not commonly involved with non-Hodgkin lymphoma, occurring next in frequency to lymph node, spleen, and bone marrow. Most hepatic lymphomas are secondary involvement by a systemic disease, frequently diffuse large B-cell lymphoma, comprising nearly half of the cases reported [1,2]. Approximately 12% of lymphomas in the liver are attributed to a T-cell lineage, mostly peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS, 9%), followed by anaplastic large cell lymphoma (ALCL, 2%) and hepatosplenic T-cell lymphoma (HSTCL, 1%) [1]. Owing to their rarity, T-cell lymphomas in the liver were often reported in single case reports or small case series [3,4], lacking epidemiologic and systemic clinicopathologic analysis.

The initial lymphoma diagnosis, particularly for T-cell neoplasms, can be very challenging in small liver biopsies [3]. For example, both HSTCL and T-cell large granular lymphocytic leukemia (T-LGL) typically infiltrate the hepatic sinusoids without discrete mass formation, mimicking a reactive condition. Other lymphomas can have portal and lobular infiltrates, indistinguishable from viral hepatitis or drug-induced liver injury by histology alone. Accurate diagnosis relies on clinical history, immunohistochemistry (IHC) to determine T-cell lineage and antigen aberrancy, polymerase chain reaction analysis on T-cell receptors (*TCRs*) to establish clonality, and sometimes cytogenetic or molecular studies to detect disease-specific alterations in certain lymphomas [5,6]. This poses significant challenges when limited biopsy material is available for evaluation, emphasizing the importance of pattern recognition and selective ancillary tests.

Herein, we performed a multi-institutional retrospective review of various types of T-cell neoplasms diagnosed in liver specimens to analyze the essential clinical and histopathologic features.

2. Materials and methods

2.1. Patients and data collection

A text-based search in the electronic pathology database between 2000 and 2020 was performed collaboratively across five large academic institutions in the United States. Clinical information regarding patients' age, sex, imaging findings, relevant medical history, clinical presentation before liver biopsy, treatment, follow-up, and disease outcomes was collected. When multiple liver specimens were available for the same patient, the imaging study and liver function test most pertinent to the final diagnosis were recorded. In particular, the image findings were divided into 4 categories: (1) sizable mass lesion (mass); (2) focal nonspecific abnormality without mass formation (abnormal); (3) hepatomegaly (enlargement); (4) no abnormality (normal). The liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase, alkaline phosphatase (ALP), and total bilirubin levels were recorded for the highest value within one month before the biopsy or autopsy. A ratio (R) value, defined as ALT/upper limit of normal: ALP/upper limit of normal, was applied to designate the pattern of liver injury, namely, hepatitis pattern if $R > 5$, cholestatic pattern if $R < 2$, and mixed pattern if R is between 2 and 5 [7]. This study was approved by the institutional review boards of all participating medical centers.

2.2. Lymphoma diagnosis, classification, and histomorphologic analysis

The pathology report and diagnosis for each case were reviewed by expert hematopathologists at each contributing institution. The classification of T-cell neoplasms was based on the 2017 WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues [8]. Specific types of T-cell neoplasms diagnosed in this study included HSTCL, peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), T-LGL, ALK-negative ALCL, cutaneous T-cell lymphoma (CTCL) specifically mycosis fungoides, angioimmunoblastic T-cell lymphoma (AITL), post-transplant lymphoproliferative disorder (PTLD), extranodal NK/T-cell lymphoma, nasal type (NK/T), T-prolymphocytic leukemia (T-PLL), and T-cell acute lymphoblastic leukemia (T-ALL). When applicable, a "primary" hepatic lymphoma is defined as lymphoma either confined to the liver or having initial and major liver involvement before spreading to other anatomic sites. A "secondary" hepatic lymphoma is defined when there is prior or concurrent systemic disease, or the same lymphoma has been diagnosed at other anatomic sites before liver involvement [9−11].

The histomorphology and infiltration pattern of lymphoma cells in relationship to liver parenchyma (portal, sinusoidal, and lobular), as well as the size of lymphoma cells in comparison to the nuclei of macrophages or endothelial cells (small, medium, and large) were recorded for each case based on slide review.

Table 1 Clinical and pathological characteristics of T-cell neoplasms in liver.

Patient	Diagnosis	Age	Sex	Pertinent clinical history	F/U (days)	Outcome	Imaging	R value	Histology pattern	Main immunophenotype	Clonality	Molecular/cytogenetics
1	HSTCL (n = 14, 35%)	3	F	Mixed phenotype acute leukemia, s/p CTx	107	DOD	Abnormal	NL	Sinusoidal + portal	CD3+, CD4-, CD8-, CD5-, CD56-, TIA-1+, TDT-	TCRgd	Isochromosome 7q
2		55	M	Cutaneous DLBCL, s/p CRTx and SCT	99	DOD	Normal	0.1	Portal + sinusoidal	CD3+, CD4+, CD7-, CD30-, CD56-, CD57+/−, TIA1+	TCRab	
3		60	M	None	65	DOD	Normal	0.2	Sinusoidal	CD2+, CD3+, CD4-, CD8-, CD5-, CD7+, CD30-, TIA1+, granzyme B-	TCRgd	
4		31	M	Recurrent HSTCL, s/p CTx and SCT	215	DOD	Normal	1.2	Sinusoidal	CD2+, CD3-, CD4-, CD8-, CD7+/−, TIA1+, granzyme B-, EBV-	TCRgd	Monosomy 7
5		49	M	Presented with HLH	6	DOD	Normal	1.1	Portal + sinusoidal	CD2-, CD3+, CD4-, CD8-, CD5-, CD7-		46,XY,del(13)(q14q22), 47,idem,+X and 92,XXYY
6		47	M	None	32	DOD	Enlarged	32.2	Sinusoidal	CD2+, CD3+, CD4-, CD8-, CD5+, CD7-, CD30-, CD56+/−, EBV-		
7		71	M	None	14	DOD	Normal	0.4	Portal + Sinosoidal	CD3+, CD25+, CD30-, EBV-		
8		4	M	None	0	DOD	Normal	N/A	Portal aggregates + sinusoidal	CD2+, CD3+, CD4-, CD8-, CD5-, CD7+, CD25-, CD30-, CD56+, TIA1+	TCRgd	
9		30	M	Ulcerative colitis	89	DOD	Normal	14.2	Sinosoidal	CD3+, CD4-, CD8+, CD5-, CD16+, CD56+, CD57+	TCRgd	
10		21	M	None	N/A	LTF	Enlarged	NL	Sinusoidal	CD2+, CD3+, CD4-, CD8+, CD5-, CD7+, CD25-, CD57-	TCRab	
11		60	F	None	37	DOD	Enlarged	0.3	Sinusoidal + portal	CD3+, CD4-, CD8-, CD5+/−, CD30-, CD56-, CD57+/−, TIA1+, EBV-	TCRgd	
12		30	M	Ulcerative colitis, PSC, AIH	NA	DOD	Abnormal	0.7	Sinusoidal	CD2+/−, CD3+, CD4-, CD8-, CD5-, CD7+, CD30-, CD56+, TIA1+, EBV-, ALK-		
13		33	M	None	619	DOD	Normal	1.2	Portal	CD2+, CD3+, CD4-, CD8+, CD5+/−, CD7+/−, CD56-, CD57-, TIA1+, granzyme B+, EBV-	TCRgd	
14		31	M	Presented with HLH	13	DOD	Normal	1.4	Sinusoidal + portal	CD2-, CD3+, CD4-, CD8-, CD5-, CD7+/−, TIA1+, EBV-	TCRgd	
15	PTCL-NOS	61	M	None	76	DOD	Mass	NL	Mass	CD2+, CD3+, CD4-, CD8-, CD5-, CD7+/−, CD30+/−, CD56-, TIA1-		
16	(n = 13, 32.5%)	70	F	None	14	DOD	Normal	5.5	Portal + lobular aggregates	CD2+, CD3+, CD4+, CD8+, CD5-, CD7-, TIA1+, granzyme B-	TCRab	
17		55	F	PTCL in LN x 4 yrs, s/p CTx	N/A	LTF	Mass	N/A	portal large aggregates + lobules	CD3+, CD4+, CD8-, CD5+, CD7+/−, CD30-, EBV-, ALK-		
18		27	M	EVAN'S syndrome	2600	Alive	Mass	1.7	Mass	CD3+, CD4+, CD8-, CD5+, CD7+/	TCRab	

(*continued on next page*)

Table 1 (*continued*)

Patient	Diagnosis	Age	Sex	Pertinent clinical history	F/U (days)	Outcome	Imaging	R value	Histology pattern	Main immunophenotype	Clonality	Molecular/cytogenetics
19		69	M	PTCL in LN x 2 mos	213	DOD	Normal	NL	Portal large aggregates + sinosoidal	−, CD30-, CD56-, graznyme B+ CD2+, CD3+, CD4-, CD8+, CD7+, CD30-, CD56+/−, TIA1+, granzyme B+, EBV-, ALK-	TCRab	STAT5 mutation
20		59	F	PTCL in LN x 8 yrs, s/p SCT	25	DOD	Normal	1.5	Portal + sinusoidal	CD3+, CD8-, CD5+, CD7-,		Trisome 7
21		57	M	Involving liver first then LN	30	DOD	Normal	0.9	Portal massive	CD2+, CD3+, CD4+, CD5+, EBV-		
22		54	M	PTCL in LN x 1 yr	72	DOD	Normal	0.4	Portal + sinusoidal	CD2+, CD3+, CD4+, CD8-, CD5+, CD7+/−, CD25+, CD30+/−, CD56+/−, TIA1+, granzyme B-, EBV-		
23		70	M	PTCL in LN x 1yr, plasma cell dyscrasia	206	DOD	Abnormal	N/A	Portal	CD2+, CD3+, CD4+, CD5+, CD7+, EBV-	TCRab	
24		51	M	PTCL in LN x 6 mos	35	Alive	Enlarged	0.2	Portal	CD3+, CD4+, CD8+/−, CD5+, CD7+/−, CD30+/−, CD57+/−, PD1+, BCL6-, CD10-, CXCL13-, EBV-	TCRab	Normal cytogenetics
25		54	M	Synchronous LN and liver involvment	N/A	LTF	Normal	9.7	Portal + lobular + sinusoidal	CD3+, CD4+, CD8-, CD5+, CD30-, CD56-, TIA1+, EBV-	TCRab	Normal cytogenetics
26		25	M	PTCL in LN x 3 mos	1800	DOD	Enlarged	0.4	Sinusoidal	CD2+, CD3+, CD8+, CD5+, CD7+, CD30-, CD56+/−, CD57+, TIA1+, granzyme B+, EBV-	TCRab	Normal cytogenetics
27		73	M	PTCL in BM x 1 yr	1629	Alive	Enlarged	NL	Portal + sinusoidal	CD2+, CD3+, CD4+, CD8-, CD5+/−, CD7+/−, CD30-	TCRab	Normal cytogenetics
28	T-LGL (n = 2, 5%)	74	M	None	132	Alive	Normal	NL	Sinusoidal	CD2+, CD3+, CD4-, CD8+, CD5-, CD7-, CD30-, CD56-, CD57+, TIA1+, granzyme B+, EBV-, ALK-	TCRab	
29		2	F	S/p liver transplant for biliary atresia	108	Alive	Normal	3.5	Sinusoidal + portal	CD2+ CD3+ CD4-CD8+ CD5+ CD7 ± CD56- CD57+ TIA1+ Granzume B + EBV-	TCRab	
30	ALCL (n = 2, 5%)	71	M	Involving liver first, then CSF	52	DOD	Mass	0.7	Mass	CD3+, CD30+, ALK-		
31		62	M	ALCL x 13 yrs	360	DOD	Mass	1.9	Mass	CD2+, CD4+/−, CD30+, EBV-, ALK-		
32	CTCL (n = 2, 5%)	73	F	Skin x 3 yrs	850	DOD	Normal	0.2	Unknown	CD2+, CD3+, CD4-, CD8-, CD5+, CD7-, CD30-, ALK-		
33		53	M	Skin, s/p CRTx; Hepatitis C	152	DOD	Mass	0.4	Portal + sinusoidal	CD2+, CD3+, CD4+, CD8-, CD5+, CD7-, CD30-, CD56-, CD57-, EBV-		

34	AITL (n = 2, 5%)	75	F	AITL in LN x 12 yrs, s/p CTx	658	Alive	Mass	NL	Mass	CD2+, CD3+, CD8+, CD30+, PD1+, Bcl6+, CD10+/−, EBV-		
35		43	M	AITL in LN x 2 yrs; Hepatitis C	747	DOD	Normal	5.3	Unknown	CD2+, CD3+, CD4+, CD8-, CD5+, CD7-, CD30-, EBV+	TCRab	
36	PTLD	46	F	S/p Liver transplant for congenital hepatic fibrosis	4	DOD	Normal	0.8	Portal aggregates + sinusoidal	CD3+, CD4+, CD8-, CD30+, CD56-, CD57-, TIA1+, granzyme B+, EBV+, ALK-	TCRab	
37	PTLD	9	F	Presented with HLH, s/p SCT	321	DOD	Mass	NL	mass	CD2+, CD3+, CD4+, CD8-, CD5-, CD7-, CD30+, CD56+, CD57-, TIA1+, granzyme B+, EBV+, ALK-	TCRab	
38	NK/T	62	M	Skin x 1 yr	1142	DOD	Normal	16.7	Portal + lobular	CD3+, CD4-, CD8-, CD7+, CD56+, TIA1+, granzyme B+, EBV+		
39	T-PLL	55	F	T-PLL in BM x 1 yr, s/p CTx and SCT	2505	DOD	Mass	NL	Portal + sinusoidal	CD3+, CD4+, CD8-, CD5+, CD7+		Complex abnormality[a]
40	T-ALL	38	M	T-ALL in BM x 3 mos	70	DOD	Mass	NL	Mass	CD2+, CD3+, CD5-, CD7-		

HSTCL, hepatosplenic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; T-LGL, T-cell large granular lymphocytic leukemia; ALCL, anaplastic large cell lymphoma; CTCL, cutaneous T-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; PTLD, post-transplant lymphoproliferative disorder; NK/T, NK/T-cell lymphoma; T-PLL, T-prolymphocytic leukemia; T-ALL, T-cell acute lymphoblastic leukemia; B, biopsy; A, autopsy; BM, bone marrow; LN, lymph node; CSF, cerebrospinal fluid; s/p, status post; CTx, chemotherapy; CRTx, chemoradiation; SCT, stem cell transplant; DLBCL, diffuse large B-cell lymphoma; HLH, hemophagocytic lymphohistiocytosis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; yr, year; mo, month; ICE, ifosfamide, carboplatin and etoposide; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin hydrochloride; CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ESHAP, etoposide, methylprednisolone, cytarabine, cisplatin; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone, DHAP, dexamethasone, cytarabine, cisplatin; BEAM, carmustine, etoposide, cytarabine, melphalan; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone; FMR, fludarabine, mitoxantrone and rituximab; FC, fludarabine, cyclophosphamide; S-HAM, sequential high-dose cytarabine and mitoxantrone; N/A, not applicable; F/U, follow-up; DOD, dead of disease; LTF, lost to follow-up; R, ratio; NL, normal; EBV, Epstein-barr virus; *TCRs,* T-cell receptors.
* CBC, complete blood count; WBC, white blood cell (x1000/uL); Hb, hemoglobin (g/dL); Hct, hematocrit (%); Plt, platelets (x1000/uL).
[a] 52−53,XY,add(2)(q35),del(6)(p21),?add(6)(?p23),+add(7)(q36)x2,+8,+20,+20,+21,+21,+i(21)(q10),+mar[cp14]/46,XY[6].

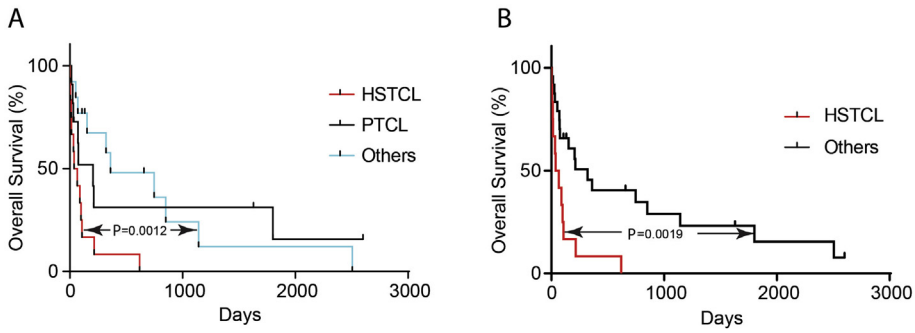

Fig. 1 Kaplan-Meier survival analysis in patients with T-cell neoplasms in liver. (A) Patients of HSTCL had worse clinical course than PTCL-NOS, but the difference did not reach statistical significance ($P = 0.078$). The clinical course was significantly worse in patients with HSTCL when compared with other types of T-cell lymphomas except HSTCL and PTCL-NOS (A), or when compared with all non-HSTCL T-cell neoplasms (B). HSTCL, hepatosplenic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

2.3. Statistical analysis

Clinicopathologic characteristics were coded as numerical (e.g. age), categorical (e.g. R value, lymphoma infiltration pattern, and lymphoma classification), or dichotomous (e.g. sex). Student's t-test, chi-square or Fisher's exact test, and Kaplan-Meier survival analysis were performed for statistical significance using Prism 8.3.0 (GraphPad Software, San Diego, CA, USA). *P*-values less than 0.05 were considered statistically significant.

3. Results

3.1. Demographic and clinical data

A total of 40 patients, 11 women and 29 men, were included in this study (Table 1 and Supplementary Table 1). The median age was 54 (range: 2−75) years; 4 (10%) were pediatric patients (<18 years old). Fever (n = 13), jaundice (n = 8), and weight loss (n = 8) were the most common presenting clinical symptoms. More than half of the cases (n = 24) showed pancytopenia in peripheral blood. Liver function test ranged from normal to the highest of 2200 IU/L for ALT, 1300 IU/L for ALP, and 28.7 mg/dL for total bilirubin. The majority of cases (n = 20) presented with cholestatic pattern liver enzyme abnormality, followed by hepatitis pattern (n = 6) and mixed (n = 1). Nine patients had normal liver function test at the time of biopsy. On imaging studies, half of the patients (n = 20) had no overt abnormalities, 10 had discrete mass lesions, 6 diffuse hepatomegaly/enlargement, and 4 focal abnormality other than mass. A total of 19 (47.5%) cases were liver primary, whereas 21 (52.5%) were secondary involvement by a previously diagnosed lymphoma/leukemia. The most common diagnoses were HSTCL (n = 14, 35%) and PTCL-NOS (n = 13, 32.5%), totaling more than two-thirds of this study cohort. The remaining 13 patients were diagnosed as follows: T-LGL (n = 2, 5%), ALCL (n = 2, 5%), CTCL (n = 2, 5%), AITL (n = 2, 5%), PTLD (n = 2, 5%), NK/T (n = 1, 2.5%), T-PLL (n = 1, 2.5%), and T-ALL (n = 1, 2.5%). Chemotherapy was the main treatment choices for all T-cell neoplasms. Six patients, including 3 with HSTCL, 3 with PTCL-NOS and 1 with T-PLL underwent stem cell transplant.

Upon follow-up, 31 of 37 (83.8%) patients died of lymphoma after a median of 82 (range: 0−2505) days, whereas 6 (16.2%) were alive after a median of 395 (range: 35−2600) days. Three patients were lost to follow-up. Both HSTCL and PTCL-NOS were highly lethal with a short overall survival, with even worse prognosis for HSTCL by Kaplan-Meier survival analysis when compared to non-HSTCL cases (Fig. 1). There were no significant clinical and survival differences between patients with "primary" vs. "secondary" T-cell neoplasms in liver (data not shown).

3.2. Histologic analysis and correlation with imaging and laboratory results

Histomorphologic analysis and correlation with imaging studies and liver enzymes were performed on all but two cases. Four major infiltration patterns were summarized (Fig. 2): sinusoidal predominant (pattern 1; n = 12), portal predominant with sinusoidal infiltrates (pattern 2; n = 13), portal and lobular infiltrates with lymphoid aggregates (pattern 3; n = 5), and mass forming (pattern 4; n = 8). In both patterns 1 and 2, the hepatic architecture was relatively preserved with no discrete lymphoid nodules or large aggregates. Pattern 3 was characterized by lymphoid aggregates or small nodules predominantly in both portal tracts and lobules (Fig. 3). In pattern 4, the lymphoma formed mass lesions and effaced the underlying hepatic architecture by high-grade tumor cells with frequent mitoses and apoptosis (Fig. 4). Pattern 4 almost always correlated with a sizable "mass" lesion on imaging studies (Table 1 and Supplementary Table 1). In all patterns, monotonous lymphoid infiltrates and/or larger cell size were usually the features that prompted lymphoma work-up, especially in cases without a prior lymphoma diagnosis.

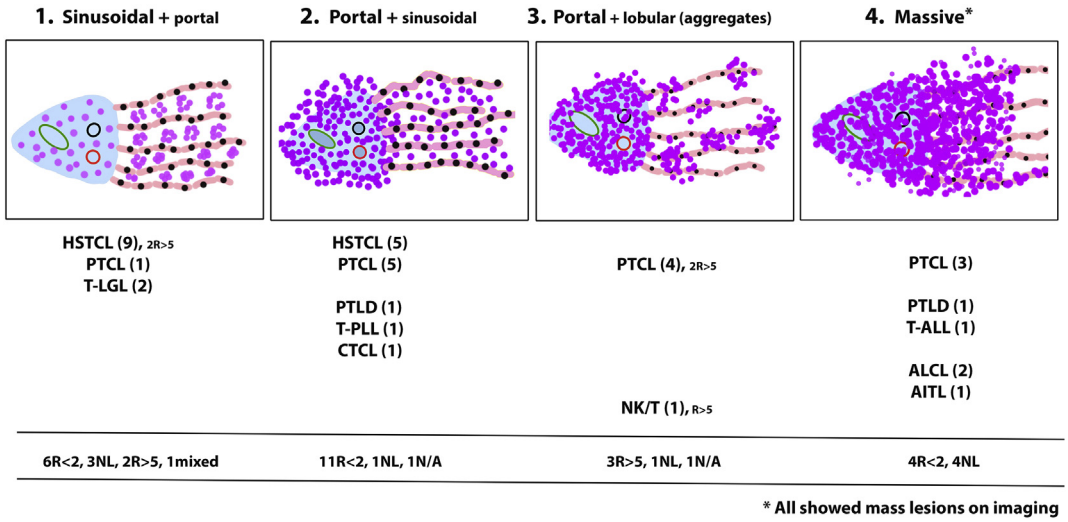

Fig. 2 Histomorphologic analysis of T-cell neoplasms in liver, and correlation with imaging studies and R value of liver enzyme tests. Number in "()" indicates total number of cases. NL, normal, N/A, not applicable or available.

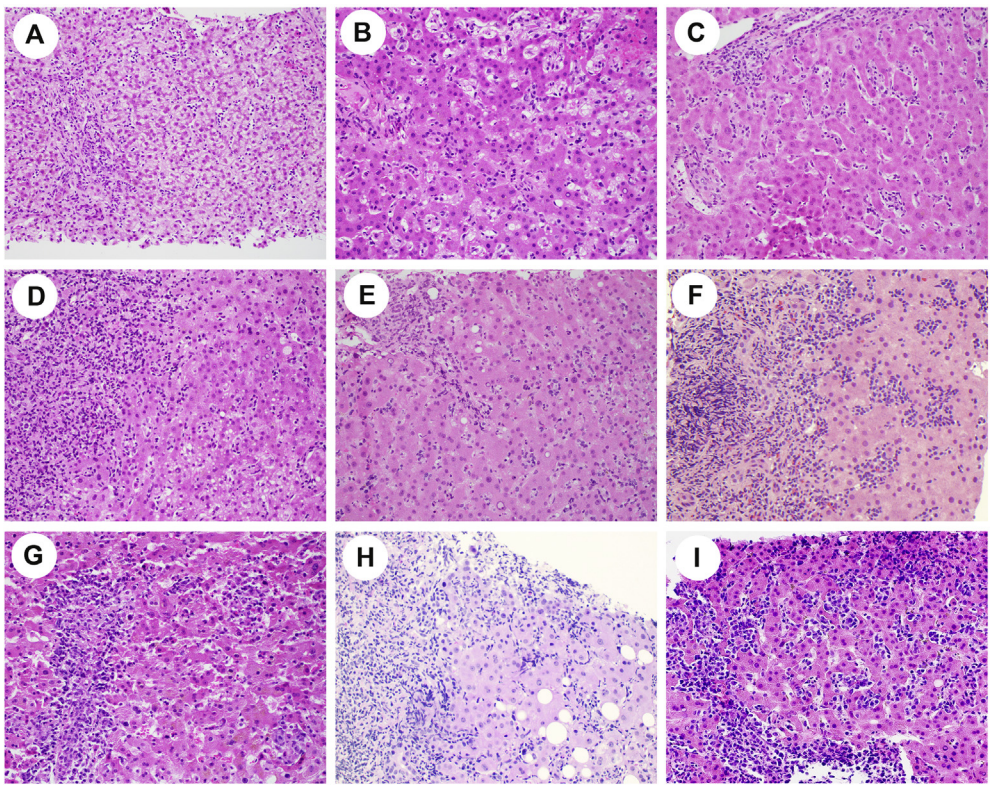

Fig. 3 T-cell neoplasms exhibiting histology patterns 1 (A–C), 2 (D–F), and 3 (G–I). Pattern 1 was represented by HSTCL with small-sized (A) and medium-sized (B) lymphoid cells expanding the hepatic sinusoid, and T-LGL with classic sinusoidal linear distribution (C). Pattern 2 was represented by HSTCL (D and E) and PTCL-NOS (F) showing portal and sinusoidal infiltrates. Pattern 3 was represented by PTCL-NOS (G and H) and NK/T (I) demonstrating prominent lymphoid aggregates in portal tracts and heavy lobular infiltrates. Magnification: 200×. HSTCL, hepatosplenic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

The lymphoma infiltration pattern did not always correlate with the pattern of liver function tests; however, the liver enzyme elevation ($R > 5$) occurred only in patterns 1 and 3, where lymphoma cells showed predominant sinusoidal infiltration (2 HSTCL), or lobular aggregates with hepatocyte injury (2 PTCL-NOS and 1 NK/T). Patterns 2 and 4 more often correlated with a cholestatic enzyme elevation or normal liver function tests (Fig. 1).

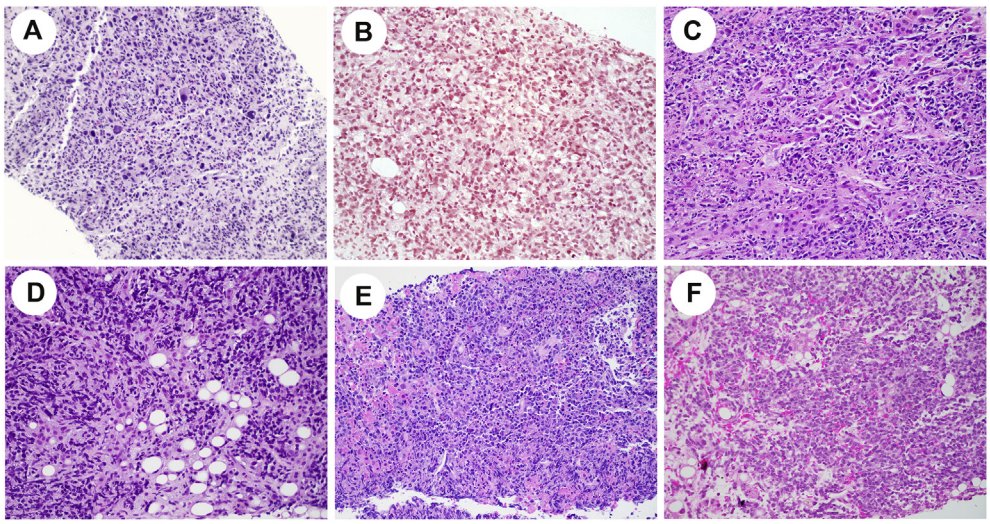

Fig. 4 T-cell neoplasms exhibiting histology pattern 4 with massive infiltration effacing underlying hepatic structures, represented by ALCL (A and B), AITL (C), PTCL-NOS (D), T-cell PTLD (E), and T-ALL (F). Magnification: 200×. PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; ALCL, anaplastic large cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; PTLD, post-transplant lymphoproliferative disorder.

3.3. Comparisons between HSTCL and PTCL-NOS

Since HSTCL and PTCL-NOS were the most frequent diagnoses in our cohort, each comprising approximately one third of the total cases, we compared these two lymphoma types regarding clinicopathologic features (Table 2). Patients with HSTCL were much younger than those of PTCL-NOS (median age 31 vs. 55, $P = 0.018$). Both were male predominant. For HSTCL, 2 patients had prior history of hematopoietic malignancies other than HSTCL, 2 had history of ulcerative colitis, and 2 presented with hemophagocytic lymphohistiocytosis (HLH) before lymphoma diagnosis. Most patients with HSTCL had either spleen and/or bone marrow involvement with typical sinusoidal infiltration. Involvement of the appendix and lymph node in one case (patient 8) was also noted. On imaging studies, three cases showed hepatomegaly and two revealed focal abnormality, whereas all others had normal imaging findings. Liver function tests were predominantly cholestatic (n = 9/14, 64%). Immunophenotypes were mostly CD3+/CD4-/CD8-/TIA1+/TCRγδ consistent with non-activated cytotoxic gamma/delta T-cells. In comparison, patients with PTCL-NOS usually had no history of other lymphomas or immunosuppression. The majority had established PTCL-NOS diagnoses in lymph nodes (10/13, 77%), spleen (2/13, 15%), and/or bone marrow (2/13, 15%) before liver involvement. Only two patients (patients 15 and 18) had exclusive liver involvement, both showing mass lesions on imaging studies and a normal or cholestatic liver function test, suggesting "primary" hepatic PTCL-NOS. Histologically, all HSTCL cases presented as small to medium-sized lymphoid cells with sinusoidal infiltrates corresponding to pattern 1 (9/14, 64%) or pattern 2 (5/14, 36%), whereas PTCL-NOS showed all four histology patterns though the majority demonstrated portal infiltrates corresponding to patterns 2 or 3 (9/13, 69%) (Figs. 2 and 3). In contrast to HSTCL, immunophenotypes in PTCL-NOS were mostly CD3+/CD4+/CD8-/TCRαβ, with rare CD4/CD8 double negative or double positive cases. Although all patients with HSTCL died of disease after a median follow-up of 51 (range: 0−619) days, at least one patient with primary hepatic PTCL-NOS survived after stem cell transplant on a follow-up of 2600 days.

3.4. Other lymphomas

Two T-LGL were identified in our cohort (Table 1 and Supplementary Table 1). One was a 74-year-old men (patient 28) with no significant past medical history, the other one was a 2-year-old women (patient 29) with a complicated history including embryonic biliary atresia status post liver transplant, EBV viremia, and upper gastrointestinal B-cell PTLD, polymorphic type. Both had liver biopsies demonstrating sinusoidal T-cell infiltration mimicking HSTCL (Fig. 3C), but an immunophenotype of CD3+/CD8+/TIA1+/Granzyme B+/CD57+/EBV-/TCRαβ+. Both patients responded to treatment well and continued to do well on clinical follow-up.

The two patients with T-cell PTLD had very aggressive clinical course and died of disease within one year of diagnosis. The first was a 46-year-old women (patient 36) status after liver transplant for congenital hepatic fibrosis. Liver biopsy showed portal/sinusoidal infiltrates with an immunophenotype of CD4+/TIA+/Granzyme B+/EBER+ (Fig. 5A). The second was a 9-year-old women (patient 37) with a history of persistent active hepatitis

Table 2 Comparisons between HSTCL and PTCL-NOS.

5–>		HSTCL (n = 14)	PTCL-NOS (n = 13)	*P* value
Age, median, range		32 (3−71)	57 (26−73)	0.015
Sex		2F, 12M	3F, 10M	NS
Immunosuppression	Prior malignancy	2	0	NS
due to prior malignancy or IBD	IBD	2	0	
	None	10	13	
R value	Cholestatic	9	6	
	Hepatitic	2	2	NS
	Normal	2	3	
	N/A	1	2	
Imaging findings	Mass	0	3	NS
	Enlarged	3	3	
	Abnormal	2	1	
	Normal/None	9	6	
Histology	1. Sinusoidal	6	1	0.008
	2. Portal + sinusoidal	8	5	
	3. Portal + lobular	0	4	
	4. Massive	0	3	
Outcomes	DOD	13	8	NS
	Alive	0	3	
	LTF	1	2	
Follow-up days		51 (0−619)	76 (14−2600)	NS

IBD, inflammatory bowel disease; DOD, died of disease; LTF, lost to follow-up; NS, not significant; HSTCL, hepatosplenic T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

(ALT up to 1430 IU/L, R = 25.3) clinically suspicious for HLH. Liver biopsy showed portal/lobular small mature lymphocytic infiltrates, retrospectively stained positive for EBV (Fig. 5B). She underwent 9 of 10 HLA-matched unrelated donor bone marrow transplant but soon developed multiple liver mass lesions. The liver biopsy showed a high-grade lymphoma with an immunophenotype of CD4+/CD56+/TIA-1+/Granzyme B+/EBV LMP-1+ (Figs. 4D and 5C).

The two ALK-negative ALCL cases, one likely being liver "primary", occurred in elderly men and presented as mass lesions on imaging, with mild cholestatic pattern liver function abnormality. Histology revealed high-grade cytology with characteristic hallmark cells (Fig. 4A and B). T-ALL and T-PLL, both secondary liver involvement by a systemic disease, presented as mass lesions and near normal liver function tests. Two CTCL (mycosis fungoides), two AITL, and one NK/T had prior diagnosis of the same lymphoma in skin or lymph node. The one case of extranodal NK/T-cell lymphoma, nasal type demonstrated portal and lobular infiltrates (pattern 3), marked hepatotoxicity (R = 16.7), and strong EBER positivity (Fig. 5D). With the exception of one AITL, all patients died of disease upon follow-up.

4. Discussion

In this multi-institutional study, we reviewed a total of 40 cases of T-cell neoplasms diagnosed in the liver to characterize the clinicopathologic features. The types of neoplasms in this study covered nearly 70% of the WHO classification of mature T- and NK-cell neoplasms, the largest and most comprehensive to date. The majority of diagnoses were made in liver biopsies with pertinent clinical history and necessary ancillary tests for confirmation. Our study showed that hepatic T-cell neoplasms occurred in a wide age range, were male predominant, and had a generally dismal prognosis. The integrated correlation analysis on imaging studies, laboratory tests, and histomorphology patterns may serve as a diagnostic guideline for surgical pathologists who frequently encounter the liver biopsies before hematopathology consultation and lymphoma work-up.

Hepatic involvement by lymphoma can be difficult to distinguish from reactive conditions or other malignancies [12]. Unlike other primary or metastatic neoplasm in the liver, lymphoma may not form a mass lesion [2]; instead, the lymphoma cells infiltrate into the hepatic sinusoids or portal tracts, compressing the hepatic plate and biliary outflow, causing liver enzyme elevation [13−15]. The damage to liver is more likely a pushing effect rather than hepatotoxic, which explains why ALP elevation is more frequent than transaminitis. The abnormal liver function tests together with an infiltrative growth pattern without mass formation frequently mimics drug-induced liver injury or viral infection. Although radiographic and laboratory tests are not always reliable in detecting lymphoma [15], correlation with histomorphology increases awareness

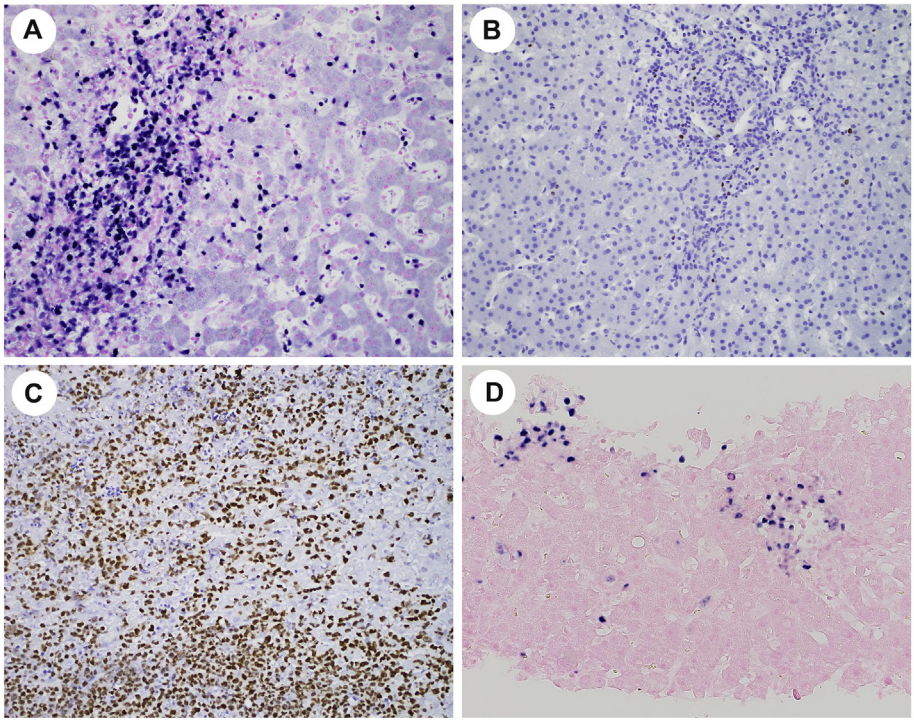

Fig. 5 Epstein-barr virus (EBV) testing in liver biopsies. EBV was detected in a PTLD with portal and sinusoidal infiltrates (A), the 9-year-old with chronic EBV infection in pre-transplant liver biopsy (B) and massive high-grade T-cell PTLD after bone marrow transplant (C), and an extranodal NK/T-cell lymphoma, nasal type (D). Magnification: 200×. PTLD, post-transplant lymphoproliferative disorder.

and diagnostic accuracy. On the other hand, a mass-forming lymphoma may be easier to recognize as a malignancy but can be difficult to distinguish from other primary or metastatic non-hematopoietic neoplasms [16,17]. Thus, pattern recognition, morphologic suspicion, and prudent work-up are key to reaching proper diagnosis.

HSTCL accounted for approximately one-third of all T-cell neoplasms in our cohort. In line with the literature showing that approximately 20% HSTCL occurred in patients with immunosuppression [18], a similar percentage of patients with inflammatory bowel disease or prior diagnosis of other lymphoma/leukemia was found in our case series. HSTCL is a well-known underlying etiology for HLH [19], an observation again recapitulated in our study. The sinusoidal infiltration pattern is characteristic for HSTCL, but not exclusive, as T-LGL and PTCL-NOS can have similar histomorphology, therefore relying on IHC or other ancillary tests for definitive diagnosis. Indeed, a European study published in 2007 showed that HSTCL only accounted for 1 of 19 T-cell lymphomas involving the liver [1], strikingly lower than the proportion of HSTCL in our series. The difference may be partially attributed to geographic factors but also likely due to more extensive diagnostic tests to accurately distinguish HSTCL from other lymphomas.

T-LGL serves as a top differential diagnosis for HSTCL by histology. Immunophenotypically, T-LGL is typically CD8+/TIA1+/Granzyme B+/CD57+/TCRαβ+, despite some variants and overlaps [20,21]. T-LGL is usually indolent with lower mortality, in contrast to the rapid progression of HSTCL. A takeaway from the pediatric T-LGL case in our cohort is to keep in mind that although T-LGL usually occurs in elderly patients with no associated risk factors, it happens in all age groups, particularly those with immunosuppression due to solid organ transplant or treatment for inflammatory bowel disease [22,23].

PTCL-NOS represented the second largest group of T-cell neoplasm in our study. As a diagnosis of exclusion, PTCL-NOS refers to a heterogeneous group of mature T cell lymphomas that cannot be classified into a specific category according to the current WHO classification [24,25]. Consistent with a general lack of a specific etiology, no prior malignancy diagnosis other than PTCL-NOS nor history of inflammatory bowel disease were identified in our case cohort. The majority were that of CD4+/CD8- or CD4-/CD8+ T cells, frequently TCR-αβ+, and with loss of one or more pan-T-cell antigens. While most PTCL-NOS were diagnosed in lymph nodes, at least two cases showed initial or predominant liver presentation with mass-forming lesions, for which we suspected a primary hepatic PTCL-NOS. Of note, primary hepatic PTCL-NOS is extremely rare, some associated with EBV infection [4]. Although we did not find significant survival differences between "primary" and "secondary" lymphomas in our study, it may warrant further studies to compare larger cohorts in each group for potential significant clinical implications.

EBV is etiologically linked to a wide range of lymphoproliferative disorders and malignant lymphomas [26,27]. In our study, EBV infection was associated with at least 3 types of lymphoproliferative disorders: NK/T, AITL, and PTLD. Interestingly, one PTLD case developed after bone marrow transplant was retrospectively found to have chronic active EBV infection in pre-transplant liver biopsy, stressing the importance of EBV test for some lymphoma types. EBV + T-cell PTLD is uncommon, and rare cases of synchronous EBV + B- and T-cell PTLD have been reported [28]. Interestingly, the current WHO classification of T-cell PTLD covers a wide range of T-cell neoplasms including HSTCL and T-LGL in the clinical setting of solid organ or bone marrow transplant [8], which makes the two HSTCL and one T-LGL in our cohort classifiable as EBV-negative T-cell PTLD under that umbrella, revealing the complexity of lymphoma etiology and overlaps in classification.

Although only a limited number of cases were tested, cytogenetics and molecular studies have been playing an increasingly important role in lymphoma diagnosis and management [29]. In our cohort, isochromosome 7q was applied to confirm HSTCL in a very complicated case with a prior diagnosis of mixed phenotype acute leukemia, stressing the diagnostic value of cytogenetics in certain cases. The molecular consequences of isochromosome 7q in HSTCL is unknown, although many candidate genes have been proposed [30]. Other genetic or molecular abnormalities are not disease-specific but are helpful in differential diagnosis. For example, activating *STAT5* mutations have been reported in multiple PTCL-NOS, HSTCL, and some aggressive variant of T-LGL [31−33], suggesting STAT signaling pathway as a common driver mutation in certain groups of T-cell lymphomas. Overlaps at the molecular levels and IHC between AITL and PTCL-NOS were also reported [34]. One study identified shared molecular features between NK-cell lymphoma and a group of non-HSTCL T-cell lymphoma with sensitivity to a novel aurora kinase A inhibitor [35], suggesting that molecular tests may not only help understanding lymphomagenesis, but also revealing therapeutic targets.

5. Conclusion

In summary, we performed the largest comprehensive study on T-cell neoplasms in the liver to characterize the clinicopathologic features, covering a wide range of low-grade vs. high-grade, precursor vs. mature, and primary vs. secondary T-cell lymphomas/proliferative disorders. An integrated analysis on imaging, laboratory liver function tests, histomorphologic features, and immunophenotypes was performed to provide clues for proper workup and accurate diagnosis. We focused specifically on common entities such as HSTCL, PTCL-NOS, T-LGL, and PTLD, the diagnostic pitfalls, and lessons learned from challenging cases. As a heterogeneous group of lymphomas that is difficult to define and classify, future studies may focus on large comprehensive testing such as next-generation sequencing for more accurate diagnosis, better classification, and targeted therapy strategies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2020.09.007.

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