Hepatosplenic and Other γδ T-Cell Lymphomas

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Abstract

The 2005 Society for Hematopathology/European Association for Haematopathology Workshop session 11 was dedicated to hepatosplenic T-cell lymphoma (HSTCL). HSTCL is a rare aggressive type of extranodal lymphoma characterized by hepatosplenomegaly, bone marrow involvement, and peripheral blood cytopenias. HSTCL exhibits a distinctive pattern of infiltration; tumor cells preferentially infiltrate the sinusoids of the splenic red pulp, liver, and bone marrow. The tumor cells have a nonactivated cytotoxic T-cell immunophenotype and frequently carry a recurrent cytogenetic abnormality, isochromosome 7q. Most cases express the γδ T-cell receptor, but cases can have an αβ phenotype and are considered to be a variant of the disease. Although HSTCL is the prototype peripheral T-cell lymphoma expressing the γδ T-cell receptor, non-HSTCL proliferations of γδ T cells can involve other extranodal sites, mainly skin and mucosa. These γδ T-cell lymphomas display marked heterogeneity in clinical and histologic features. In contrast with HSTCL, non-HSTCL γδ T-cell lymphomas frequently have an activated cytotoxic phenotype and most likely are not a single disease entity.

In 1981 Kadin et al[1] described 2 cases of an unusual T-cell lymphoma that they termed erythrophagocytic T-γ lymphoma. These cases had many of the clinical and histologic features of hepatosplenic T-cell lymphoma (HSTCL) and may represent the first description of HSTCL in the literature. In 1990, Farcet et al[2] and Gaulard et al[3] suggested the existence of a new type of peripheral T-cell lymphoma characterized by hepatosplenic involvement, marked sinusoidal tropism, and expression of the γδ T-cell receptor (TCR) by the malignant cells. Because of its characteristic clinical, histologic, and immunophenotypic features, HSTCL was proposed as a provisional entity in the Revised European-American Classification of Lymphoid Neoplasms and is now recognized as a distinct clinicopathologic entity in the World Health Organization (WHO) classification system.

γδ T Cells

γδ T cells constitute only a small proportion (1%-5%) of peripheral blood lymphocytes. γδ T cells are, however, more widespread within epithelial-rich tissues and mucosal surfaces, such as the skin, intestine, and reproductive tract, and within sinusoidal areas of the splenic red pulp.[4,5] At these sites, γδ T cells can constitute up to 40% of T cells. γδ T cells are considered part of the innate immune response, providing first-line defense to the mucosa. Malignant neoplasms derived from these cells are rare and, after precursor T-cell lymphoblastic leukemia/lymphoma, HSTCL is most common. γδ T-cell lymphomas involving mucosal surfaces and skin also have been recognized.

Hepatosplenic T-Cell Lymphoma

Clinical Features

HSTCL has a male predominance and occurs predominantly in young adults at a median age of 35 years.[2,3,6-8] A number of HSTCL cases have been reported in the setting of chronic immune suppression or prolonged antigen stimulation, particularly in patients receiving long-term immunosuppressive therapy for solid organ transplantation.[8-12] There is no association with infection by known viruses, including human T-lymphotropic virus 1, human herpesvirus 8, and Epstein-Barr virus (EBV).

At initial examination, patients have clinically significant cytopenias and hepatosplenomegaly and minimal or absent lymphadenopathy. Systemic (B-type) symptoms and an elevated serum lactate dehydrogenase level are also common. Thrombocytopenia is a constant feature and frequently is associated with anemia and/or leukopenia.[8] The degree of thrombocytopenia correlates with progression of disease, even in patients who have undergone splenectomy. An overt leukemic picture is rare at initial examination, and lymphocytosis is uncommon. However, a minor population of atypical lymphocytes can be identified in the peripheral blood smears of many patients.[13] Irrespective of the presence of hepatomegaly or abnormal liver function test results, liver involvement is frequently seen in liver needle biopsy specimens at initial examination. Bone marrow involvement, although often subtle, is virtually constant. The disease remains preferentially localized within the spleen, liver, and bone marrow, without apparent lymph node enlargement. Involvement of other sites, such as skin, oral mucosa, and kidney, has been rarely reported.[8] Patients with HSTCL usually have a rapidly progressive clinical course and poor prognosis. Therapeutic strategies efficacious for aggressive B-cell lymphomas have proved ineffective for HSTCL, and efficient treatment modalities need to be defined. Recently, the efficacy of a platinum-cytarabine–based induction regimen and 2'-deoxycoformycin (pentostatin) has been suggested.[8,14]

Pathologic Features

Bone Marrow

Neoplastic cell infiltration is usually subtle and can be difficult to recognize in routine H&E-stained sections but is easily accentuated by immunohistochemical stains for T-cell antigens **Image 1** and **Image 2**. In the early stages of HSTCL, the neoplastic cells are located predominantly in the sinusoids. However, an interstitial infiltrate is also present in most cases. The neoplastic cells are relatively monotonous, but they can range from small to large in case to case. The small neoplastic cells have nuclei with irregular contours and coarse chromatin. The medium-sized neoplastic cells have more open chromatin and frequently small but conspicuous nucleoli. The large cells can resemble blasts. The small and larger cells have a moderate amount of basophilic cytoplasm with indistinct cell borders. There is frequently a change in the pattern of bone marrow infiltration and cytologic features during the disease course.[13] With progression, the pattern of bone marrow involvement becomes increasingly interstitial and the neoplastic cells became larger and blastic. Thus, a predominant interstitial pattern and the presence of a blastic component does not rule out the diagnosis of HSTCL, especially in advanced stages of disease.

The noninvolved hematopoietic bone marrow is frequently hypercellular with trilineage hyperplasia. Large hyperlobated megakaryocytes can be seen. If the neoplastic cells are misinterpreted as blasts, the overall picture may be confused with a myelodysplastic syndrome. Slight to moderate plasmacytosis can be seen in some cases. Conspicuous and tortuous blood vessels can be present.[13]

Spleen

The spleen is usually massively enlarged, and the cut surface is homogeneous and red-purple without gross lesions **Image 3**. The red pulp is diffusely infiltrated by small to medium-sized atypical lymphocytes. The atypical lymphocytes are present within the cords and the sinuses of the red pulp. Dilated sinuses filled with sheets of neoplastic cells can be observed. Hemophagocytosis can be present.[15] Characteristically, there is a marked reduction or complete loss of the white pulp. Splenic hilar lymph nodes, although usually not enlarged, commonly show involvement confined to the sinuses without distortion of the normal lymph node architecture.

Liver

The liver is also constantly involved and always shows sinusoidal infiltration by neoplastic cells **Image 4**.[8] A mild portal and periportal lymphomatous infiltrate may also be observed but is not usually predominant.

Immunophenotypic Features

Flow cytometric immunophenotyping is extremely helpful for establishing the diagnosis of HSTCL. The most frequent immunophenotype is the following: CD2+, CD3+, CD4–, CD5–, CD7+/–, CD8–, CD16+/–, CD38+, and CD56+ (Image 1D). The neoplastic cells can rarely be CD4–/CD8+. CD5 positivity has been reported in few cases.[13] Most cases are CD57–. The activation antigens CD25 and CD30 are usually negative. Expression of the γδ TCR is also easily assessed by flow cytometry. In contrast, γδ TCR expression cannot be reliably determined by using routinely processed and fixed material. However, in our experience, absence of the αβ TCR (using the βF1 antibody) may be used to infer a γδ T-cell immunophenotype under

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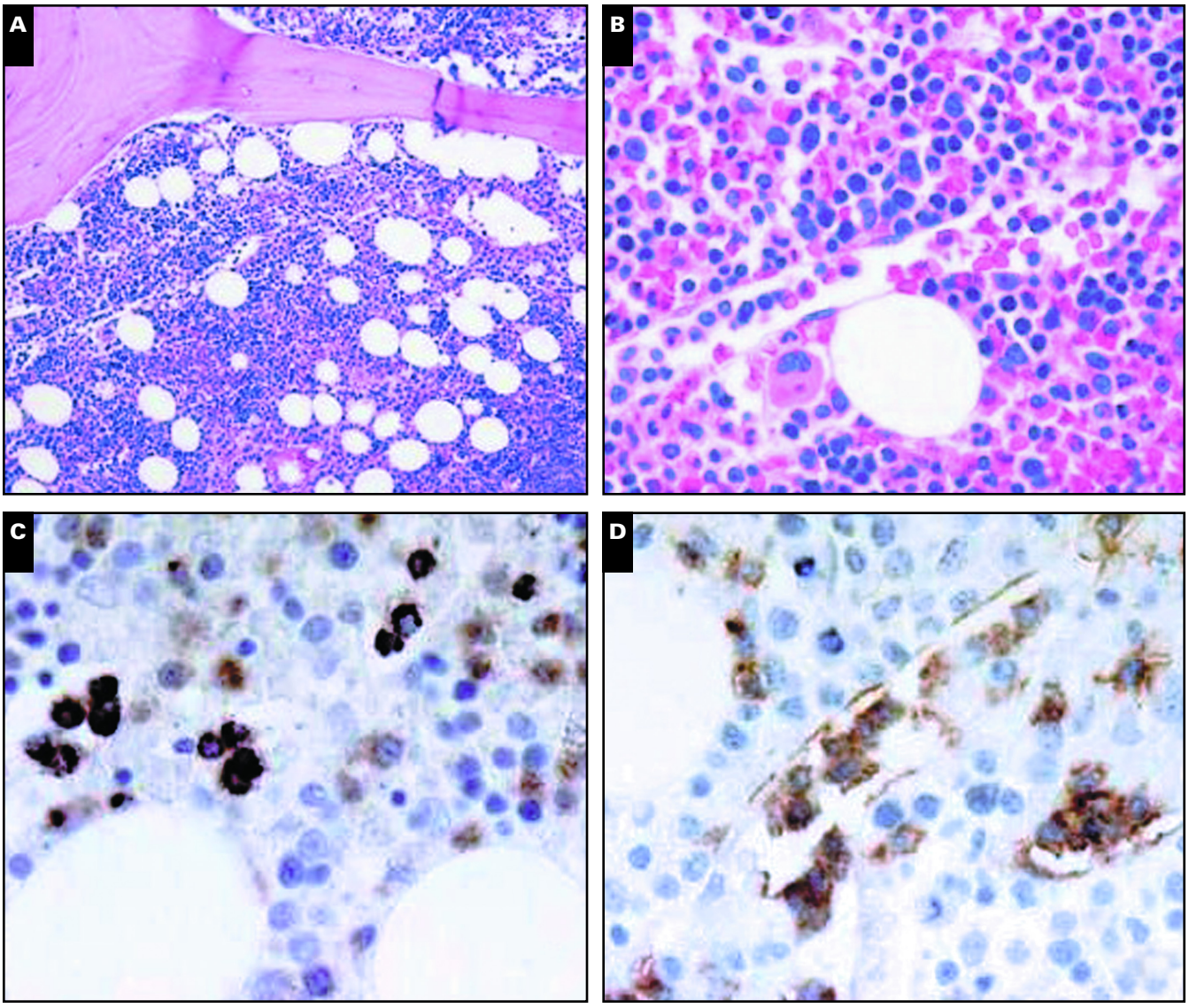

Image 1 (Case 82) Hepatosplenic T-cell lymphoma (HSTCL). **A** and **B**, The neoplastic cells can be difficult to recognize in the H&E-stained slides. **C** and **D**, The neoplastic cells are highlighted using immunostains for TIA-1 (**C**) and CD56 (**D**), which are characteristically positive in HSTCL. Contributed by L. Colomo and colleagues.

appropriate circumstances.[16] Although most cases express the γδ TCR, some cases express the αβ TCR. αβ HSTCL has clinicopathologic and cytogenetic features similar to those of γδ HSTCL cases and, therefore, is currently considered a variant of the disease **Image 5**.[17-19] The neoplastic cells of HSTCL also usually have an inactive (or immature) cytotoxic profile, ie, positive for T-cell–restricted intracellular antigen (TIA-1) (Image 1C) and negative for granzyme B and perforin.[3,13,20,21] γδ HSTCL cells usually express the serine protease granzyme M, a finding consistent with derivation from lymphocytes involved in innate immunity.[22] Loss of γδ TCR expression has occasionally been observed during the course of the disease, resulting in a TCR silent immunophenotype. EBV infection has been reported rarely and has been associated with cytologic features of transformation, suggesting that EBV might be involved secondarily.[8,18,23]

Cytogenetic and Molecular Features

Isochromosome 7q is a consistent cytogenetic abnormality in HSTCL that expresses the γδ TCR (Image 4B).[24] The same abnormality also has been found in HSTCL cases that express the αβ TCR.[17-19] In addition to conventional cytogenetics, isochromosome 7q can also be detected by fluorescence in situ hybridization using paraffin-embedded tissue sections.[25] Other reported cytogenetic changes include trisomy 8 and loss of chromosome Y. Southern blot and polymerase chain reaction studies have demonstrated monoclonal *TCRδ, TCRβ,* and *TCRγ* chain gene rearrangements.[8,13,26]

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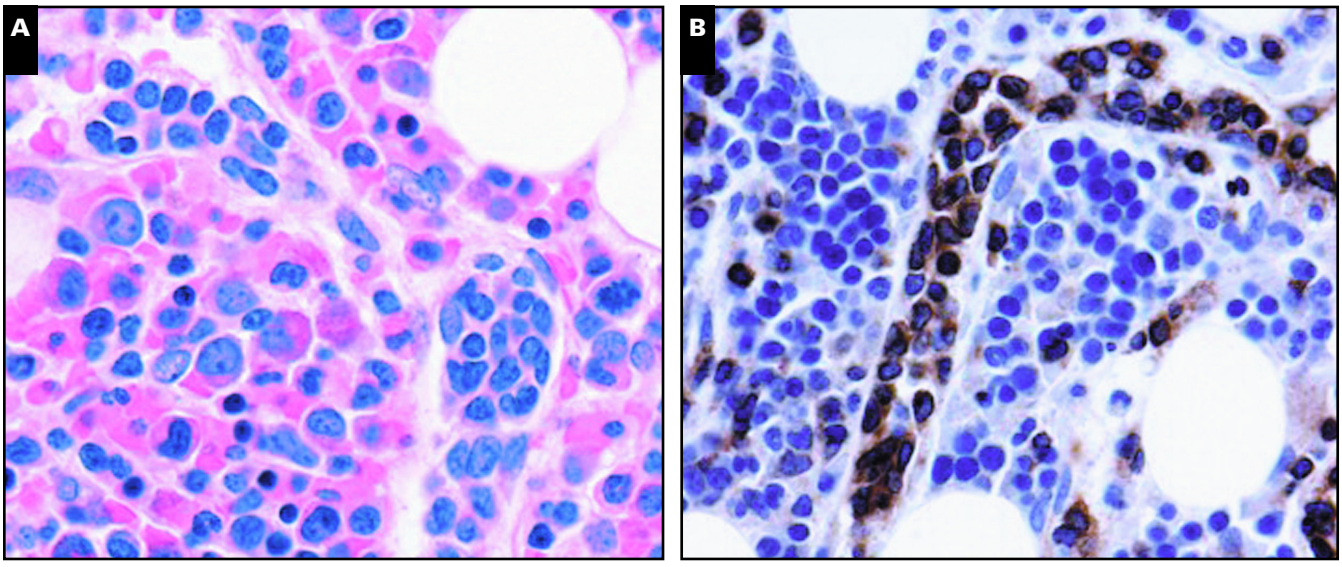

Image 2 (Case 117) Hepatosplenic T-cell lymphoma. **A**, Bone marrow. Intrasinusoidal infiltrate of small cells with coarse chromatin and irregular nuclei (H&E). **B**, Immunostain for CD3 accentuates the neoplastic lymphocytes. Contributed by B.L. McRae and colleagues.

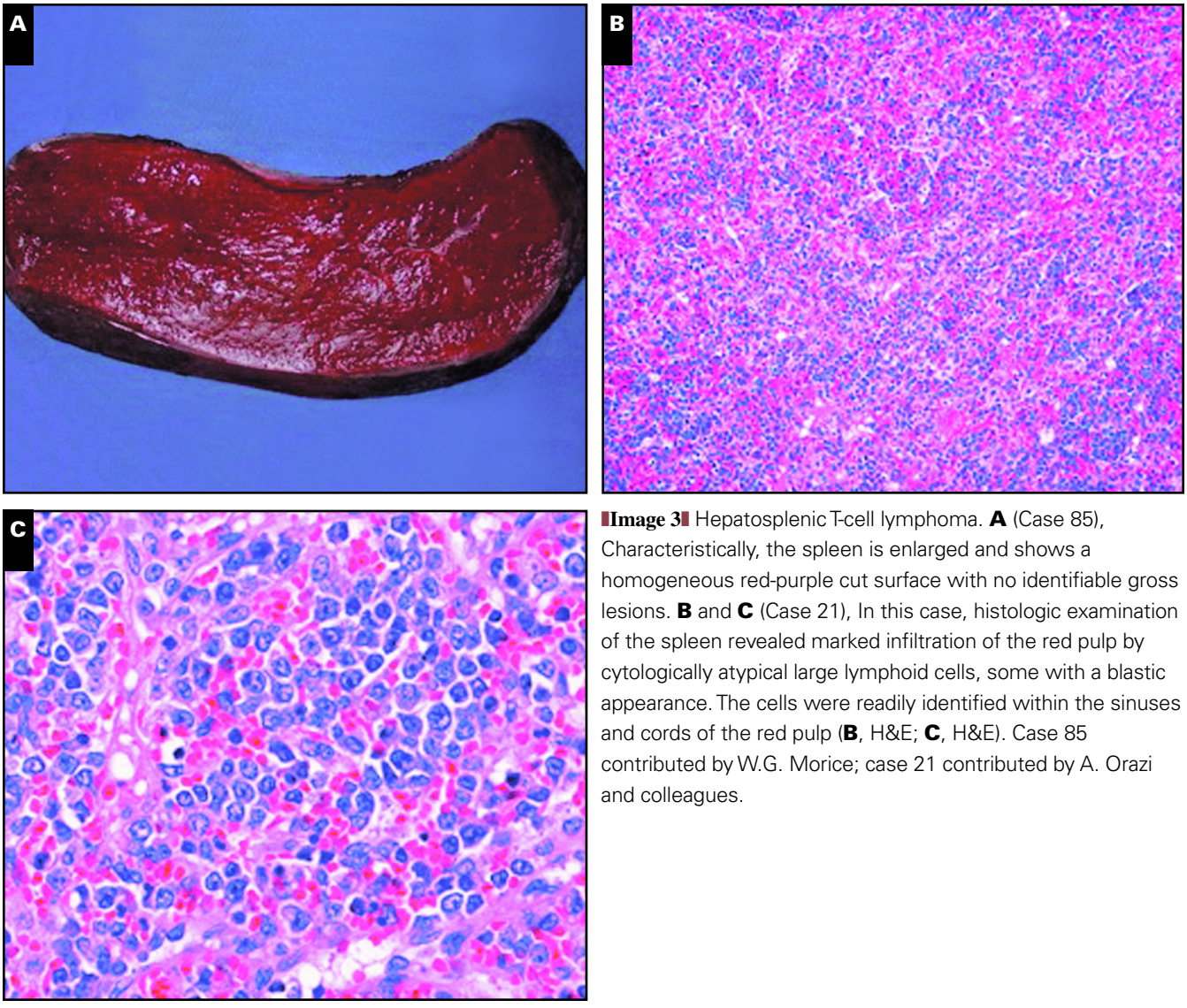

Image 3 Hepatosplenic T-cell lymphoma. **A** (Case 85), Characteristically, the spleen is enlarged and shows a homogeneous red-purple cut surface with no identifiable gross lesions. **B** and **C** (Case 21), In this case, histologic examination of the spleen revealed marked infiltration of the red pulp by cytologically atypical large lymphoid cells, some with a blastic appearance. The cells were readily identified within the sinuses and cords of the red pulp (**B**, H&E; **C**, H&E). Case 85 contributed by W.G. Morice; case 21 contributed by A. Orazi and colleagues.

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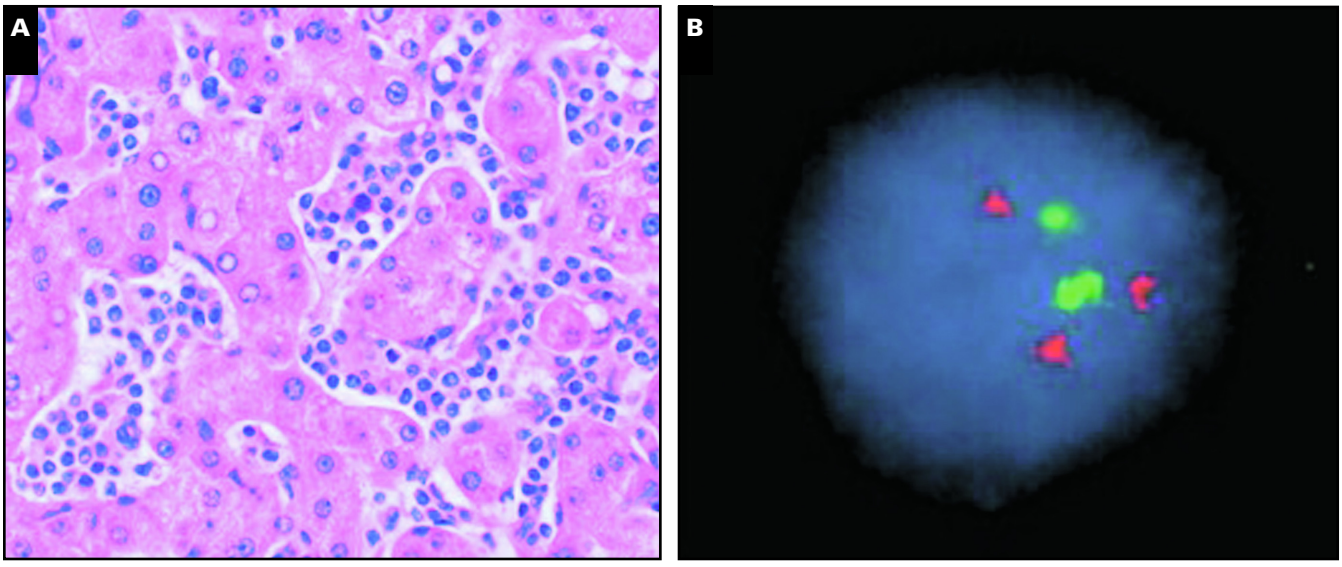

Image 4 (Case 89) Hepatosplenic T-cell lymphoma (HSTCL). **A**, Characteristic pattern of infiltration of HSTCL in the liver with neoplastic lymphocytes located within the hepatic sinuses (H&E). **B**, Isochromosome 7q. The image shows an interphase cell showing 3 red signals after fluorescence in situ hybridization with a probe for 7q31 (D7S4586) and 2 green signals with a probe for the centromere of chromosome 7. This result is consistent with the presence of an isochromosome 7q. Contributed by J.Z. Gong and colleagues.

Mucosal γδ T-Cell Lymphomas

Mucosal and cutaneous γδ T-cell lymphomas are regarded as a subset of activated and cytotoxic (TIA-1+, granzyme B+, and perforin+) T-cell lymphomas with heterogeneous clinicopathologic features. Mucosal γδ T-cell lymphomas most often involve the nasopharynx, intestine, and respiratory tract and occasionally involve thyroid gland, breast, and testis.[27] Clinically, γδ T-cell lymphomas involving the nasopharyngeal region usually manifest as destructive nasal lesions or midline facial tumors. Those arising in the gastrointestinal tract can be localized or multifocal. Despite localized disease at initial examination, most mucosal γδ T-cell lymphomas have an aggressive clinical course.[27]

Morphologically, the neoplastic cells vary in size and shape among patients, ranging from small to large and pleomorphic. Epitheliotropism, necrosis, angiocentrism, and angioinvasion are frequently seen. Most cases are CD4– and CD8– (CD8 may be positive), and they show an activated cytotoxic immunophenotype (TIA-1+, granzyme B+, and perforin+), in contrast with the nonactivated cytotoxic immunophenotype of HSTCL. EBV is detected in a significant proportion of cases.[27]

Cutaneous γδ T-Cell Lymphomas

Cutaneous γδ T-cell lymphomas also have been recognized. Cutaneous γδ T-cell lymphomas are composed of a clonal proliferation of mature, activated γδ T cells with a cytotoxic immunophenotype. In the WHO/European Organization for Research and Treatment of Cancer classification, this group includes a subset of cases previously designated as subcutaneous panniculitis-like T-cell lymphoma.[28] Cutaneous γδ T-cell lymphomas have more aggressive clinical behavior and a poorer prognosis than subcutaneous panniculitis-like αβ T-cell lymphomas, justifying the separation of these neoplasms and their own designation.[16,28] In contrast with HSTCL, cutaneous γδ T-cell lymphomas frequently involve other extranodal sites, but involvement of spleen, bone marrow, and lymph nodes is uncommon.[27]

Several patterns of involvement of the skin (epidermotropic, dermal, and subcutaneous) can be observed within a single case of γδ cutaneous T-cell lymphoma **Image 6**.[28] The neoplastic cells are usually medium to large. Angioinvasion, apoptosis, and necrosis are common. The subcutaneous cases may show rimming of fat cells, similar to typical cases of subcutaneous panniculitis-like αβ T-cell lymphoma (Images 6C, 6D, and 6E).[29,30] Cutaneous γδ T-cell lymphomas display an activated cytotoxic profile and are CD56+ and usually CD4–/CD8– or rarely CD8+ (Images 6D and 6E). It is important to remember that expression of markers of cytotoxic differentiation (eg, TIA-1, granzyme B, and perforin) is not specific to cutaneous γδ T-cell lymphomas and can also be seen in other primary cutaneous lymphomas, such as anaplastic large cell lymphoma and large cell transformation of mycosis fungoides.[31,32]

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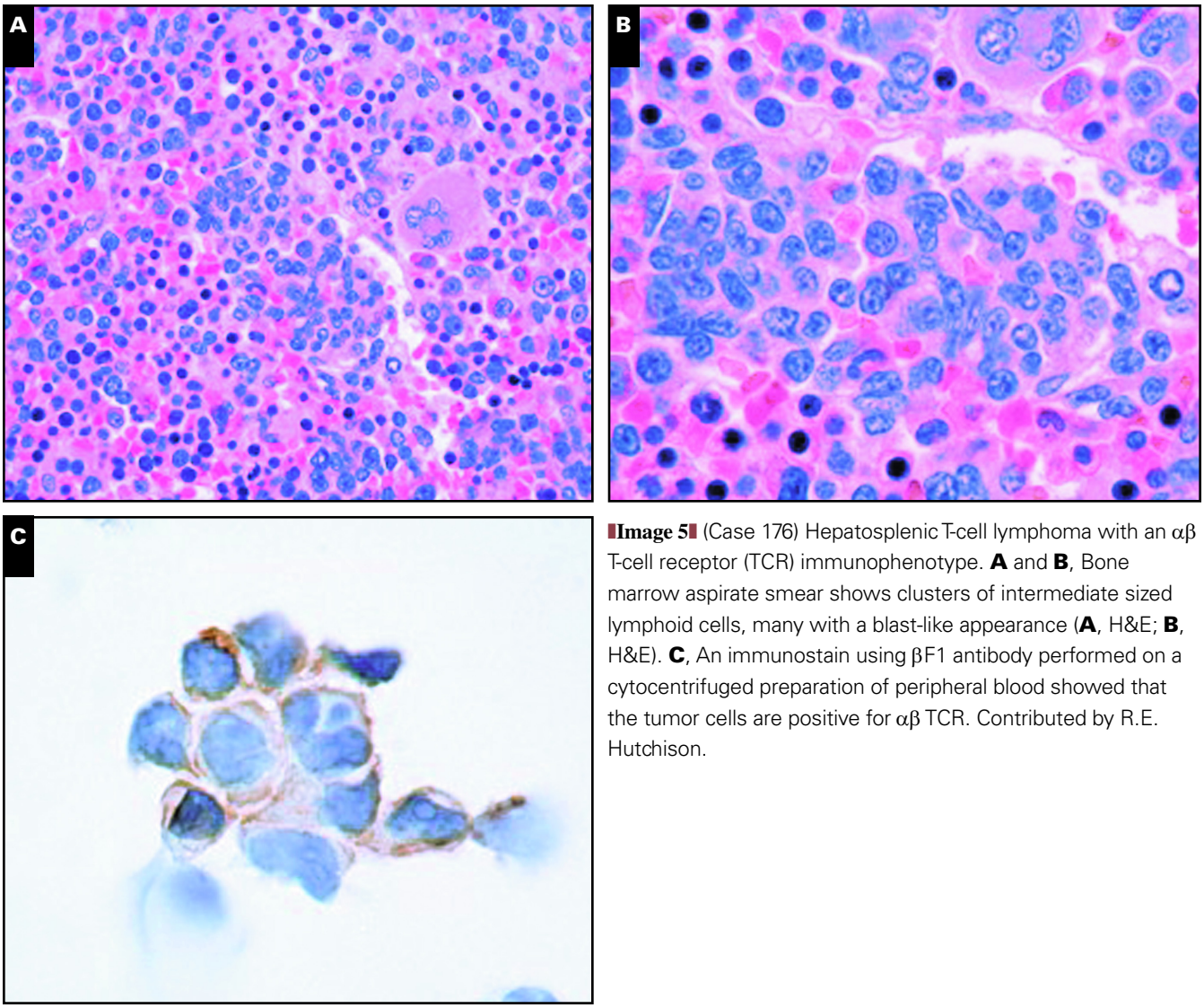

Image 5 (Case 176) Hepatosplenic T-cell lymphoma with an αβ T-cell receptor (TCR) immunophenotype. **A** and **B**, Bone marrow aspirate smear shows clusters of intermediate sized lymphoid cells, many with a blast-like appearance (**A**, H&E; **B**, H&E). **C**, An immunostain using βF1 antibody performed on a cytocentrifuged preparation of peripheral blood showed that the tumor cells are positive for αβ TCR. Contributed by R.E. Hutchison.

Workshop Cases of HSTCL

Nine cases were submitted to the Workshop that closely fit the entity of HSTCL as described in the literature **Table 1**. Six patients were male and 2 were female; their ages ranged from 16 to 61 years (median, 41 years). In 1 case, demographic information was not available. Physical examination revealed splenomegaly in all, and hepatomegaly was documented in 5 patients. Only 1 patient had lymphadenopathy of the hepatic hilum (case 107), and the biopsy showed coexistent metastatic adenocarcinoma and HSTCL. Clinically, most patients had thrombocytopenia and anemia. A background of long-standing immunosuppression was reported in 4 of 9 cases.

The morphologic, immunophenotypic, and cytogenetic features of the Workshop HSTCL cases are summarized in **Table 2**. All cases showed the distinctive sinusoidal pattern of infiltration of the spleen, liver, and bone marrow. Cytologically, the atypical lymphoid cells were small to medium in size (5 cases), large and blastic (3 cases), and pleomorphic (1 case). Most cases expressed a mature and aberrant nonactivated cytotoxic T-cell immunophenotype with expression of TIA-1 and CD56 but absence of CD57 and granzyme B. One case (case 89) demonstrated expression of granzyme B in half of the tumor cells. However, in this case, the morphologic features, immunophenotype, and presence of isochromosome 7q supported the diagnosis of HSTCL. In 7 cases, TCR expression by the tumor cells was documented: 6 were γδ and 1 was αβ. Seven cases were negative for CD4 and CD8, the most common immunophenotype reported in HSTCL. Of the 2 CD8+ cases, 1 (case 107) had a γδ immunophenotype and the other (case 176) had an αβ immunophenotype (Image 5C). In addition, case 176 expressed CD5 and was EBV+.

The presence of isochromosome 7q was documented in 4 of 5 cases (isochromosome 7q was not detected in case 117).

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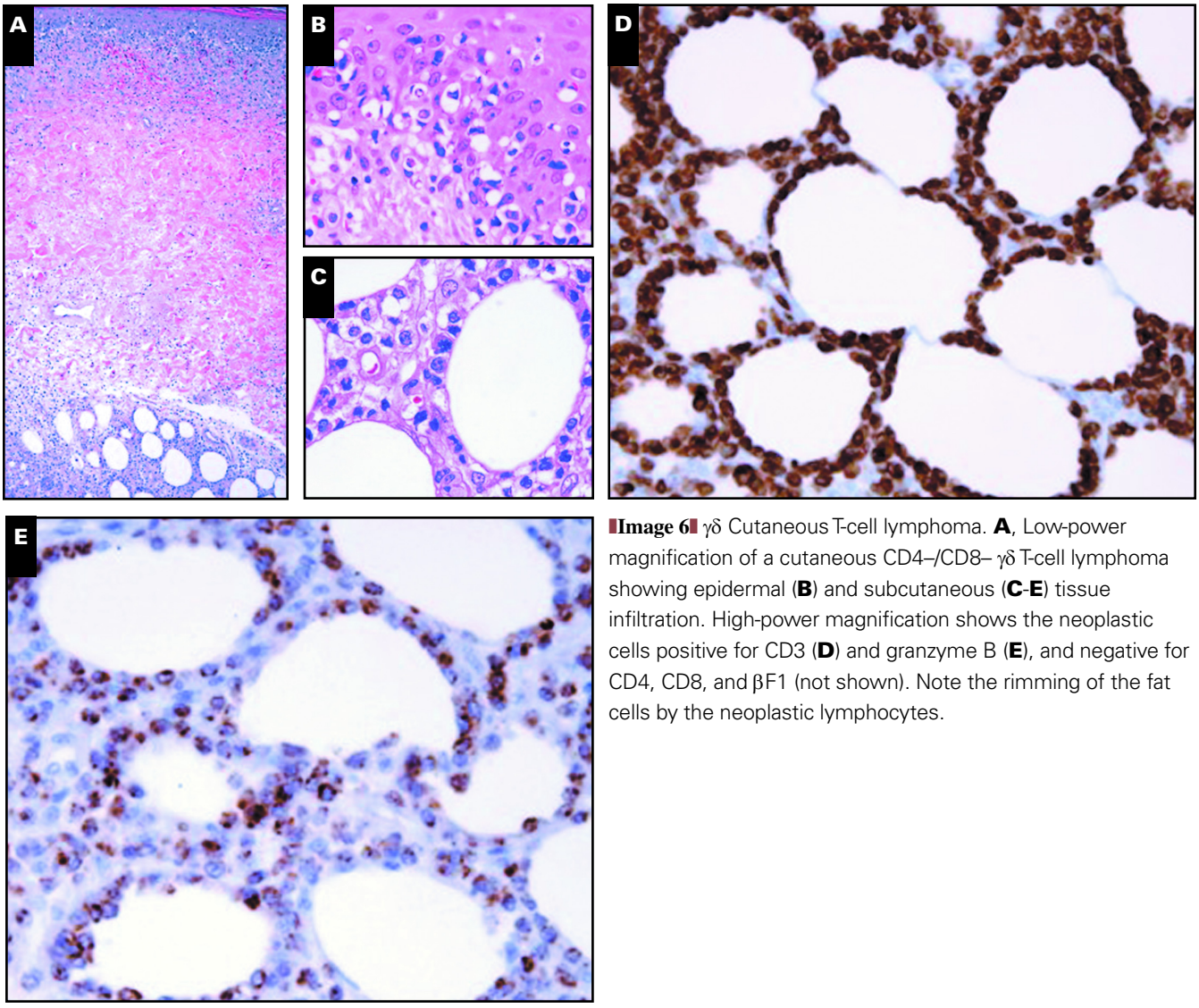

Image 6 γδ Cutaneous T-cell lymphoma. **A**, Low-power magnification of a cutaneous CD4–/CD8– γδ T-cell lymphoma showing epidermal (**B**) and subcutaneous (**C**-**E**) tissue infiltration. High-power magnification shows the neoplastic cells positive for CD3 (**D**) and granzyme B (**E**), and negative for CD4, CD8, and βF1 (not shown). Note the rimming of the fat cells by the neoplastic lymphocytes.

Table 1
Workshop Cases of Hepatosplenic T-Cell Lymphoma: Clinical Features*

Case No./ Sex/Age (y)	History	Anemia	Thrombocytopenia	Splenomegaly	Hepatomegaly	LN	Outcome
85/F/59	NR	+	+	+	NA	NA	
44/M/46	Post–renal transplantation (5 y)	+	+	+	+	–	DOD, 5 mo
89/M/49	HIV+	+	+	+	+	NA	NA
176/M/16	Infectious mononucleosis (EBV)	+	+	+	NA	NA	Persistent disease, 17 mo
117/F/38	NR	+	+	+	+	NA	NA
21/M/27	Sickle/thalassemia trait	+	NA	+	+	NA	NA
125/M/35	Post–renal transplantation (10 y)	NA	NA	+	NA	NA	NA
82/M/61	NR	+	+	+		NA	
107/NA	Ulcerative colitis treated with azathioprine for 17 y	NA	NA	+	+	+	DOD, 2 mo

DOD, died of disease; EBV, Epstein-Barr virus; LN, lymphadenopathy; NA, not available; NR, no relevant medical history; +, present; –, absent.
* If a specific finding was not mentioned as positive or negative, it is listed in this table as NA.

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Molecular studies for rearrangement of the *TCRγ* chain gene demonstrated monoclonal rearrangements in all 7 cases tested. In 1 case, the *TCRδ* chain gene was shown to be rearranged by Southern blot analysis.

Workshop Cases of γδ T-Cell Lymphomas Other Than HSTCL

Table 3 summarizes the clinicopathologic features of the cases submitted to the Workshop in which the panel favored a diagnosis other than HSTCL. Case 14 represents a case of peripheral T-cell lymphoma expressing γδ TCR with an inactivated cytotoxic immunophenotype. This case had some features of HSTCL, including a nonactivated cytotoxic immunophenotype and presence of isochromosome 7q but lacked apparent hepatosplenic involvement. The tumor involved the abdominal wall and segments of colon and small bowel **Image 7A**. Microscopically, there was necrosis and angiocentrism. The tumor cells were large and pleomorphic **Image 7B**, and were positive for CD3, CD8 (dim), CD56, TIA-1, and TCRγδ and negative for CD4 and granzyme B **Image 7C**. Perforin was not assessed. The best classification of this neoplasm and its relationship to HSTCL is uncertain. Examination of bone marrow and liver biopsy specimens would have been helpful in this case.

HSTCL also should be distinguished from other T-cell lymphoproliferative disorders that commonly manifest with hepatosplenic disease and bone marrow involvement and show a similar pattern of infiltration of the spleen, liver, and/or bone marrow. In T-cell large granular lymphocyte (LGL) leukemia, for example, affected patients are usually older adults who often have a preexisting or concurrent autoimmune disease, such as rheumatoid arthritis.[33] The disease is indolent and characterized by a persistent increased number of circulating large granular lymphocytes. In the bone marrow, T-cell LGL leukemia usually has an interstitial pattern of involvement, but a sinusoidal pattern resembling HSTCL can be also observed in some cases (Image 7).[34] Although HSTCL and T-cell LGL share expression of CD8, T-cell LGL leukemia usually also expresses granzyme B and/or perforin and CD57 and has dim rather than absent CD5 expression.[34,35]

However, the distinction between HSTCL and T-cell LGL leukemia can be difficult in some cases, and a combination of clinical and pathologic features are needed to establish the diagnosis **Image 8**. Rare cases of T-cell LGL express the γδ TCR instead of the usual αβ TCR, and these cases may be relatively more cytologically atypical or lack cytoplasmic granules.[36,37] Cases 46 and 220 submitted to the Workshop showed clinical and pathologic features of T-cell LGL. Case 46 was a 67-year-old man at initial examination with a 9-year history of progressive anemia. The indolent course of the disease and the expression of CD5 and granzyme B by the tumor cells supported the diagnosis of γδ T-cell LGL instead of HSTCL. In case 220, the patient had a history of rheumatoid arthritis, and the neoplastic cells exhibited the morphologic features of LGL cells with cytoplasmic azurophilic granules. Case 38 exhibited some morphologic and immunophenotypic features of HSTCL; however, the presence of intracytoplasmic azurophilic granules, the absence of isochromosome 7q, and the indolent clinical course favored the diagnosis of T-cell LGL.

Table 2
Workshop Cases of Hepatosplenic T-Cell Lymphoma: Morphologic and Immunophenotypic Features

Case No.	Site	Morphologic Features	TCR	Immuno	Cytogenetics	TIA-1	GrB	EBV	Clonality/ Test
85	Spleen, BM	Typical pattern; blastic	γδ	3+, 5–, 4–, 8–,16+, 56+, 57–	NA	+	–	–	+/TCRγ
44	Spleen, BM, liver	Typical pattern; pleomorphic	γδ ($V_δ1$)	3+, 5–, 4–, 8–,16+, 56+	i(7)(q10),+8 (by FISH)	+	NA	–	+/TCRδ
89	Spleen, liver	Typical pattern and morphologic features	γδ	3+, 5–, 4–, 8–, 16–, 56+	i(7)(q10) (by FISH)	+	+/–	–	NA
176	Spleen, BM, PB, liver	Typical pattern; blastic	αβ	3+, 5–/+, 4–, 8+, 56+, 57–	47,XY,add(4)(p16), i(7)(q10),+8	NA	NA	+	+/TCRγ
117	BM, spleen, liver	Typical pattern and morphologic features	NA	3+, 5–, 4–, 8–	46,XX; negative also by FISH	+	–	NA	+/TCRγ
21	Spleen, BM	Typical pattern; blastic	NA	3+, 5–, 4–, 8–	46,X,–Y,del(6)(q22q25), i(7)(q10),+8,add(16)(p13.2)	+	–	–	+/TCRγ
125	Spleen	Typical pattern and morphologic features	NA	3+, 5–, 4–, 8–	NA	+	–	–	+/TCRγ
82	Spleen, BM	Typical pattern and morphologic features	γδ	3–, 5–, 4–, 8–, 56+	NA	+	–	–	+/TCRγ
107	Liver, BM, LN	Typical pattern and morphologic features	γδ	3+, 5–, 4–, 8+(dim), 56+/–	NA	+	–	–	+/TCRγ

BM, bone marrow; EBV, Epstein-Barr virus; FISH, fluorescence in situ hybridization; GrB, granzyme B; Immuno, immunophenotype (numbers indicate CD reactivity); LN, lymph node; NA, not available; PB, peripheral blood; TCR, T-cell receptor; TIA-1, T-cell–restricted intracellular antigen.

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Aggressive NK-cell leukemia/lymphoma may be difficult to distinguish from HSTCL. The neoplastic cells in aggressive NK-cell leukemia/lymphoma are usually medium to large, contain cytoplasmic azurophilic granules, express granzyme B and perforin, lack surface CD3 and TCR expression, and lack TCR gene rearrangements.[38] Many of these cases are EBV+, and this subset may represent the systemic variant of nasal-type NK/T-cell lymphoma. Case 175 was an example of an aggressive, EBV+ T/NK-cell leukemia/lymphoma. In this case, the neoplastic cells were positive for CD3 (probably cytoplasmic), granzyme B, and perforin and negative for CD56 and CD57. EBV-encoded RNA was detected in the neoplastic cells, and there was no evidence of clonal TCR rearrangements by polymerase chain reaction.

Questions

What Are the Minimal Criteria for the Diagnosis of HSTCL?

Overall, the clinicopathologic features of HSTCL are quite distinctive and allow the diagnosis in most cases. Patients with HSTCL have hepatosplenomegaly, bone marrow involvement, and peripheral blood cytopenias. HSTCL exhibits a peculiar and distinctive pattern of infiltration; the neoplastic cells preferentially infiltrate the red pulp of the spleen and are seen within the splenic, hepatic, and bone marrow sinusoids. The neoplastic cells have a nonactivated cytotoxic T-cell immunophenotype and frequently carry isochromosome 7q. The demonstration of, a CD3+, CD4–, CD5–, CD8–, CD56+, CD57–, TIA-1+, granzyme B– immunophenotype, and usually γδ TCR, in the right clinical and morphologic setting, is highly predictive of HSTCL.

Should HSTCL With TCRαβ Expression Be Regarded as a Different Entity?

Currently, there are no significant clinicopathologic differences reported between cases of γδ and αβ HSTCL.[17,21] Thus, αβ HSTCL is currently considered a variant of HSTCL. This could be explained by the fact that γδ T cells and some cytotoxic αβ T cells share the same cytotoxic and regulatory functions. It is interesting that the expression of multiple KIR isoforms along with aberrant dim or absent CD94 expression (case 85) has been reported in γδ and αβ HSTCL cases.[39] Because KIR expression is induced by chronic antigenic stimulation, KIR expression by HSTCL is consistent with the concept that chronic antigenic stimulation in the setting of immunodeficiency—frequent in both HSTCL variants—may have a role in disease pathogenesis.

Table 3
Workshop Cases of γδ TCL Other Than Hepatosplenic T-Cell Lymphoma

Case No./ Sex/Age (y)	Diagnosis	Site/History	Morphologic Features	TCR	Immuno	Cytogenetics	TIA-1	GrB	EBV
14/M/49	γδ TCL	Colon, small bowel, abdominal wall	Angiocentrism, necrosis; pleomorphic	γδ	3+, 5–, 4–, 8+ (dim), 56+	i(7)(q10) (by FISH)	+	–	–
46/M/67	γδ LGL	Spleen, BM, PB; long, indolent course (>14 y)	Intrasinusoidal, small cells	γδ	3+, 5+/–, 4–, 8–	NA	+	+ (20%)	–
38/F/46	HSTCL vs γδ LGL	BM	Interstitial	γδ	3+, 5–, 4–, 8–	46,XX	+	–	NA
220/M/78	γδ LGL	Spleen, BM; Mtx for RA	Interstitial; intracytoplasmic granules	γδ	3–, 5–/+, 4–, 8–, 56+	46,XY	+	–	NA
175/M/46	Aggressive NK cell lymphoma/ leukemia	Spleen, BM, liver; HIV+	Red pulp and within liver sinusoids	–	3+, 5–, 4–, 8–, 56–, 57–	NA	+	+	+
181/F/36	EBV+ PTCL-U vs HSTCL	BM, spleen, liver	Nodular infiltrated (spleen) and within liver sinusoids; pleomorphic	βF1–	3+, 5–, 4–, 8–, 25–, 30+, 56+, ALK–	46,XX	+	+	+
205/M/66	PTCL (possible HSTCL)/PTLD	Liver; post–renal transplant (>10 y)	Portal and sinusoidal; small to medium sized	NA	3+, 5–, 4–, 8–	Complex including +1,+3p+16	+	NA	–
70/F/63	PTCL-U	Flank mass (subcutaneous mass)	Pleomorphic	NA	3+, 4+, 8–, 56–	NA	–	–	+ (B cells)
225/M/53	PTCL-U	Liver, LN, spleen	Lymphohistiocytic; no sinusoidal infiltrate; granulomas	NA	3+, 5+, 4+, 8+, S-100+	NA	+	–	NA
56/M/36	ETCL	Intestine and mesentery; no history of enteropathy	Pleomorphic	–	cyto3+, 5–, 8+, 16+, 56+, 103+	Complex	+	+ (20%)	–

ALK, anaplastic lymphoma kinase; BM, bone marrow; ETCL, enteropathy-type T-cell lymphoma; FISH, fluorescence in situ hybridization; GrB, granzyme B; HSTCL, hepatosplenic T-cell lymphoma; Immuno, immunophenotype (numbers indicate CD reactivity); LGL, large granular lymphocyte leukemia; LN, lymph node; Mtx, methotrexate; NA, not available; NK, natural killer; PB, peripheral blood; PTCL-U, peripheral T-cell lymphoma, unspecified; PTLD, posttransplantation lymphoproliferative disorder; RA, rheumatoid arthritis; TCL, T-cell lymphoma; TCR, T-cell receptor; TIA-1, T-cell–restricted intracellular antigen.

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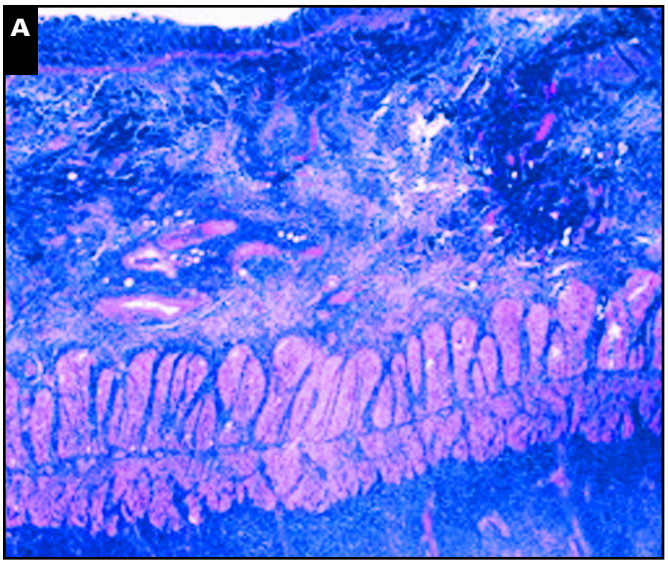
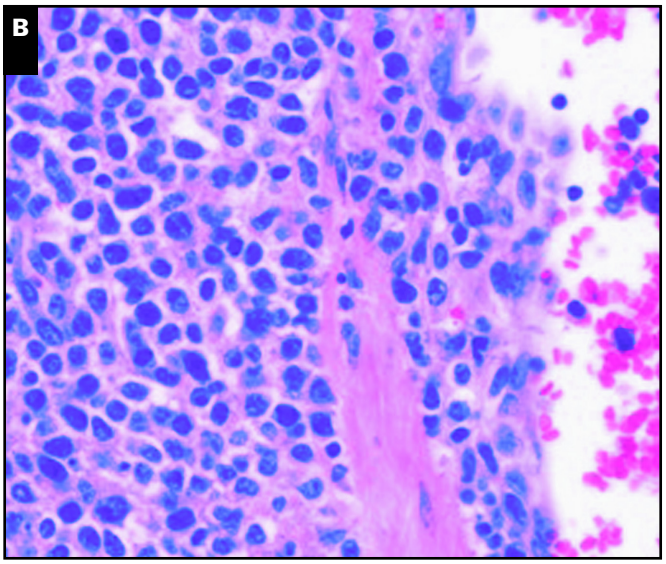




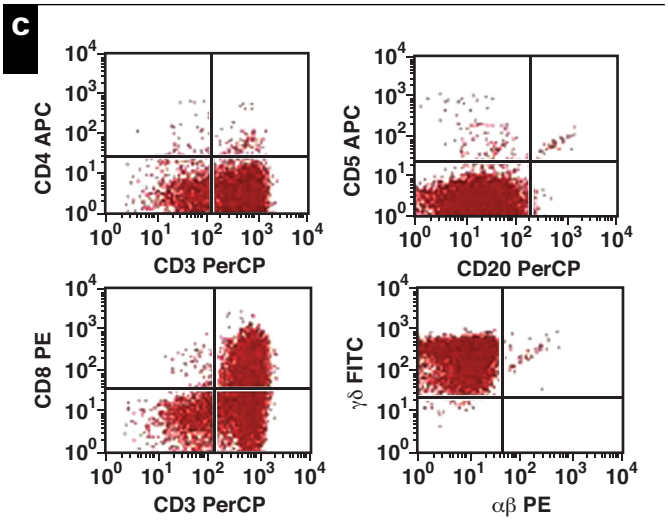
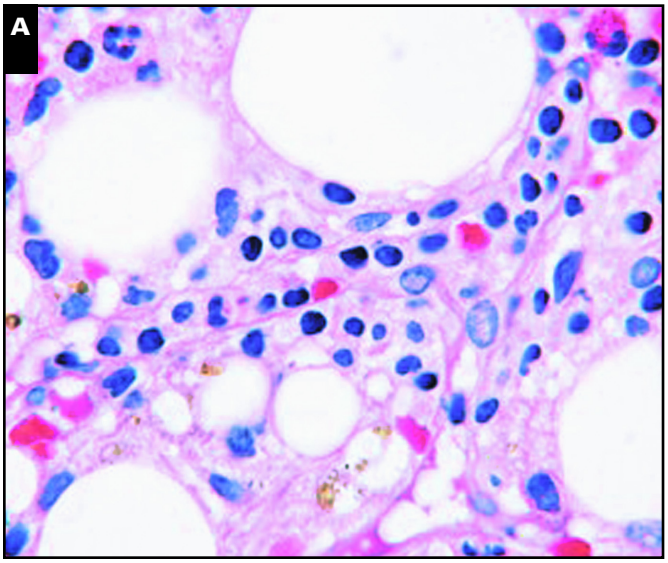


Image 7 (Case 14) γδ T-cell lymphoma, unspecified. **A**, The neoplasm involved omentum, intestinal wall (predominantly serosa), and abdominal wall soft tissue. Angiocentrism and foci of necrosis are noted, but there was no epitheliotropism (H&E). **B**, At high power, the neoplastic cells were large and pleomorphic (H&E). **C**, The neoplastic cells were positive for CD3, CD8, and TCRγδ and negative for CD4, CD5, CD20, and TCRαβ. APC, allophycocyanin; PE, phycoerythrin; PerCP, peridinin chlorophyll protein; TCR, T-cell receptor. Contributed by R.P. Hasserjian.



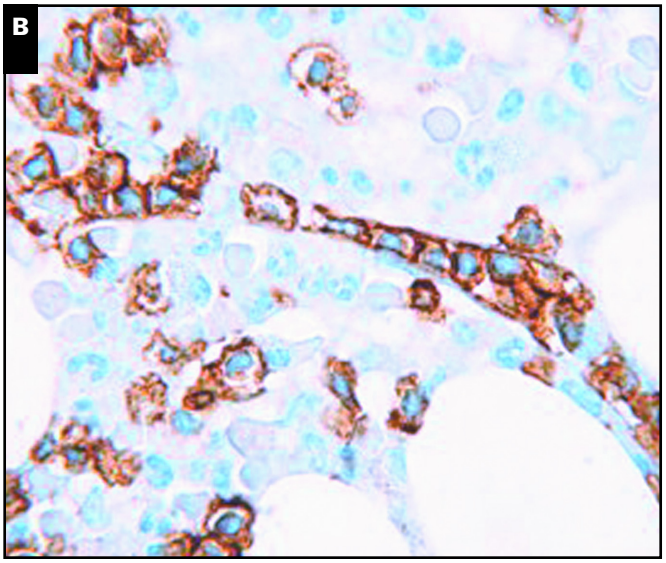


Image 8 (Case 86) T-cell large granular lymphocyte leukemia (LGL). **A**, Some cases of T-cell LGL can have a prominent intrasinusoidal pattern of infiltration simulating hepatosplenic T-cell lymphoma (H&E). **B**, CD3 immunostain highlights the neoplastic cells within the sinusoids. Contributed by K.K. Reichard.

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What Is the Clinical Significance of γδ TCR Expression in Lymphomas That Do Not Resemble HSTCL Clinically or Histologically?

The current WHO classification recognizes several types of T-cell lymphomas/leukemias in which TCR expression is heterogeneous (αβ vs γδ). As discussed earlier, in the 2001 WHO classification, this was also true for subcutaneous panniculitis-like T-cell lymphoma, but the more recent WHO/European Organization for Research and Treatment of Cancer classification designates cutaneous γδ TCR+ cases separately because they have more aggressive clinical behavior and a poorer prognosis than subcutaneous panniculitis-like αβ T-cell lymphomas.[16,28] It is postulated that γδ HSTCL and γδ T-cell lymphomas arising in skin and mucosal sites derive from different γδ T-cell subsets.[8,26,27] Additional studies are needed to better understand the biologic differences between neoplasms derived from γδ T cells vs those derived from αβ T cells and their potential clinical significance.

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