Hepatosplenic T-Cell Lymphoma

A Clinicopathologic Review With an Emphasis on Diagnostic Differentiation From Other T-Cell/Natural Killer–Cell Neoplasms

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Hepatosplenic T-cell lymphoma (HSTL) is an aggressive T-cell lymphoma that accounts for less than 1% of non–Hodgkin lymphoma and about 3% of all T-cell lymphomas/leukemias.1 It is characterized by a primary extranodal involvement of medium-sized lymphoid cells, typically with sinusoidal infiltration of the liver, spleen, and bone marrow, which results in hepatospleno megaly, peripheral blood cytopenias, and other related systemic symptoms. Most cases are of γ/δ T-cell origin, with a few expressing α/β T-cell receptor. Hepatosplenic T-cell lymphoma exhibits a rapidly progressive clinical course and a poor response to currently available therapies, with a 5-year overall survival rate of 7%.1 In the past, splenectomy was usually performed for diagnostic and therapeutic purposes, and a characteristic sinusoidal distribution of neoplastic T cells could be readily identified on immunohistochemically stained tissue sections. Presently, computed tomography–guided needle biopsy of liver, bone marrow biopsy, and peripheral blood smear are more frequently received for a diagnostic evaluation, which sometimes creates difficulty in establishing a definitive diagnosis or classification. In particular, when the bone marrow is involved and the lymphoma cells circulate in the peripheral blood, the neoplasm may mimic some types of T-cell leukemia. In this review, we highlight the clinicopathologic features of this rare T-cell neoplasm and emphasize a combination of clinical findings, histologic features, immunophenotyping, and cytogenetic/molecular tests to approach the diagnosis.

HISTOGENESIS AND PATHOGENESIS

It is believed that HSTL arises from peripheral γ/δ (or less commonly α/β) cytotoxic memory T cells of the innate immune system, especially from the Vα1 subset that shows a predilection for homing to the splenic red pulp.2 In normal circumstances, γ/δ T cells represent only 1% to 3% of the lymphocytes in the peripheral blood; however, they are more prevalent in lymphoid tissues and in lymphocytes associated with mucosa, skin, and gastrointestinal tract. They develop from CD4+CD8− thymocytes in the bone marrow. Using T-cell receptors (TCRs) that are closely associated with the CD3 complex on their surface, γ/δ T cells provide instant defense against pathogens in a nonspecific way at those sites.3 They are also involved in acquired immune responses to microbial infections and may have a role in the pathogenesis of autoimmune disorders and other cellular trauma.4

Although the pathogenesis of HSTL is poorly understood, it has been postulated that chronic antigen stimulation in the setting of immune deficiency or dysregulation might be important. Approximately 20% of cases occur in young patients with immune suppression, including organ transplant recipients and patients with leukemia receiving chemotherapy.5 In addition, HSTL has been associated with the use of tumor necrosis factor α inhibitors and immunomodulators in patients with inflammatory bowel disease or rheumatoid arthritis.6 Chronic antigen stimulation may be related to viral infection. A few hepatosplenic T-cell lymphomas described in this article.

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lymphomas are positive for Epstein-Barr virus (EBV), and a few cases have been reported in association with hepatitis B virus infection. Although viruses do not seem to transform the T cells directly by integration into their DNA, the chronic antigen stimulation from viral infection may drive the proliferation of polyclonal γ/δ T-cells, setting the stage for cytogenetic and molecular anomalies, such as isochromosome arm 7q, and eventually transforms a T-cell clone.

Anemia and thrombocytopenia in patients with HSTL have largely been attributed to hypersplenism and to infiltration of the bone marrow by neoplastic cells; however, cytokines may also be involved. Activated γ/δ T cells can produce various cytokines, including interferon λ, tumor necrosis factor α, granulocyte-macrophage colony-stimulating factor, interleukin (IL) 2, IL-4, IL-5, and IL-10. Hepatosplenic T-cell lymphoma cells have also been shown to produce interferon γ, along with some cytolytic activity. The interferon γ released by the neoplastic γ/δ T cells may suppress hematopoiesis in the bone marrow, leading to severe neutropenia. In some patients, the cytokines produced by HSTL cells are thought to induce hemophagocytic syndrome.

**CLINICAL PRESENTATION**

Hepatosplenic T-cell lymphoma occurs predominantly in adolescents and young adults, with a median age of 35 years (range, 15–65 years) at initial presentation. The male to female ratio is about 9:1. Patients often present with fever, fatigue, weight loss, and abdominal discomfort from hepatosplenomegaly, and sometimes, with jaundice because of liver involvement. Hepatosplenomegaly is the most common finding on physical and radiographic examination (Figure 1). Lymphadenopathy is usually absent. The predominant laboratory findings include pancytopenia and abnormal serum liver enzymes with elevated alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. In particular, thrombocytopenia is seen in more than 50% of patients, and its severity has been shown to correlate with disease progression, even in patients who have undergone splenectomy. Moreover, the recurrence of thrombocytopenia may suggest a relapse in patients who have achieved complete clinical remission. Because of deficiency in coagulation factors caused by the liver infiltration and thrombocytopenia caused by hypersplenism/bone marrow infiltration, patients might have coagulopathy, manifesting as bleeding diathesis. Associated hemophagocytic syndrome has been reported in a few cases. These patients usually present with more-exacerbated systemic findings, including fever, pancytopenia, elevated lactate dehydrogenase, and wasting. The clinical course is fulminant and rapidly progressive. Abnormal cytokine release from the neoplastic T-cells are thought to be responsible for the systemic signs and symptoms and abnormal laboratory results. Although absolute peripheral lymphocytosis is uncommon, a small population of circulating neoplastic lymphocytes may be seen at initial presentation in approximately 50% of patients with HSTL. As the disease progresses, the circulating neoplastic lymphocytes may increase in number and size, and their morphology may undergo a “blastic evolution.” At the terminal stage, HSTL often resembles acute leukemia (leukemic phase). Pancytopenia usually gets worse as the disease progresses because of a combination of bone marrow failure, hypersplenism, and/or hemophagocytosis associated with the disease.

Of particular interest, up to 20% of HSTL cases arise in patients with chronic immune suppression—in recipients of solid organ transplants, in patients with leukemia receiving chemotherapy, or in those with Crohn disease on immunosuppressive agents, specifically purine analogs and inhibitors of tumor necrosis factor like infliximab. In this setting, HSTL is considered an iatrogenic immunodeficiency-associated lymphoproliferative disorder.

**HISTOPATHOLOGY**

Hepatosplenic T-cell lymphoma usually involves the spleen, liver, and bone marrow. On gross examination, the spleen is moderately to markedly enlarged (weight, 570–6500 g), with a deep-brown cut surface. Microscopically, there is an expansion of the red pulp and a reduction or complete atrophy of the white pulp. The neoplastic cells infiltrate both splenic cords and sinuses. At higher magnification, the lymphoid cells in the sinusoidal distribution usually exhibit medium-sized monomorphic morphology with slightly irregular nuclei, dispersed but condensed chromat, indistinct nucleoli, and a moderate amount of clear cytoplasm. Mitotic figures are rare. The sinusoidal pattern is also noted in the liver (Figure 2, A), causing sinusoidal dilation and sometimes perisinusoidal fibrosis without portal triad involvement. On either splenic section or liver biopsy, the sinusoidal distribution of neoplastic lymphocytes can be highlighted by immunohistochemical staining for T-cell antigens, such as CD3 (Figure 2, B). In many liver biopsies, it may be difficult to appreciate the neoplastic infiltration on hematoxylin-eosin–stained slides because the biopsies are often small, and the neoplastic infiltration can be inconspicuous. Therefore, an immunohistochemical panel is mandatory for liver biopsies with suspicion of lymphoma involvement, even though lymphoma is not overtly identified on hematoxylin-eosin section. Hepatosplenic T-cell lymphoma involves the bone marrow in 80% of cases. Although involving the bone marrow, the neoplastic cells tend to circulate in the peripheral blood, and
Figure 2. Morphologic features and immunohistochemical findings in hepatosplenic T-cell lymphoma (HSTL). A, Representative section of a liver needle core biopsy reveals sinusoidal infiltration by medium-sized lymphoid cells. B, The CD3 stain highlights the sinusoidal infiltration of the liver by neoplastic T cells. C, Peripheral blood smear shows the circulating neoplastic cells in a case of leukemic-phase HSTL. Note the irregular nuclear contours, dispersed chromatin, indistinct nucleoli, and moderate amount of lightly basophilic cytoplasm in the neoplastic lymphoid cells. D, Neoplastic cells in the bone marrow aspirate show a relatively high nuclear to cytoplasmic ratio, condensed but dispersed chromatin, indistinct nucleoli, and a scant to moderate amount of light-blue cytoplasm. Note the “hand mirror” cytoplasmic projection in the neoplastic cells. E, The neoplastic cells are associated with hypercellularity in the bone marrow; the sinusoidal infiltration of lymphoid cells is obscured by the reactive proliferation of hematopoietic elements. F, The HSTL cells in the bone marrow are positive for CD3, which highlights the sinusoidal infiltrating pattern (hematoxylin-eosin, original magnification ×400 [A and E]; original magnification ×400 [B and F]; Wright-Giemsa, original magnification ×1000 [C and D]).
the number of circulating neoplastic cells varies depending on the extent of bone marrow involvement. In contrast to the small lymphocytes seen on tissue sections, the neoplastic cells on the peripheral blood smear are often intermediate to large sized with irregular nuclear contours, condensed but dispersed chromatin, indistinct nucleoli, and a moderate amount of lightly basophilic cytoplasm. A few neoplastic cells may contain cytoplasmic vacuoles, mimicking blasts with monocytoid differentiation (Figure 2, C). The neoplastic cells in the bone marrow aspirate smear often show morphologic features resembling lymphoblasts characterized by “hand mirror”-like projections of cytoplasm (Figure 2, D). In rare cases, the cytoplasm of neoplastic cells might contain fine, azurophilic granules. Histiocytic cell phagocytosis of mature red blood cells and hematopoietic precursors may be seen, particularly in patients with clinical and laboratory evidence of hemophagocytic syndrome. The initial section of the involved bone marrow biopsy usually demonstrates hyperplastic trilineage hematopoiesis (Figure 2, E) and, thus, may sometimes be mistakenly considered as myelodysplastic syndrome in the setting of peripheral pancytopenia/cytopenia. As seen in the liver and spleen, involvement, the neoplastic cells assume sinusoidal infiltration, which is often inconspicuous and tends to be overlooked without immunohistochemistry. The sinusoidal distribution of the neoplastic cells can be highlighted by anti-CD3 or other T-cell antigen stains (Figure 2, F). As the disease progresses, the neoplastic cells infiltrate beyond the sinuses, resulting in an interstitial or diffuse pattern. The neoplastic lymphocytes may also become larger and more pleomorphic in later stages of the disease.

ANCILLARY STUDIES

As discussed above, one of the important utilities of immunohistochemistry is to highlight the characteristic pattern of neoplastic infiltration in HSTL. Other than that, it can be used to demonstrate the immunophenotype of the neoplastic cells, including phenotypic aberrancy. By immunohistochemistry, the neoplastic cells of HSTL are typically positive for CD3 (Figure 2, B and F) and CD2 and are negative for B-cell-associated antigens. They are often negative for both CD4 and CD8 (double negative), although CD8 may be expressed in some cases. The neoplastic cells are frequently positive for CD56 and may or may not express CD16, CD57, CD25, and CD30 are usually negative. Hepatosplenic T-cell lymphoma shows phenotypic aberrancy through frequent loss of CD5 and/or CD7, as well as reactivity with multiple killer immunoglobulin-like receptors and a weak to negative reaction to CD94. The neoplastic cells express molecules associated with cytotoxic T cells, such as TIA1. Perforin and granzyme B are usually negative, suggesting that these cells are not activated. In summary, HSTL is characterized by a lymphoid infiltrate in the sinusoids of the liver, spleen, and bone marrow, with a CD3+, CD5−, and TIA1− immunophenotype. In most cases, the neoplastic cells are negative for the β chain of TCR, suggesting their expression of the γ/δ receptor; however, a few cases show expression of α/β TCR. Interestingly, this “variant” with an α/β receptor is usually noted in female patients, and one-third of cases occur in patients older than 50 years.

Flow-cytometric analysis is the best tool for immunophenotyping of hematolymphoid malignancies and is valuable in establishing the diagnosis of HSTL, especially in cases with extensive bone marrow involvement and circulating neoplastic cells. The neoplastic cells usually express bright CD45 and show a slightly upper-shifted side scatter compared with normal lymphocytes (Figure 3, A). They are typically positive for surface CD3, but frequently lose expression of CD5 (Figure 3, B). They are generally double negative for CD4 and CD8 (Figure 3, C) with some cases positive for CD8. Besides those antigens associated with T cells or natural killer (NK) cells described above, flow cytometry is superior to immunohistochemistry for detection of the surface TCR subtypes. Most HSTLs show γ/δ subtype of the surface TCR (Figure 3, D), although rare cases express the α/β subtype. Because γ/δ TCR antibodies are often not reliably interpreted on decalcified, formalin-fixed, paraffin-embedded tissue, flow cytometry is a better tool for assessing the expression of surface TCR in HSTL. Of note, occasional cases of HSTL might lose γ/δ TCR expression, and HSTL with TCR-silent phenotype has also been reported in rare cases. Additionally, lymphoid infiltrates may induce fibrosis, particularly in some cases where the neoplastic infiltration is expanded beyond sinusoids (interstitial infiltration), and the bone marrow may not be aspirable. In that circumstance, the flow cytometric study may thus not be quantitatively representative for the neoplastic process in the bone marrow. Thereafter, a portion of the biopsy can be sent for flow-cytometric analysis if the aspirate specimen is hemodiluted.

Characteristic cytogenetic findings may support the diagnosis of HSTL. Isochromosome arm 7q is a primary and consistent chromosomal abnormality detected in most patients with HSTL, suggesting that has a critical role in disease pathogenesis. Ring chromosome 7 has also been described, in which the ring chromosome contains amplification of 7q with a deleted 7p, resulting in a variant of i(7)(q10). This inversion has been reported in HSTL of both γ/δ and α/β types, providing strong evidence that the 2 TCR variants of HSTL belong to the same neoplastic entity. Trisomy 8 is another frequently observed cytogenetic abnormality in HSTL. Other cytogenetic aberrations include loss of chromosome 21, loss of the Y chromosome, deletion of 11q14, (7,14)(q34;q13), and the interstitial deletion of chromosome 2q23;q37, but these are much less common. Of note, isochromosome arm 7q has also been observed in acute myeloid leukemia, acute lymphoblastic leukemia, myelodysplastic syndrome, and Wilms tumor and has been reported in rare cases of anaplastic large cell lymphoma and extranodal NK/T-cell lymphoma, nasal type. Thus, cytogenetic studies support the diagnosis of HSTL but are not specific and should be interpreted in the context of clinical and histopathologic findings.

Molecular findings may also support the diagnosis of HSTL. Southern blot analysis for a TCR gene rearrangement is the gold standard for detecting T-cell clonality and defining the T-cell genotype. However, this technique is often limited to large, fresh tissues. At present, a polymerase chain reaction based study of TCR gene rearrangement is often used for detection of T-cell clonality. The assay is straightforward, requires only a small piece of tissue, and can be performed on formalin-fixed, paraffin-embedded tissue sections. Irrespective of the γ/δ or α/β phenotype, HSTL shows clonal rearrangement of the TCRγ chain gene (TRG). In cases of γ/δ type HSTL, Southern blot or polymerase chain reaction studies often demonstrate a biallelic clonal rearrangement of TRG genes. In cases of the α/β type, a clonal rearrangement of the TCRβ chain gene.
TRB is usually detected, in addition to clonal TRG rearrangement. Sometimes, a clonal rearrangement of TRB is detected in cases showing restricted surface TCR of the γ/δ subtype by flow-cytometric analysis. This suggests unproductive rearrangement of the gene, as observed in normal γ/δ T-cells. Through gene expression profiling, an overexpression of the genes encoding killer immunoglobulin-like receptor molecules may also be seen.

**DIFFERENTIAL DIAGNOSES**

In the past, the diagnosis of HSTL was usually made on splenectomy specimens. The diagnosis is now usually established using a combination of clinical findings, morphology on liver biopsy, bone marrow biopsy, and peripheral blood smear, immunophenotypic profile, and cytogenetic/molecular findings. Among those, the morphologic and immunophenotypic findings are crucial for diagnosis. As discussed above, a prominent sinusoidal infiltrate in the liver, spleen, and/or bone marrow of medium-sized lymphoid cells with the characteristic immunophenotype (CD2+/CD3+, CD5+, CD4+/CD8-, restricted γ/δ TCR) is sufficient for diagnosis of HSTL, if the clinical picture is appropriate. However, in many cases, the morphology and immunophenotype are equivocal, and a diagnosis of HSTL may be overlooked because of its rarity in comparison to many other T-cell/NK-cell neoplasms. Because of similar clinical presentation, morphology, and immunophenotype, HSTL must be distinguished from the following lymphoid neoplasms: aggressive NK-cell leukemia, T-cell large granular lymphocytic leukemia (T-LGL), T-
lymphoblastic leukemia (T-LBL), other peripheral T-cell lymphomas, splenic marginal zone lymphoma, and hairy cell leukemia. Myelodysplastic syndrome, myelodysplastic/myeloproliferative neoplasm, infectious mononucleosis, type II enteropathy-associated T-cell lymphoma (EATL), and primary cutaneous γ/δ T-cell lymphoma should also be included in the differential diagnosis. In addition to extensive immunophenotypic analysis, correlation with cytogenetic studies and molecular tests may be needed for a definitive diagnosis of hepatosplenic T-cell lymphoma.

Aggressive NK-cell leukemia may have a clinical presentation similar to HSTL. It usually has a fulminant clinical course with hepatosplenomegaly, bone marrow involvement, pancytopenia, coagulopathy, hemophagocytic syndrome, and multiorgan failure. Patients frequently present as young to middle-aged adults with a median age of 42 years. The neoplastic cells are medium to large and often demonstrate an immunophenotypic profile similar to HSTL, including CD2+, CD5–, CD56–, CD4+ /CD8+ and positivity for cytotoxic granule-associated proteins. Although aggressive NK-cell leukemia is typically negative for surface CD3, the ε chain of CD3 is expressed, and so, cytoplasmic staining for CD3 is seen by immunohistochemistry. Therefore, flow-cytometric immunophenotyping is more useful than immunohistochemistry for distinguishing aggressive NK-cell leukemia from HSTL. Flow-cytometric analysis can also detect surface CD3 and surface TCR in HSTL (Figure 3, B and D), for which aggressive NK-cell leukemia is characteristically negative. Molecular studies are also useful for differentiating aggressive NK-cell leukemia from HSTL. In HSTL, there is clonal rearrangement of TCR genes, whereas in aggressive NK-cell leukemia, the genes are typically in germline configuration. The genotypic identity in HSTL can be routinely detected by polymerase chain reaction–based TRG/B gene rearrangement analysis. Another distinguishing feature of aggressive NK-cell leukemia is the expression of FAS ligand, which is increased in the serum. Also, aggressive NK-cell leukemia is an EBV-driven lymphoproliferative neoplasm. The neoplastic NK cells typically harbor the EBV genome, from which viral RNA may be detected by in situ hybridization. In contrast, for the few patients with HSTL in which EBV is detected, it is often found in the bystander B cells.

T-cell large granular lymphocytic leukemia is similar to HSTL in many respects. Like HSTL, T-LGL can occur in the setting of immunosuppression and manifests with neutropenia, anemia, and/or thrombocytopenia. Splenomegaly can also be seen in rare cases, particularly in a late stage of disease. Moreover, T-LGL often infiltrates in a sinusoidal pattern on bone marrow biopsy, a finding highlighted by immunohistochemistry for T-cell antigens. However, subtle differences can be seen between T-LGL and HSTL. T-cell large granular lymphocytic leukemia forms linear arrays in the sinusoids, whereas HSTL cells often expand or “stuff” the sinusoids. Unlike HSTL (Figure 3, B and C), T-LGL is usually positive for CD7 and CD8, although a very small subset is CD4+ /CD8+. The expression of CD5 is often down-regulated but is detectable either by flow cytometry or immunohistochemistry. Most T-LGLs are restricted to expression of surface α/β TCR, however, a few are restricted to the γ/δ TCR, making it difficult to distinguish from HSTL. T-cell large granular lymphocytic leukemia is usually negative for CD56. Unlike HSTL, T-LGL is an indolent disease. In the rare cases when a distinction is impossible by immunophenotyping alone, an aggressive clinical course and detection of isochromosome arm 7q favors a diagnosis of HSTL.22

As discussed above, HSTL can sometimes resemble T-ALL when it involves the bone marrow and peripheral blood in its leukemic phase (Figure 2, C and D). Like HSTL, T-ALL often occurs in young patients and frequently involves the spleen and liver. The double negative (CD4− /CD8−) immunophenotype seen in most cases of HSTL (Figure 3, C) may mimic the pro–T-cell or pre–T-cell immunophenotype sometimes seen in T-ALL. Some cases of HSTL have been initially misdiagnosed as T-ALL because of its CD4− /CD8− immunophenotype. In contrast to HSTL (Figures 3A and 3B), T-ALL should have dim to negative CD45, express terminal deoxynucleotidyl transferase, and be negative for surface CD3. Other immunophenotypic features of T-ALL include expression of CD10 in 15% to 40% and CD34 in 30% of cases.23,24 Although CD10 is expressed in rare cases of HSTL, all cases should be negative for CD34, including those with blastoid morphology.25 A careful examination of the flow-cytometric data and immunohistochemical stains should establish the correct diagnosis.

Peripheral T-cell lymphomas other than HSTL may also involve the spleen and liver, as well as the bone marrow and peripheral blood; however, most are associated with lymphadenopathy. The neoplastic cells of other peripheral T-cell lymphomas are not usually distributed in the sinusoids of the spleen, liver, and bone marrow. Other peripheral T-cell lymphomas commonly have loss of pan–T-cell antigens, including CD5, but they frequently express CD4 and are often restricted to α/β TCR.

Like HSTL, splenic marginal zone lymphoma and hairy cell leukemia often present with cytopneasias and splenomegaly without lymphadenopathy. Additionally, when splenic marginal zone lymphoma involves the bone marrow, it is often seen in a sinusoidal pattern. However, both entities arise from mature B cells, rather than T cells, so a distinction from HSTL is readily achieved by immunophenotyping.

The sinusoidal infiltrate of HSTL can be subtle on the bone marrow core biopsy and, sometimes, entirely obscured by a reactive proliferation of hematopoietic elements. In these cases, the bone marrow may appear hyperplastic. In the context of peripheral cytopenias, myelodysplastic syndrome or myelodysplastic/myeloproliferative neoplasm may be considered at initial evaluation, which could lead to an excessive diagnostic workup in the wrong direction. Therefore, we emphasize a careful flow-cytometric evaluation in every bone marrow aspirate taken for peripheral cytopenias and a low threshold for immunohistochemical analysis if flow cytometry is not informative.

Hepatosplenic T-cell lymphoma should also be differentiated from infectious mononucleosis. Infectious mononucleosis often occurs in early life, but patients in all age groups can be infected. In the United States, the peak incidence is between ages 10 and 19 years, which is younger than the average age for HSTL. The typical presentations include sore throat, fever, and lymphadenopathy. Splenomegaly can be found in approximately 50% of the patients, whereas hepatomegaly is seen in about 10% of the cases. Examination of peripheral blood smear usually reveals lymphocytosis, with at least 10% atypical lymphocytes (95% T cells). The patients often have a positive immunoglobulin M monospot test, which is more sensitive but less specific. Serology tests often demonstrate the presence of high-titer EBV antibodies, whereas most patients with HSTL...
have negative EBV test findings. Lymph node biopsy shows variable degrees of paracortical hyperplasia, follicular hyperplasia, and sinus histiocytosis. Bone marrow biopsy or liver biopsy is seldom performed in these patients. In rare cases in which biopsies are done, they are negative for clonal lymphoid cells by ancillary tests.

Additionally, HSTL also needs to be differentiated from nonhepatosplenic γ/δ T-cell lymphomas, such as type II EATL. Type II EATL can be associated with celiac disease, but in most cases, it is found in otherwise healthy patients. The EATL often occurs in jejunum and/or the ileum. It usually shows multifocal mucosal ulceration, stricture, and less commonly, large masses. However, dissemination to mesenteric lymph nodes, liver, spleen, lung and skin can also be seen. Patients can present with small-bowel perforation or bowel obstruction, abdominal pain, and diarrhea. Type II EATL cells are monomorphic, demonstrating CD3+, CD4+, CD8+, and CD56+ immunophenotype. Approximately two-thirds of cases express γ/δ TCRs, one-third of cases show α/β TCRs, and rare cases demonstrate both TCRs. Molecular studies show complex segmental amplifications of 9q31.1 or deletions in 16q12.1. Amplification of MYC (8q24) can also be seen. Another important differential diagnosis is primary cutaneous γ/δ T-cell lymphoma. Patients usually present with skin patches or plaques, with some cases involving deep dermal or subcutaneous tissue as nodules or mass lesions. Dissemination to other extranodal sites, such as mucosa, is often seen, but lymphadenopathy, splenomegaly, hepatomegaly, or bone marrow involvement is infrequent. The immunophenotypes of the neoplastic cells are very similar. They are usually CD3+, CD2+, CD5+, CD4+, CD8+, and CD56+ with strong expression of cytotoxic proteins. For both EATL type II and primary cutaneous γ/δ T-cell lymphoma, clinical findings and their correlation with pathologic features are critical in making the correct diagnosis.

TREATMENT AND CLINICAL OUTCOME OF THE DISEASE

Hepatosplenic T-cell lymphoma manifests a rapidly progressive disease course. Additionally, the disease exhibits a marked resistance to current chemotherapeutic regimens and, thus, carries a dismal prognosis. The patients with histories of organ transplantation show an especially poor clinical outcome. A complete remission is extremely uncommon. Most patients die from disease progression within 2 years of diagnosis. Although some patients initially respond to chemotherapy, relapse is seen in most cases, and the 5-year overall survival rate is about 7%.

A standard treatment for HSTL has not been established. A review on 45 cases since the first report describing the disease as a distinct lymphoma entity in 1990. Leukemia. 2000;14(6):991–997.


