An unusual presentation of an uncommon lymphoma, hepatosplenic T-cell lymphoma

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ABSTRACT

Hepatosplenic T-cell lymphoma (HSTCL) is a rare T-cell lymphoma, primarily characterized by extranodal distribution of the malignant cells with intrasinusoidal infiltration of the liver, spleen, and bone marrow, which is associated with a poor outcome. We describe a unique case of a 47-year-old woman with a clinical presentation of headaches, fevers, elevated liver function tests, and hepatosplenomegaly. A liver biopsy revealed a striking hepatic intrasinusoidal infiltrate of lymphocytes. These were confirmed to be T cells by immunohistochemical stains (CD8⁺, CD4⁺, CD3⁺, CD20[−]). Molecular studies demonstrated a T-cell gamma receptor gene rearrangement. Clinically, the patient appeared to improve without therapeutic intervention; however, because of the pathologic diagnosis, the patient was initiated on chemotherapy and ultimately underwent a bone marrow transplant.

KEYWORDS Gamma-delta hepatosplenic T-cell lymphoma; hepatosplenic T cell lymphoma; HSTCL

Hepatosplenic T-cell lymphoma (HSTCL) is a rare T-cell lymphoma, primarily characterized by extranodal distribution of the malignant cells with intrasinusoidal infiltration of the liver, spleen, and bone marrow. It most commonly occurs in adults with a median age of 34 years and B symptoms of fever, fatigue, weight loss, abdominal pain, splenomegaly, and jaundice.¹ The disease has been associated with immunosuppressed states, including patients with solid organ transplants as well as patients taking tumor necrosis factor blockers or thiopurine.^{1,2} It is hypothesized that T cells in these patients are subject to increased antigenic stimulation because of decreased pathogen clearance. Antigenic stimulation acts as a promoter of increased cell proliferation, facilitating mutations. Most cases of HSTCL express $\gamma\delta$ T-cell receptor (TCR); however, rare cases of $\alpha\beta$ TCR expression have been described. HSTCL has a poor prognosis, with a 5-year overall survival rate of 7%.¹ We describe a unique case of HSTCL in a patient with a primarily indolent course.

CASE REPORT

A 47-year-old white woman presented with a 3-week history of headache, intermittent fevers of 103°F, dizziness,

nausea, and vomiting. Her surgical, social, and family history was unremarkable. Physical examination was significant for mild epigastric abdominal tenderness. A complete blood count revealed a hemoglobin of 13.9 g/dL, a platelet count of 186 K/ μ L, and a white blood cell count of 8.7 K/ μ L with a lymphocyte predominance of 51%. Flow cytometry was negative for an aberrant lymphoid population. Activated partial thromboplastin time, prothrombin time, and international normalized ratio were in the normal range. Lactate dehydrogenase was markedly elevated at 435 U/L. Liver function tests were as follows: alanine aminotransferase of 200 U/L, aspartate aminotransferase of 119 U/L, alkaline phosphatase of 204 U/L, and total bilirubin of 0.9 mg/dL. Infectious etiologies were investigated and viral panels were negative for Epstein-Barr virus, cytomegalovirus, West Nile virus, hepatitis B, and human immunodeficiency virus.

Abdominal ultrasound of the liver revealed a diffusely echogenic hepatic parenchyma concerning of hepatic steatosis and a wall echo shadow pattern suggestive of multiple gallstones within a contracted gallbladder. Computed tomography scan of the abdomen revealed an enlarged spleen of 14.4 cm and radiologic changes of the mesentery of the left mid abdomen with associated prominent lymph nodes and

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Figure 1. (a) Computed tomography of the abdomen demonstrating an enlarged spleen of 14.4 cm and a misty mesentery of the left mid abdomen with associated prominent lymph nodes and subtle mass effect. (b) Liver with atypical lymphocytes within sinusoids. (c) Strong cytomembranous staining for CD8 within atypical cells.

subtle mass effect suspicious for a lymphoproliferative disorder (Figure 1a). Biopsies of the liver and mesentery were pursued.

Needle core biopsy of the liver showed portal tracts and sinusoids infiltrated by atypical lymphocytes, including small, round lymphocytes associated with spotty hepatocellular apoptosis and rare foci of confluent multicellular necrosis (Figure 1b). Immunohistochemistry confirmed that the cells were of a T-cell lineage, with positive staining for CD8 (Figure 1c) and CD3 and negative staining for CD4 and CD20. TIA-1 was positive and Ki-67 showed positive staining within 90% of the cells. Staining for $\alpha\beta$ TCR and $\gamma\delta$ TCR were negative, but a $\gamma\delta$ TCR rearrangement was identified on polymerase chain reaction (PCR). A bone marrow biopsy was done. Although an infiltrate was not appreciated by morphology or by stains and flow cytometry on the bone marrow biopsy, a $\gamma\delta$ TCR rearrangement was detected by PCR. A mesenteric biopsy showed no evidence of a lymphoproliferative disease.

Clinically, the patient's presenting symptoms improved dramatically and spontaneously without any anti-lymphoma intervention, in contrast to the typical aggressive course of this entity. However, because of the pathologic diagnosis, the patient was initiated on multiagent chemotherapy (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone) and ultimately underwent a bone marrow transplant.

DISCUSSION

This case presented as a diagnostic challenge for several reasons. Firstly, HSTCL is very rare, accounting for only 3%

of T-cell lymphoma subtypes in the United States.¹ It primarily presents in young men with constitutional B symptoms as well as patients who are chronically immunosuppressed, which was not the case for our 47-year-old female patient, who initially presented with fevers and headaches but shortly after presentation had a seemingly complete resolution of symptoms without therapeutic intervention. Though constitutional symptoms are often present, diagnosis of HSTCL is usually made after a splenectomy or a liver/bone marrow biopsy with adequate immunophenotyping.² Anemia and thrombocytopenia are also typically seen but were not present in our patient.¹ On biopsy, the morphology was consistent with a hepatosplenic lymphoma; however, the immunohistochemical staining for $\gamma\delta$ TCR was repeatedly negative. Most reported cases have shown positive staining for $\gamma\delta$ TCR or less commonly $\alpha\beta$ TCR (which was also negative in our case).¹ $\gamma\delta$ TCR or $\alpha\beta$ TCR expression is not pathognomonic in the diagnosis of HSTCL. In a study by Wei et al, three of eight cases of HSTCL did not show $\gamma\delta$ TCR immunostaining on routinely formalin-fixed and paraffin-embedded tissue sections, possibly due to antigen denaturation during the formalin fixation process.³ However, PCR analysis for T-cell gene rearrangements demonstrated a γ rearrangement in our patient, further supporting the diagnosis of HSTCL. In HSTCL, the TCR γ gene is almost always rearranged and the β TCR gene can be rearranged as well.¹⁻⁴

In the future, cytogenetic testing may help in diagnosing of this disease. The TCR beta and gamma alleles are encoded on chromosome 7 and isochromosome 7q is the most consistently found chromosomal abnormality detected in HSTCL patients.¹ However in one review of 28 cases of HSTCL showed detection for isochromosome 7q in only 42% of the cases.⁴ Unfortunately, this was not done in our case due to specimen limitations.

This case highlights a unique presentation of a rare disease with unusual clinical findings. Immunohistochemistry and molecular tests helped establish the diagnosis.

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