Successful Treatment of Hepatosplenic T-Cell Lymphoma With ESHAP Followed by Autologous Stem Cell Transplant

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Introduction

Hepatosplenic T-cell lymphoma (HSTCL) was first described as a distinct clinicopathologic entity in 1990.¹ HSTCL is a rare type of non-Hodgkin lymphoma that was originally recognized by its characteristic clinical presentation, distinct histologic pattern, and expression of the γδ T-cell receptor (TCR).¹ Recent scientific advances have allowed for better understanding of the histologic, immunophenotyping, and cytogenetic characteristics of HSTCL, including identification of HSTCL with αβ TCR expression. γδ HSTCL and αβ HSTCL are now considered immunophenotypic variants of the same disease.

Despite these advances, HSTCL remains a very aggressive subset of T-cell lymphoma and confers a poor prognosis, with a reported median survival of 6–11 months.²,³ There has been no consensus to date regarding therapeutic modalities in these patients, and effective treatment of HSTCL is lacking. A review of the literature reveals the use of various treatment regimens in patients with HSTCL. The majority of these treatment modalities appear to be ineffective in most patients, although there are some case reports and case series that describe complete remissions with certain chemotherapy regimens with or without stem cell transplantation.²,⁴ In this case report, we describe the successful treatment of HSTCL in a 44-year-old woman with etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP) followed by autologous stem cell transplant (auto-SCT).

Case Report

A 44-year-old woman with a medical history of hypertension, gout, and eczema presented to her primary care physician for evaluation of a new maculopapular rash involving her upper extremities. Routine laboratory studies revealed leukopenia and thrombocytopenia, at which time the patient was referred to our hematology clinic for further evaluation. History of present illness was notable for a 6-month history of nausea, emesis, early satiety, and severe left upper quadrant abdominal pain that radiated to her shoulder. Review of systems was positive for occasional night sweats and gingival bleeding. The patient denied weight loss or fevers.

Physical examination was significant for a palpable spleen 4 cm below the costal margin, as well as a maculopapular rash between skin folds in the elbows and knees bilaterally. The remainder of the physical examination was unremarkable; no lymphadenopathy or hepatomegaly was noted. Laboratory studies revealed the following: white blood cell count of 2,040/mcL (absolute neutrophil count, 850/mcL), hemoglobin of 12.7 g/dL, and platelet count of 90,000/mcL. Renal function and liver function tests were within normal limits. Serum lactate dehydrogenase (LDH) was 164 U/L (normal level, 84–240 U/L) and uric acid was 9.0 mg/dL (normal level, 2.6–6.8 mg/dL).

Figure 1. Computed tomography scan of the abdomen revealed splenomegaly at 15.5 cm × 8.9 cm without hepatomegaly.

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Computed tomography (CT) of the chest, abdomen, and pelvis revealed splenomegaly, measured at 15.5 cm × 8.9 cm, with hypodensities in the anterior and posterior aspects of the spleen, most likely representing lymphomatous involvement; there was no evidence of lymphadenopathy (Figure 1). Bone marrow biopsy revealed a mildly hypercellular marrow with sinusoidal infiltration by hepatosplenic T-cell lymphoma (Figures 2 and 3). Flow cytometry revealed tumor cells that expressed CD2, CD3, and CD7 positivity, but lacked expression of CD5, CD4, and CD8. In addition, tumor cells expressed the natural killer (NK) cell marker CD56, but not CD57. Cytogenetics revealed a normal female karyotype.

The patient was diagnosed with stage IVB hepatosplenic T-cell lymphoma and was treated with 3 cycles of ESHAP. Treatment was well tolerated, with 1 hospitalization for neutropenic fever of unknown etiology that resolved with supportive care. Three months after diagnosis and following 3 cycles of ESHAP, physical examination was remarkable for a non-palpable spleen. CT scan at this time revealed decreased splenic size, measured at 13.8 cm × 6.9 cm, along with decreased size of the splenic hypodensities. Repeat bone marrow biopsy demonstrated normocellular marrow with no evidence of abnormal lymphocytes, consistent with morphologic remission.

Nearly 2 months following the third and final cycle of ESHAP, the patient underwent auto-SCT following conditioning with carmustine, etoposide, cytarabine, and melphalan (BEAM) chemotherapy. Auto-SCT was complicated by mucositis, neutropenic fevers, and acute renal failure, which all resolved. Bone marrow biopsy obtained on day +79 revealed no suspicious lymphoid infiltrates and no evidence of lymphoma by flow cytometry. Positron emission tomography (PET) scan obtained on day +85 failed to demonstrate areas of increased metabolic activity. CT scan revealed stable splenomegaly with no evidence of lymphadenopathy. The patient is currently 22 months from time of diagnosis and 18 months post auto-SCT. She has remained in clinical remission.
Peripheral T-cell lymphomas (PTCLs) account for 7–10% of all non-Hodgkin lymphomas in Western countries, with HSTCL identified as a rare entity within this group. HSTCL is a malignancy that usually affects young men in the third or fourth decade of life, but has been reported in patients ranging in age from 5 to 68 years. In approximately one-third of patients, HSTCL is associated with a history of immunosuppression, as seen in the treatment of inflammatory bowel disease or organ transplant; it is less commonly associated with immunosuppression related to Hodgkin lymphoma or malaria. It is hypothesized that chronic antigen stimulation in states of immunosuppression may contribute to the pathogenesis of HSTCL. While the possibility of an infectious connection has been explored, there is no proven association between Epstein-Barr virus (EBV) and HSTCL.

Patients with HSTCL typically present with hepatosplenomegaly and constitutional symptoms, including night sweats, weight loss, and fevers. Lymphadenopathy is present in a minority of patients. Predominant laboratory findings include cytopenias, with thrombocytopenia being a near constant finding with frequently associated anemia and/or leukopenia. The severity of thrombocytopenia has been shown to correlate with disease progression. An elevated serum LDH and abnormal liver function tests may also be noted at the time of diagnosis.

HSTCL universally involves the spleen, and the liver and bone marrow have near constant involvement. Involvement of other sites, such as the skin, oral mucosa, and kidney, has been rarely reported. Usually, the spleen is massively enlarged, with pathologic features revealing the red pulp to be diffusely infiltrated by small to medium-sized atypical lymphocytes. These atypical cells are seen within the cords and sinuses of the red pulp. The liver is usually involved, as observed in liver biopsy specimens, regardless of the presence of hepatomegaly or abnormal liver function tests at the time of diagnosis. Liver pathology demonstrates sinusoidal infiltration by malignant cells. Bone marrow involvement is common, with findings of neoplastic cell infiltration progressing from sinusoidal involvement to interstitial involvement over time, though it may initially be difficult to recognize.

Immunophenotypic features, along with cytogenetic and molecular features, aid in the diagnosis and understanding of HSTCL. The most common immunophenotype in patients with HSTCL is as follows: CD2+, CD3+, CD5, CD43, CD45RO, and CD79a. CD30 is usually negative, and CD25 expression is variable. Cytogenetic abnormalities are uncommon, but when present, they are often complex and may include translocations involving the TCR locus. Molecular analyses may reveal rearrangements of the TCR genes, which are characteristic of PTCLs.
CD4−, CD5−, CD7+/−, CD8−, CD16+/−, CD 3 8+ , and CD56+. Our patient had a common immunophenotypic profile of CD2+, CD3+, CD4−, CD5−, CD7+, CD8−, and CD56+. Neoplastic cells usually have a non-activated cytotoxic phenotype (TIA1+, granzyme B−). HSTCL was first described with γδ TCR expression. While γδ TCR expression is seen in the majority of patients, there are increasing reports of αβ TCR expression. Both are now considered immunophenotypic variants of the same disease. A diagnostic approach using immunohistochemistry of bone marrow showing CD3+, CD5− lymphocytes with sinusoidal distribution is sufficient. Despite these criteria, a large pathologic review showed only a 72% agreement for the diagnosis of HSTCL. Certain cytogenetic and molecular features have been found in patients with HSTCL, most notably, isochromosome 7q and less commonly, trisomy 8. Various treatment regimens and modalities have been reported in the literature, including splenectomy; steroids; alkylating agents; cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy; purine analogues; multi-agent approaches; and autologous or allogeneic hematopoietic SCT. While the majority of patients observed showed initial clinical improvement, very few obtained complete remissions, with the majority of patients clinically progressing until time of death. HSTCL has a poor overall survival, with the only positive prognostic factor being female sex. The International Prognostic Indicator has no impact on outcome. A history of immunocompromise is associated with a poorer prognosis. ESHAP was selected because of the known ineffectiveness of CHOP chemotherapy in PTCL.

Treatment with ESHAP for HSTCL was described by Nagai and associates in a patient with chronic hepatitis B who achieved a partial durable remission. The patient was first treated with CHOP and dexamethasone, etoposide, ifosfamide, and carboplatin (DeVIC), with minimal response. Following subsequent treatment with 3 cycles of ESHAP, the patient was noted to have a durable partial remission, with bone marrow biopsy revealing 3% residual lymphoma cells in the marrow. The patient subsequently underwent allogeneic SCT. However, the patient’s lymphoma became refractory to ESHAP treatment, as well as salvage chemotherapy. The patient ultimately died of sepsis while undergoing conditioning in preparation for another SCT. Based on their clinical experience and a review of the literature, the authors hypothesized that early allogeneic SCT while patients are in partial or complete remission may be the most successful treatment approach.

Larger case series have shown partial success with other regimens. Falchook and colleagues analyzed 15 cases of HSTCL at their institution, where complete remission (CR) was achieved in 7 patients. Of the 3 patients in their series who were treated with liposomal doxorubicin, vincristine, and dexamethasone (HyperCVIDDoxil) alternating with methotrexate and cytarabine, all achieved CR. One patient was treated with pentostatin/alemtuzumab followed by allogeneic SCT and was in CR 36 months post-treatment. The 3 additional patients who achieved CR had a maximum survival of 25 months. Though not significant, patients with a history of immunosuppression or significant liver involvement trended toward worse outcomes.

Recent smaller case reports have reported successful treatment of HSTCL. Humphreys and coworkers used interferon α to treat patients with HSTCL. This approach was based on successful treatment of other PTCLs, especially cutaneous T-cell lymphoma, with interferon α. Two patients with a history of immunosuppression went into CR following treatment with interferon α. It is unclear whether immunocompromised patients represent a distinct clinicopathologic entity. Other successful treatment strategies have included bortezomib (Velcade, Millennium Pharmaceuticals) with high-dose CHOP-like chemotherapy and 2-deoxycoformycin therapy. It has also been suggested that patients may benefit from splenectomy in the setting of severe thrombocytopenia, as this may allow for patients to receive more aggressive chemotherapy. As our patient was not severely pancytopenic, she was able to tolerate chemotherapy without requiring prior splenectomy.

In 2008, the International T-Cell Lymphoma Project completed the largest clinicopathologic study of PTCL and natural killer T-cell lymphoma (NKTCL) in an attempt to better characterize this rare disease. A diagnosis of PTCL or NKTCL was confirmed in 1,153 (87.8%) of the cases examined. Of these, the most common subtype of PTCL was PTCL not otherwise specified (25.9%), with HSTCL comprising 1.4% of the cases. Additionally, this study examined the relative frequencies of the various lymphoma subtypes by geographic region, with HSTCL comprising 3% of cases in North America compared with 2.3% and 0.2% of cases in Europe and Asia, respectively. Clinical characteristics of the various subtypes of PTCL and NKTCL were compared. Patients with HSTCL typically had more bone marrow involvement (74%) compared with other subtypes (range, 0–29%). In other forms of PTCL, a complete response following chemotherapy and transplant predicted long-term response, with a 5-year survival of 50%. HSTCL has a 5-year overall survival rate of 7% and a 5-year failure-free survival rate of 0%, the lowest among all PTCLs and NKTCLs. Despite obtaining a CR and successfully undergoing auto-SCT, most patients with HSTCL relapse early, and 2-year survival is rare. There is no standard of care for patients with HSTCL, as the majority of treatment modalities are ineffective. This case report
demonstrates that ESHAP followed by auto-SCT may be an effective way to achieve CR in patients with HSTCL. However, treatment strategies for a sustained response are still needed. Continuing efforts to understand PTCL and actively enroll these patients in clinical trials are crucial.

References

Review
Hepatosplenic T-Cell Lymphoma: Is Cure Possible?
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Discussion
Chalmers and associates describe a case of hepatosplenic T-cell lymphoma (HSTCL) presenting in a 44-year-old woman without history of immunologic disorder or immunosuppressive therapy. The patient presented with typical clinical features of HSTCL, including splenomegaly with resultant left upper quadrant pain and early satiety, peripheral blood cytopenias, and systemic symptoms. Bone marrow evaluation revealed characteristic findings, including a sinusoidal pattern of infiltration by medium-sized monomorphic lymphoid population with malignant clonal T-cell phenotype. Imaging studies showed no lymph node involvement or hepatomegaly. No mention was made regarding T-cell receptor phenotype. A complete remission (CR) was achieved with 3 cycles of etoposide, methylprednisolone, cytarabine, and carboplatin (ESHAP), which was confirmed by post-treatment bone marrow examination. After initial therapy, the patient underwent autologous hematopoietic cell transplantation (HCT) following conditioning with carmustine, etoposide, cytarabine, and melphalan (BEAM) chemotherapy. The authors reported continuous CR 18 months after SCT; however, minimal residual disease (MRD) assessment is lacking. While the outcome described in this case report is encouraging and compares favorably to historic data,
Peripheral T-cell lymphomas (PTCLs) are a rare and diverse group of aggressive neoplasms that are associated with a poor prognosis. As a group, they represent 7–10% of non-Hodgkin lymphomas. However, the modern World Health Organization (WHO) classification recognizes 11 subtypes of systemic PTCL, some of which are exceptionally rare. Based on the reported relative frequency of PTCL and PTCL subtypes, it can be estimated that only 30–60 cases of HSTCL will be diagnosed in the United States in 2013. This rarity poses several challenges. First, trials of new therapeutics are unlikely to accrue a sufficient number of these cases to make a reasonable assessment of efficacy, and extrapolation from other subtypes is dangerous due to the biologic diversity of the group. Second, anecdotal reports and case series are flawed by lack of statistical power and publication bias toward positive results. Third, it makes it nearly impossible to develop a clinical- or molecular marker–based risk stratification system. These challenges make it difficult to relate any of the published reports on HSTCL to a particular clinical situation. This difficulty applies to choice of initial therapy, salvage treatments, type of HCT, and the role of new agents. Evolving national and international collaborative efforts, as well as the expansion and development of T-cell lymphoma registries, will hopefully provide a better understanding of rare types of PTCL and improve treatment options.

**How to Monitor Remission in HSTCL**

Due to the unique clinical presentation of HSTCL, standard response criteria and remission monitoring modalities may not truly represent disease status. As such, new techniques are necessary. Absence of lymphadenopathy and "metastatic" involvement of extranodal sites make computed tomography (CT) findings ambiguous. In addition, regression of splenomegaly and/or hepatomegaly is usually a gradual, slow process, and in many cases complete resolution is never achieved, even in the case of CR. Similarly, inflammatory/reparative processes in the spleen might create erroneous readings on positron emission tomography (PET), especially in the setting of autologous or allogeneic HCT. On the other hand, it is known that some of the non-Hodgkin lymphomas with low-to-moderate proliferative rates may not be detected by PET. Bone marrow status can hardly be assessed by any imaging modality. The role and significance of MRD detection in the blood and/or bone marrow is largely unknown, and it may be very useful in HSTCL. While the authors report clinical remission in their patient, it is unclear whether there is any evidence of MRD. If present, this could potentially offer the opportunity for preemptive treatment. At our institution, bone marrow evaluation with MRD assessment is the primary monitoring method for HSTCL patients following therapy. Expert consensus is needed in order to standardize response and monitoring criteria for HSTCL.

**HSTCL: Auto Versus Allo**

Autologous HCT and allogeneic HCT are often considered the “ultimate curative therapy” for patients with high-risk, newly diagnosed, or relapsed/refractory hematologic malignancies. However, there are few randomized studies demonstrating the benefit of this approach for the majority of clinical scenarios. While autologous HCT relies on high-dose therapy to cure the disease, allogeneic grafting offers the chance of cure via graft-versus-lymphoma effect. Although mortality from autologous HCT is very low with current supportive care, up to 10–35% of patients would die from treatment-related mortality (TRM) with allogeneic grafting. Therefore, the choice of HCT should be individualized to a particular clinical scenario after careful assessment of risks and potential benefits. Several anecdotes describe long-term disease control and survival in patients with HSTCL after allogeneic HCT. However, in the largest series to date reported by Belhadj and colleagues, all 3 patients with HSTCL who underwent allogeneic HCT died within 6, 9, and 25 months post allograft, while the only 2 long-term survivors at 42 and 52 months received autologous HCT. Of note, the latter 2 surviving patients received platinum-containing regimens, as did the patient in this current case report. Therefore, using either the autologous or allogeneic approach remains experimental and should preferably be performed in the context of clinical trials. At our institution, we generally offer allogeneic HCT to HSTCL patients if CR or near CR is obtained and a suitable donor is available. This decision is based on reports of the limited benefit of autologous HCT in high-risk PTCL patients and encouraging cure rates in otherwise incurable situations with allografting. Future studies should focus on introducing post-transplant maintenance therapy, preferably with agents that are known to affect the biology of malignant cells.

**HSTCL and Novel Agents**

The last 3 years were marked by rapid progress in PTCL biology and therapy, with approval of 3 T-cell-specific
agents that showed significant activity in relapsed and refractory PTCL. Pralatrexate (Folotyn, Allos) and romidepsin (Istodax, Celgene) were studied and approved for all PTCL subtypes, and brentuximab vedotin (Adcetris, Seattle Genetics) demonstrated marked activity in CD30-expressing anaplastic large cell lymphoma. While few patients with rare PTCL subtypes were enrolled in these studies, broad-spectrum activity of pralatrexate and romidepsin across all histologic subtypes suggests unique mechanism(s) of action and makes the case for their empiric use in all subtypes of PTCL, including HSTCL, at relapse. In fact, case reports already suggest high efficacy with these novel agents in HSTCL. Of particular interest is a recent report of possible high efficacy of the novel aurora kinase inhibitor alisertib in primary cutaneous γδ T-cell lymphoma. Given the common origin and possibly common biology of γδ T cells, it is intriguing to hypothesize that these agents will be highly active in other γδ TCLs, including HSTCL. Particular effort should be made toward utilizing these novel agents in pre- and post-HCT settings, as well as in other maintenance protocols.

References