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Hepatosplenic T-cell Lymphoma Arising in Patients with Immunodysregulatory Disorders: A Study of 7 Patients Who Did Not Receive TNF- α Inhibitor Therapy and Literature Review

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Abstract

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive extranodal T-cell lymphoma that can arise in patients with underlying immune disorders. Others have suggested that tumor necrosis factor alpha (TNF- α) inhibitor therapy for immune disorders increases the risk of HSTCL. To assess for a potential relationship between HSTCL and the use of TNF- α inhibitors, we searched for patients with HSTCL and underlying immune disorders at our institution. We identified 7 patients with a median age of 38 years. Five patients had Crohn disease, 1 ulcerative colitis and 1 rheumatoid arthritis. In 6 patients, medication history for the immune disorder was available: 6 patients received 6-mercaptopurine or azathioprine, 2 patients received steroids; no patients received TNF- α inhibitors. In all 7 patients, the histologic, immunophenotypic, and cytogenetic findings were similar to cases of HSTCL that arise in immunocompetent patients. We reviewed the literature and identified 60 patients with immune disorders who subsequently developed HSTCL. These patients were treated with immunosuppressive drugs in 89%, TNF- α inhibitors in 56%, both therapies in 54%, and one (2%) patient was treated with TNF- α inhibitors only. Our cohort and literature review indicates that TNF- α inhibitor therapy is not essential for the development of HSTCL in patients with immunodysregulatory disorders, and implies that immunosuppressive drugs or other factors (e.g. genetic predisposition, chronic antigenic stimulation) may be more critical in the pathogenesis in this context. Although these data are observational, they have implications for the use of TNF- α inhibitors in patients with inflammatory bowel disease and other immunodysregulatory disorders.

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Keywords

Inflammatory Bowel Disease; Autoimmune disorders; Immunosuppression; Azathioprine; 6-Mercaptopurine

1. Introduction

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive extranodal T-cell lymphoma that often affects adolescents and young adults and commonly males.^{1,2} Patients with HSTCL usually present with B-symptoms, massive splenomegaly, and advanced stage disease.² These tumors have a distinctive immunophenotype characterized by CD4⁺, CD5⁺, CD8⁺, and CD56⁺ and are often associated with isochromosome 7q.^{1,3} Although most patients present *de novo*, a subset of cases arises in the setting of immune disorders, most commonly inflammatory bowel disease (IBD). Whether HSTCL is more common in patients with immune disorders is controversial.⁴

Immunosuppressive drugs such as 6-mercaptopurine (6-MP) or its pro-drug azathioprine, or tumor necrosis factor alpha (TNF- α) inhibitors are commonly used to treat patients with immunodysregulatory disorders. Inhibitors of TNF- α are approved by the Food and Drug Administration (FDA) for the management of Crohn disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis and psoriasis. When TNF- α inhibitors are used concomitantly with 6-MP or azathioprine in patients with IBD, there is a reported approximately four-fold increased risk of lymphoma, including B-cell lymphomas and HSTCL.⁴⁻⁷ However, the role of TNF- α inhibitors in predisposing patients specifically to HSTCL is controversial.⁵

In this study, we present the clinicopathologic, immunophenotypic, and cytogenetic findings of 7 patients with immunodysregulatory disorders who developed HSTCL. We also searched the literature and identified 60 additional cases of HSTCL in patients with immune disorders. Our patient cohort and literature review indicate that TNF- α inhibitors are not essential for the onset of HSTCL in patients with IBD and other immune disorders and implicate other immunosuppressive drugs or other factors such as genetic predisposition or chronic antigenic stimulation in the pathogenesis of HSTCL in the clinical context of immunodysregulation.

2. Materials and methods

2. 1. Study group

We searched the files of the Department of Hematopathology at The University of Texas MD Anderson Cancer Center between January 1, 2000 and December 31, 2015, for cases of HSTCL in patients with a history of immunodysregulatory disorders. The diagnosis of HSTCL fulfilled the criteria specified in the World Health Organization.¹ Clinical data were collected from review of the medical records, which included demographic information, clinical presentation, underlying immune disorders or immunosuppression, laboratory information, imaging studies for evidence of splenomegaly, hepatomegaly or lymphadenopathy, therapy and clinical follow-up. The clinicopathologic features of these

cases were included in a study of 28 cases of HSTCL reported recently.² We also reviewed the literature for similar cases of HSTCL that arose in the setting of immune disorders and/or immunosuppression and extracted clinical and pathologic information as well as follow-up and therapy. The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this study.

2. 2. Histopathologic assessment

Bone marrow specimens obtained at initial diagnosis were evaluated. Hematoxylin and eosin stained slides of core and/or clot specimens, with corresponding Wright-Giemsa-stained aspirate smears and/or touch imprints were reviewed. Splenectomy and liver biopsy specimens were reviewed when available.

2. 3. Immunophenotypic analysis

Immunohistochemical analysis was performed using formalin-fixed, paraffin-embedded tissue sections at the referring institutions or in our own laboratory at the time of diagnosis. At our institution, we used 4- μ m thick tissue sections, heat-induced epitope retrieval, and an avidin-biotin complex detection method. 3,3'-Diaminobenzidine was used as a chromogen, and staining was performed in an automated immunostainer (Ventana Medical Systems, Tucson, AZ) as described previously.² Antibodies specific for the following antigens were used: CD2, CD3, CD4, CD5, CD7, CD8, CD56, TIA-1, granzyme B, (Dako, Carpinteria, California), CD57, TCR-Beta (β F1), and TCR- $\gamma\delta$ (Thermo Scientific, Pittsburgh, Pennsylvania). The tumor burden was semi-quantified based on CD3 reactivity.⁸ *In situ* hybridization analysis for Epstein-Barr virus (EBV) encoded small RNA (EBER) was performed as described previously.²

Flow cytometry immunophenotypic analysis was performed using bone marrow aspirate specimens, either at the submitting institution or in our laboratory. In all cases, at least four-color analysis was performed and lymphocytes were gated using CD45 and side scatter. In our laboratory, cases were analyzed with FACSCalibur cytometers (BD Biosciences, San Jose, California, USA) prior to 2009, and with Canto II 8-color instruments (BD Biosciences, San Jose, California, USA) after 2009 as described previously.² A variable panel of antibodies was used at different institutions; most included CD2, CD3, CD4, CD5, CD7, CD8, CD16, CD19, CD20, CD43, CD52, CD56, CD57, CD94, TCR $\alpha\beta$ chain, and TCR $\gamma\delta$ chain, as well as immunoglobulin kappa and lambda light chains. Immunophenotypic aberrancies were defined as altered expression/expression levels of antigens on lymphoma cells.

2. 4. Conventional cytogenetics and fluorescence *in-situ* hybridization (FISH) analysis

Conventional chromosomal analysis was performed on G-banded metaphases on bone marrow aspirate specimens as described previously.⁹ The karyotype was documented according to the International System for Human Cytogenetic Nomenclature (ISCN 2013).¹⁰

Fluorescence *in situ* hybridization (FISH) analysis was performed using air dried slides of bone marrow smears or formalin-fixed, paraffin embedded tissue sections on a subset of cases to assess for isochromosome 7q (i7q) and trisomy 8 (+8), using a D7S522/CEP7 dual

color probes and CEP8 probe (Abbott Molecular/Vysis, Downers Grove, IL, USA). A total of 200 interphases were analyzed. The positive cutoff established in our laboratory was 3.2% for i(7q), and 2.4% for +8.²

2. 5. Molecular Analysis

The T-cell receptor (TCR) γ chain gene was assessed by polymerase chain reaction (PCR)-based methods on DNA extracted from bone marrow aspirate or tissue biopsy specimens. At our institution, a mixture of four family-specific, multicolored, fluorescently labeled variable region primers and four unlabeled joining primers was used in a multiplex assay as previously described.¹¹ Cases from other institutions were assessed at other laboratories using a variety of methods.

2. 6. Statistical Analysis

Statistical analyses were performed using the GraphPad Prism 6 (La Jolla, CA). Overall survival (OS) was calculated from the date of initial diagnosis to the date of death or last follow-up on our cases as well as those accrued from the literature review. The Student's t-test and chi-square test were used for the analysis between two groups. A *p* value of <0.05 was considered statistically significant.

3. Results

3. 1. Antecedent immunodysregulatory disorder

We identified 7 patients, 6 men and one woman, with HSTCL who also had a history of an immunodysregulatory disorders at our institution. This group represents 24% of all cases of HSTCL accessioned at our institution since January 1, 2000. The immune disorders included Crohn disease (n=5), ulcerative colitis (n=1) and rheumatoid arthritis (n=1). The interval from onset of immunodysregulatory disease to onset of HSTCL was available for 4 patients, and ranged from 5 to 16 years (median, 9 years); no information regarding interval was available for 3 patients (cases 3, 6 and 7). Data regarding therapy for the immune disorder were available in 6 patients (Table 1). All 6 patients had received immunosuppressive medications, either 6-MP or azathioprine; 2 patients (33%) also received steroids at some point during their disease course. No patients (0%) received TNF- α inhibitors. No data were available regarding the duration of these therapies.

The clinical findings for the study group at time of diagnosis of HSTCL are summarized in Table 1. The median age at the time of diagnosis was 38 years (range, 18 to 72 years). All patients had splenomegaly, 5 (71%) patients had hepatomegaly, and 2 (29%) patients had lymphadenopathy. No patients had skin lesions. A complete blood count (CBC) was available for all patients. The median white blood cell (WBC) count was $5.2 \times 10^9/L$ (range, 0.5 to $38.6 \times 10^9/L$); median hemoglobin level was 118 g/L (range, 90 to 150 g/L); and median platelet count was $100 \times 10^9/L$ (range, 20 to $234 \times 10^9/L$). Other laboratory findings at the time of diagnosis were variably available. The median serum LDH level was 1263 IU/L (range, 485 to 3163 IU/L, reference range 313-618 IU/L); with 5/6 (83%) patients having levels above upper reference limit (URL); total bilirubin, 1.2 mg/dL (range, 0.5 to 2.9 mg/dL; reference range 0.2 to 1.3 mg/dL); with 2/6 (33%) patients having levels above

URL; alkaline phosphatase, 170 IU/L (range, 51 - 240 IU/L); aspartate aminotransferase, 67 IU/L (range, 24 to 359 IU/L); alanine aminotransferase, 62.5 IU/L (range, 12 to 517 IU/L); β 2 microglobulin, 4.75 mg/dL (range, 2.2 to 6.7 mg/L); all 4 patients tested had a serum β 2 microglobulin above URL.

3. 2. Histologic findings

Bone marrow core biopsy and/or aspirate clot specimens were examined in all 7 patients at the time of diagnosis. The median bone marrow cellularity was 90% (range, 60 – 95); trilineage hematopoiesis was detected in all cases (Figure 1A). The median tumor burden in the bone marrow was 30% (range, 20 - 60). All 7 bone marrow specimens showed an interstitial and sinusoidal pattern of involvement by HSTCL (Figure 1B). Splenectomy specimens, available in 2 patients (cases 1 and 5), showed expansion of the red pulp by small to intermediate-size lymphoma cells with scant cytoplasm (Figure 1C). CD3 immunohistochemical stain highlighted the neoplastic cells and showed an intrasinusoidal pattern of infiltration (Figure 1D). A liver biopsy specimen available in one patient (case 2) showed extensive portal and sinusoidal expansion by numerous small-to-intermediate sized lymphoma cells.

3. 3. Immunophenotypic, cytogenetic and molecular features

Immunohistochemistry and flow cytometry were used in all patients and many markers were assessed by both methods. The lymphoma cells in all cases were positive for CD2, surface CD3 and CD7, and were negative for CD4, CD8, CD57 and EBER. CD56 was positive in 6 (86%), TIA-1 in 4 (57%), CD5 was dimly positive in 2 (29%) and granzyme B was positive in 2 (29%) cases. The T-cell receptor was $\gamma\delta$ in 5 (71%) and $\alpha\beta$ in 2 (29%) cases.

Conventional cytogenetic and FISH findings are summarized in Table 2. Conventional cytogenetic analysis at the time of diagnosis was available in 6 patients; 2 (33%) had a normal diploid karyotype. Four (66%) patients had an aberrant karyotype, all displaying isochromosome 7q (i7q) and 2 (33%) also had trisomy 8. FISH for i(7q) was positive in all 4 tested cases, including 1 case with a normal diploid karyotype. Thus, 5/6 cases (83%) had i(7q). Assessment of clonality for TCR γ revealed monoclonal rearrangements in all 7 cases.

3. 4. Therapy and outcome

All patients received chemotherapy for induction therapy (Table 1). The regimens used included cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone (CHOP); etoposide, prednisolone, vincristine, cyclophosphamide, and hydroxydaunorubicin (EPOCH); or hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD). Three patients received hematopoietic stem cell transplant. The median overall survival was 11 months; 4/7 (57%) patients were alive at the time of last follow up, including 3 patients who received stem cell transplant and were in complete remission at the time of last follow up.

3. 5. Literature Review

3. 5. 1. Clinicopathologic findings—In the literature we identified 60 cases of HSTCL arising in a background of immunodysregulatory disorders (Table 3).¹²⁻³⁵ Crohn disease was

most common, observed in 35 (58%) patients, ulcerative colitis in 6 (10%), rheumatoid arthritis in 5 (8%); and solid organ transplant in 7 (12%), of which 5 patients had a kidney transplant and 2 liver transplant. Data regarding treatment for the antecedent immunodysregulatory disorder were available in 57 patients. Fifty-one (89%) patients received immunosuppressive drugs: 27/57 (47%) azathioprine; 17/57 (30%) 6-MP; 8/57 (14%) cyclosporine, and 5/57 (9%) methotrexate. Thirty-two (56%) of 57 patients received TNF- α inhibitors including 28 infliximab, 8 adalimumab and 1 etanercept (Table 4 and Figure 2). Thirty-one (54%) patients received both immunosuppressive drugs and TNF- α inhibitors and 20 (35%) patients received immunosuppressive drugs without TNF- α inhibitors. Only one patient (2%) was treated with TNF- α inhibitors only (Table 4, Figure 2). Other therapies included steroids in 29/40 (73%), mesalazine or sulfasalazine in 13/40 (33%), rituximab in 1/57 (2%) and MOPP/ABV in 1/57 (2%). Among 5 patients who received neither immunosuppressive drugs nor TNF- α inhibitors, one patient received steroids only, one patient received mesalazine, and 3 patients did not receive mesalazine, and information for steroid administration was not available.

At time of diagnosis of HSTCL the median patient age was 31 years (range, 7-79 years); 50 (83%) patients were male and 10 (17%) female. Twenty-nine of the 60 patients in the literature had a CBC. The median WBC count was $4.0 \times 10^9/L$ (range, $0.5 - 13.7 \times 10^9/L$); the median hemoglobin level was 102.5 g/L (range, 69- 156 g/L); and the median platelet count was $76 \times 10^9/L$ (range, $14 - 485 \times 10^9/L$).

In all cases reported the morphologic findings were consistent with HSTCL. The HSTCL cells were positive for CD2 (n= 21) and CD3 (n= 25). CD7 was positive in 18/20 (90%); CD56 in 20/21 (95%); TIA-1 in 8/10 (80%); CD8 in 7/22 (32%); CD4 in 3/24 (13%), and EBER in 1/9 (11%) cases. TCR expression was determined in 35 cases; $\gamma\delta$ in 26 (74%) cases, $\alpha\beta$ in 8 (23%) cases, and 1 (3%) was double negative ("TCR silent"). No cases showed dual positivity for TCR expression. CD5 (n=20), CD57 (n=8), and granzyme B (n=6) were negative in all cases assessed. (Table 3)

Twenty of 60 reported cases had cytogenetic data including conventional karyotype and/or FISH. Fourteen (70%) tumors were associated with isochromosome (7q), and 2 additional cases had duplication of 7q31 and monosomy 7. Seven (35%) of 20 neoplasms were associated with trisomy 8. (Table 3)

3. 5. 2. Therapy and outcome—Treatment histories for HSTCL were available in 30 (50%) patients and are summarized in Table 5. A CHOP or a CHOP-like regimen was administered to 14 patients, hyper CVAD or hyper CVAD-like to 2 patients, and ifosfamide, carboplatin, etoposide (ICE) to 3 patients. Seventeen patients received a stem cell transplant; 5 autologous and 12 allogeneic. Outcome was available in 41 patients. The median overall survival (OS) was 10 months. The OS of 15 patients who were treated with SCT was 17 months.

4. Discussion

We report 7 patients with immunodysregulatory disorders who developed HSTCL; we further identified 60 patients with immunodysregulatory disorders reported in the literature. Most patients were treated with drugs including immunosuppressive agents, TNF- α inhibitors, steroids, and mesalazine/sulfasalazine. These drugs were often administered in combination. About half of these patients were treated with both an immunosuppressive agent and a TNF- α inhibitor (Table 4).

Herrinton et al reported that inflammatory bowel disease (IBD), by itself, is not associated with an increased lymphoma risk.⁴ However, a number of studies have suggested that thiopurines and TNF- α inhibitors, used alone or in combination, increase the overall lymphoma risk in patients with IBD, including B-cell lymphomas and HSTCL.³⁶ Our analysis shows that 89% of patients received immunosuppressive drugs with or without TNF- α inhibitors. There were 32 patients who received TNF- α inhibitors, however, 31 also received immunosuppressive drugs. Furthermore, all 7 patients in the cohort we present did not receive TNF- α inhibitors. These findings show that TNF- α inhibitors are not essential for onset of HSTCL and suggest that others are more critical in the pathogenesis of HSTCL in patients with immunodysregulatory disorders. Other factors that may be involved include immunosuppressive drugs, genetic predisposition, or chronic antigenic stimulation or perhaps all of these factors may be involved.

Thai et al reviewed the literature and analyzed 238 reported cases of HSTCL of which 73% of HSTCL arose “de novo”, 18% developed in immunocompromised patients, and 10% were found in IBD patients who received thiopurines and/or TNF- α inhibitors.³⁷ In our analysis, we show a strong association between HSTCL and long-term immunosuppression, in particular with the thiopurines, including 6-MP and azathioprine. In effect, 89% of patients with underlying immune disorders had received immunosuppressive drugs, mainly thiopurines (Table 4, Figure 2). However, considering the rarity of HSTCL and the severe morbidity of IBD, the estimated risk of using highly beneficial thiopurines and/or TNF- α inhibitors to treat patients with IBD is considered acceptable.³⁷ The possible mechanisms by which thiopurines may lead to HSTCL have not been explored.

While $\gamma\delta$ T-cells represent approximately 5% of the adult T-cell population, they have an important role in mucosal immunity, and $\gamma\delta$ T-cells display an affinity for the epithelial layer of the intestines, skin, and red pulp of the spleen.^{38,39} It has been postulated that excessive antigenic stimulation of $\gamma\delta$ T-cells caused by underlying immunodysregulatory disorders induces a polyclonal $\gamma\delta$ T-cell expansion. Subsequently, additional transforming events, including i(7q) and/or trisomy 8, lead to development of HSTCL. Despite the increasing number of reported cases of HSTCL associated with the use of thiopurines and TNF- α inhibitors, this risk is not quantifiable due to the rarity of HSTCL. It is of interest that thiopurine S-methyltransferase modulates the clinical response to 6-MP and its pro-drug azathioprine in patients with IBD through the production of pharmacologically active and toxic metabolites.⁴⁰ Since thiopurines may lead to severe myelosuppression, and patients with HSTCL commonly present with pancytopenia, it is possible that analysis of metabolites

of thiopurines may shed light on the susceptibility to develop HSTCL among patients with IBD.

Combining patient cohort with 41 reported cases with available data, the prognosis of patients with immunodysregulatory disorders who then develop HSTCL appears to be poor. In the cohort we present, the median survival was 11 months and the only longer term survivors successfully underwent hematopoietic stem cell transplant. For the cases in the literature, the median survival was 10 months. We can only speculate on the reasons for poor prognosis based on the findings in this study, but it seems reasonable to suggest that the compromised immune status of these patients play a role in the overall poor prognosis, possibly by predisposing patients to greater complications after treatment, or perhaps by precluding some patients from receiving optimal therapy.

In conclusion, we present 7 patients with HSTCL with underlying immunodysregulatory disorders seen at our institution, as well as the largest literature review of this entity. Most patients with HSTCL arising in patients with underlying immunodysregulatory disorders have a history of receiving immunosuppressive drugs. The cohort of 7 patients in this study did not receive TNF- α inhibitor therapy. At the minimum, our data indicate that TNF- α inhibitors are not essential for HSTCL to arise in the context of immunodysregulation and/or immunosuppression. In addition, these observations imply that other factors are involved in the pathogenesis of HSTCL. These factors potentially include immunosuppressive agents, genetic predisposition, and/or chronic antigenic stimulation. These observations have obvious implications for using TNF- α inhibitor therapy in patients with inflammatory bowel disease and other immunodysregulatory disorders. Although this study cannot assess potential mechanisms to explain these associations, the role of thiopurine metabolites in HSTCL pathogenesis needs to be explored. In addition, the study group presented as well as the cases in the literature suggests that patients with HSTCL arising in the context of immune disorders have a particularly aggressive form of disease and a very poor prognosis.

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Highlights

- Hepatosplenic T-cell lymphoma (HSTCL) is known to arise in patients with immunodysregulatory disorders, and TNF- α inhibitor therapy has been suggested to increase the risk.
- However, our experience with 7 patients and additional literature review suggests that TNF- α inhibitor therapy is not essential for the development of HSTCL.
- Our findings imply that immunosuppressive drugs or other factors are more critical to development of HSTCL in this context.

Figure 1.

Bone marrow involvement by hepatosplenic T-cell lymphoma (HSTCL). A. The bone marrow shows 80% cellularity with trilineage hematopoiesis. (hematoxylin and eosin stain, x400, Case 4). B. Immunohistochemistry for the CD3 highlights lymphoma cells with an interstitial and sinusoidal pattern. (CD3 immunohistochemistry with hematoxylin counterstain, x400, Case 4). C. Histologic section of spleen shows expansion of the red pulp by small to intermediate-size lymphoma cells (hematoxylin and eosin stain, x100, Case 5). D. CD3 immunohistochemical stain of spleen highlights the neoplastic cells infiltrating sinusoids (CD3 immunohistochemistry with hematoxylin counterstain, x400, Case 5).

n	%	Treatment history for underlying immune disorders
51	89%	Immunosuppressive drugs
32	56%	TNF- α inhibitors
31	54%	Both Immunosuppressive and TNF- α inhibitors
52	91%	Either immunosuppressive or TNF- α inhibitors
5	9%	Neither (Received Steroids, Mesalazine, Sulfasalazine)

Figure 2.

Venn diagram of therapy patients with HSTCL received for their underlying immune disorders. A total of 51 (89%) patients received immunosuppressive drugs and 31 (54%) received both immunosuppressive drugs and TNF- α inhibitors; 1 patient (2%) received TNF- α inhibitors only, and 5 patients (9%) received neither immunosuppressive drugs nor TNF- α inhibitors.

Table 1
Clinical findings of 7 patients with hepatosplenic T-cell lymphoma associated with underlying immune disorders

Case #	Gender	Age	Under lying disease	Immunosuppressive drugs	TNF- α inhibitor	Steroids	Time to develop HSTCL		Therapy for HSTCL	SCT	Follow up time (months)	Outcome
							From immune disorder (years)	From drug exposure (years)				
1	M	21	CD	6-MP, Mes	No	Yes	13	NA	CHOP, ESHAP, DHAP, Pentostatin, Alemtuzumab	No	7	Dead
2	M	49	UC	6-MP, Mes	No	No	5	NA	Hyper-CVDD, MTX, Ara-C	Allogeneic	86	Alive
3	M	31	CD	6-MP, Mes	No	No	NA	NA	Hyper CVAD	No	3	Dead
4	M	18	CD	Aza, Mes	No	No	5	2	Hyper CVAD, MTX, AraC, VP-16, Ifosfamide	Autologous	50	Alive
5	M	38	CD	6-MP	No	Yes	16	NA	CHOP, DHAP, ICE	No	11	Dead
6	M	51	RA	NA	NA	NA	NA	NA	EPOCH, Asparaginase	Allogeneic	7	Alive
7	F	72	CD	Aza, Mes	No	No	NA	NA	CHOP	No	1	Alive

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CD, Crohn's disease; HSTCL, Hepatosplenic T-cell lymphoma; RA, Rheumatoid arthritis; UC, Ulcerative colitis; NA, Not available

Aza, azathioprine; 6-MP, 6-mercaptopurine; Mes, mesalazine

CHOP: Cyclophosphamide, Hydroxydaunorubicin, Vincristine, Prednisolone; CVDD: Cyclophosphamide, Vincristine, pegylated doxorubicin, dexamethasone;

Ara-C: Cytosine arabinoside; MTX, methotrexate; hyper CVAD: Hyper fractionated Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone

EPOCH: Etoposide, Prednisolone, Vincristine, Cyclophosphamide, Hydroxydaunorubicin; ESHAP: Etoposide, Solumedrol, high dose Cytarabine, Platinum;

DHAP: Dexamethasone, Cytarabine, Cisplatin; ICE: Ifosfamide; Carboplatin, Etoposide;

Table 2
Cytogenetic findings of 7 patients with hepatosplenic T-cell lymphoma associated with underlying immune disorders

Case #	Cytogenetics		
	Karyotype at diagnosis	FISH i(7q)	FISH trisomy 8
1	46,XY[19]	NA	NA
2	43,XY,-4,i(7)(q10),-13,-18[1]/46XY[17]	Positive	NA
3	46,X,-Y,i(7)(q10),+8[6]/46,X,-Y,i(7)(q10),+8,t(9;20)(q13;q11.2)[1]/46,XY[13]	NA	Positive
4	46,XY[20]	Positive	NA
5	46,XY,add(5)(p13),i(7)(10q),add(13)(q34)[3]/46,XY[17]	Positive	NA
6	NA	NA	NA
7	48,X,-X,+7,i(7)(q10)×2,+8,+mar[4]/XX[26]	Positive	NA

NA, not available; FISH, fluorescence in situ hybridization i(7q), isochromosome 7q

Table 3
Clinicopathologic, immunophenotypic and cytogenetic features of patients with HSTCL
with immune disorders: Literature Review

		HSTCL with immune disorders	
		(n= 60, literature review)	
Age, median (range)		31	7-79
Gender	Male	50	83%
	Female	10	17%
Underlying immune disorders			
	Crohn's disease	35	
	Ulcerative colitis	6	
	Rheumatoid arthritis	5 *	
	Post renal transplant	5	
	Post liver transplant	2	
	Post allogeneic stem cell transplant	1	
	Churg Strauss syndrome	1	
	Sjogren syndrome	1	
	Systemic lupus erythematosus	1	
	Psoriasis	1	
	Hodgkin lymphoma, treated	1	
	ALPS, Evans syndrome	1	
Hematologic data		n= 29 cases	
	WBC × 109/L, median (range)	4.0	0.5 -13.7
	Hb g/L, median (range)	102.5	6.9 -15.6
	Plt × 109/L, median (range)	76	14 - 485
Immunophenotype (% positive cases)			
	CD2	21/21	100%
	CD3	25/25	100%
	CD4	3/24	13%
	CD5	0/20	0%
	CD7	18/20	90%
	CD8	7/22	32%
	CD56	20/21	95%
	CD57	0/8	0%
	TIA-1	8/10	80%
	Granzyme B	0/6	0%
	EBER	1/9	11%
TCR chain usage			
	γδ	26/35	74%

		HSTCL with immune disorders	
		(n= 60, literature review)	
	$\alpha\beta$	8/35	23%
	Double negative (Silent)	1/35	3%
Cytogenetics			
	i(7)(q10)	14/20	70%
	Aberration of chr 7 ***	16/20	80%
	Trisomy 8	7/20	35%

ALPS, autoimmune lymphoproliferative syndrome

EBER, Epstein-Barr virus encoded small RNA; HSTCL, hepatosplenic T-cell lymphoma

TCR, T cell receptor; TIA-1, T-cell intracellular antigen 1

Hb, hemoglobin; Plt, platelets; WBC, white blood cell count

*
2 cases were diagnosed with juvenile RA

**
Statistic performed between 67 patients with immune disorders and 22 patients without immune disorders

Include i(7q), Monosomy 7, dup7q31

Table 4
Immunomodulator and immunosuppressive therapy used for underlying immune disorders in patients who developed HSTCL (n=57): A review of the literature

	n positive/n total	%
Immunosuppressive drugs	51/57	89%
Azathioprine	27/57	47%
6-Mercaptopurine	17/57	30%
Cyclosporine	8/57	14%
Methotrexate	5/57	9%
Tumor necrosis factor α inhibitors	32/57	56%
Infliximab	28/57	49%
Adalimumab	8/57	14%
Etanercept	1/57	2%
Miscellaneous		
Steroids	29/40	73%
Mesalazine or Sulfasalazine	13/40	33%
Rituximab	1/57	2%
MOPP/ABV	1/57	2%
Both immunosuppressive drugs and TNF- α inhibitor	31	54%
Immunosuppressive drugs only	20	35%
TNF- α inhibitor only	1	2%
Neither Immunosuppressive drugs nor TNF- α inhibitor	5	9%
Steroid (+), Mesalazine/Sulfasalazine (–)	1	2%
Steroid (NA), Mesalazine/Sulfasalazine (+)	1	2%
Steroid (NA), Mesalazine/Sulfasalazine (–)	3	5%

MOPP/ABV, mechlorethamine, vincristine, procarbazine, prednisone, doxorubicin

bleomycin, vinblastine

HSTCL, hepatosplenic T-cell lymphoma

Table 5
Treatment and outcome of patients with HSTCL with underlying immune disorders: A review of the literature

	Underlying immune disorders
Treatment	(n= 30)
Chemotherapy	
CHOP/CHOP-like	14
Hyper CVAD/Hyper CVAD-like	2
ICE	3
DHAC	2
IVAC	2
Pentostatin	1
Other	6
Stem cell transplant	(n=17)
Autologous	5
Allogeneic	12
Outcome	(n=41)
Median overall survival	10 months
	(n=15)
Median overall survival, patients treated with SCT	17 months

CHOP or CHOP-like, cyclophosphamide, doxorubicin, vincristine, prednisone

Hyper CVAD or hyper CVAD-like, cyclophosphamide, vincristine, doxorubicin, dexamethasone

ICE, ifosfamide, carboplatin, etoposide

DHAC, dexamethasone, doxorubicin, cytarabine, carboplatin

IVAC, ifosfamide, Vepesid (VP-16, etoposide), Ara-C (cytarabine)

EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin

SCT, Stem cell transplant