

CASE REPORT

A rare case of hepatosplenic gamma-delta T-cell lymphoma and secondary hemophagocytic lymphohistiocytosis

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Key Clinical Message

Hepatosplenic gamma-delta T-cell lymphoma with concurrent hemophagocytic lymphohistiocytosis is a rare but well-recognized clinical scenario, associated with a grim prognosis. Clinicians must be aware of this aggressive type of lymphoma so that a prompt diagnosis can be made with timely initiation of systemic therapy and referral for bone marrow transplant.

KEYWORDS

hemophagocytic lymphohistiocytosis, hepatosplenic T-cell lymphoma

1 | INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a rare type of lymphoma with a poor prognosis. A few cases of HSTCL and hemophagocytic lymphohistiocytosis (HLH) have been described in literature. We report a case of a man with a background of Crohn's disease, which was diagnosed with HSTCL and HLH.

Hepatosplenic gamma-delta T-cell lymphoma (HSGDTL) is a rare type of peripheral T-cell lymphoma and comprises less than 1% of all non-Hodgkin lymphomas.¹ It is characterized by an aggressive clinical course.^{1,2} It is included in the World Health Organization (WHO) classification.³ HSGDTL is an extranodal lymphoma that most commonly develops in young adults with a median age of 35 years and it tends to have a male predominance.^{2,4} Less than one third of cases arise in patients with a history of immune suppression.^{5,6} One literature review of over 238 cases of HSGDTL reported that 10% of cases occurred in patients with inflammatory bowel disease, who received tumor necrosis factor alpha (TNF- α) inhibitors and/or thiopurines.⁶

HSGDTL is typified by extranodal infiltration and localization within sinusoids of the liver, sinuses and splenic red

pulp.^{1,2,4} Classical presenting symptoms are B symptoms,¹ and typical physical findings are hepatomegaly and splenomegaly.¹ Characteristic features also include pancytopenia with bone marrow involvement in 80% of cases.^{1,2} Additional laboratory abnormalities include high serum lactate dehydrogenase, beta-2 microglobulin level, a transaminitis, and hyperbilirubinemia.⁷

The prognosis of patients with this rare lymphoma is generally poor. Due to its rarity and subsequent paucity of available literature, optimal management remains unknown.^{1,2,4} Response rates and survival rates are poor and current treatment options are limited.^{1,2,4} The median overall survival of patients with HSGDTL is reported to range between 3 and 28 months with the use of several anthracycline-based chemotherapeutic regimens.⁷⁻⁹

A number of cases of HSGDTL reported in literature have been associated with hemophagocytic lymphohistiocytosis (HLH), another rare disorder, characterized by an overactivated immune system.¹⁰ In adults HLH is generally precipitated by an underlying condition.¹⁰ We report a case of a male with a background of Crohn's disease on chronic immunosuppression, diagnosed with secondary HLH and concurrent HSGDTL.

2 | CASE PRESENTATION

A 55 year-old Caucasian male with a background of Crohn's disease previously on immunomodulating therapy with azathioprine and adalimumab, presented with subacute fevers, epistaxis, and lethargy. He was noted to have pancytopenia and hepatomegaly, and splenomegaly (21 cm) on CT scan (Figure 1). Physical examination was remarkable for fevers up to 103°F, a diffuse erythematous pruritic rash and splenomegaly without lymphadenopathy. Laboratory revealed a WBC of $1.4 \times 10^3/\text{mm}^3$, hemoglobin 7.8 g/dL, platelet $44 \times 10^3/\text{mm}^3$, LDH 460 units/L (3.4-4.8 units/L), ferritin 936 ng/mL (16-294 ng/mL), triglycerides 244 mg/dL, and soluble interleukin-2 receptor 1898 units/mL (<1100 units/mL) and normal liver function tests. An infectious workup was unremarkable.

A bone marrow aspirate and biopsy revealed T-cell lymphoma, compromising about 5% of the cellularity as well as a moderate number of hemophagocytes (Figure 2). There is bone marrow involvement in most patients at diagnosis^{7,11} and hemophagocytosis is a recognized but infrequent phenomenon that can develop in patients with HSTCL.⁷ The aspirate demonstrated a hypercellular marrow and normal erythroid number and maturation. Myeloid elements also demonstrated normal maturation and megakaryocytes were present in normal number. Lymphocytes overall did not appear increased however occasional atypical forms were recognizable, although identification of lymphoma cells was difficult. The bone marrow biopsy core demonstrated increased cellularity of 80%. A hypercellular bone marrow is also a typical finding at diagnosis.^{7,11} Lymphoid aggregates were not identified but were appreciated within sinusoidal spaces. Iron stains demonstrated adequate iron stores (3+/6) without pathologic ringed sideroblasts, and

reticulin stain showed no increase in reticulin fibrosis. Immunohistochemistry (IHC) stains demonstrated the following: CD20 was negative in neoplastic cells and positive in sparse background small B-cells. CD3 was positive in neoplastic cells (Figure 3), many within marrow sinusoids, with intermediate nuclei, open chromatin, and a variably prominent nucleolus, overall comprising about 5% of the cellularity. The IHC stain was also positive for KP1 (CD68), highlighting the nuclei of engulfed cells within macrophages (Figure 4). Immunophenotyping by flow cytometry demonstrated the following phenotype: CD3 positive (dim/moderate; dimmer than background small T-cells), CD2 positive, CD16 positive, and CD56 positive. CD7 was partially positive. CD5, CD4, CD8, and CD57 were all negative. The population comprised about 1% of the cellularity in about 20% of lymphocytes, the remainder predominated by background small T-cells. HSTCL cells are positive for CD2, CD3, and CD7, and are negative for CD1a, CD5, CD10, TdT, and B-cell antigens. Approximately 75% of cases express CD56 and the majority of HSGDTL cases are negative for CD57, CD4, and CD8.^{4,7,9,12,13} Cytogenetics was negative for isochromosome 7q; however, the majority of HSTCL cases have an isochromosome 7q [i(7q)] chromosomal abnormality.^{3,7} The lack of isochromosome 7q raised suspicion for other diagnoses including T-cell large granular lymphocytic (LGL) leukemia and T-prolymphocytic leukemia. In literature the reported frequency for i(7q) is 25%-68%.^{9,12,13} The other cytogenetic abnormality that may be found in HSTCL is trisomy 8, reported to have

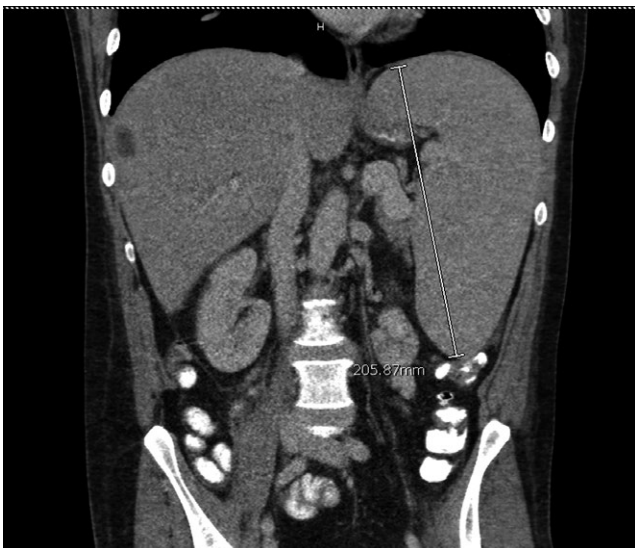


FIGURE 1 CT scan of the abdomen demonstrates hepatomegaly and splenomegaly

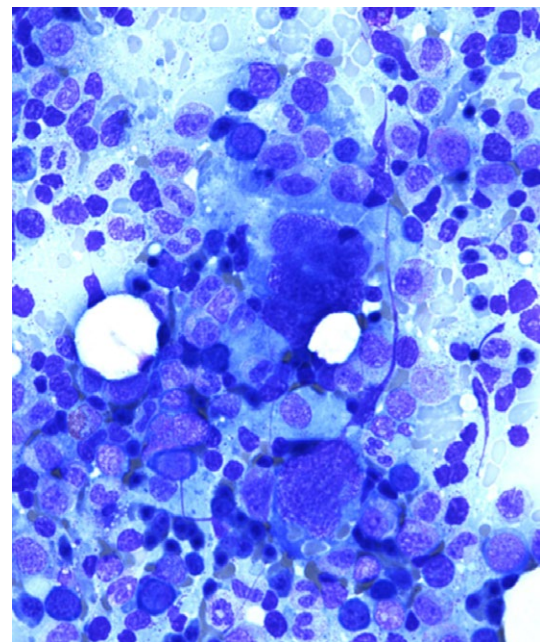


FIGURE 2 Bone marrow aspirate. High power view. Hypercellular for age (80%). Demonstrates involvement with T-cell lymphoma and hemophagocytes

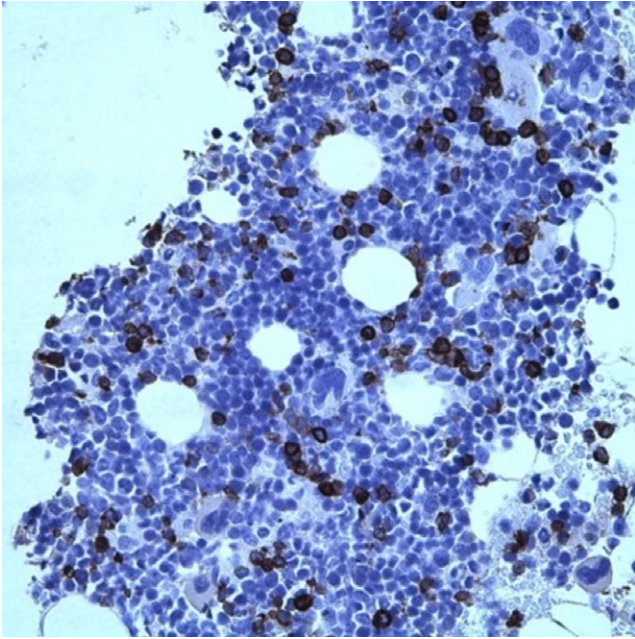


FIGURE 3 Bone marrow biopsy. Low power view. CD3 immunohistochemical staining consistent with lymphoma cells. Immunophenotyping was positive for CD16, and CD57 and was double negative for CD4 and 8

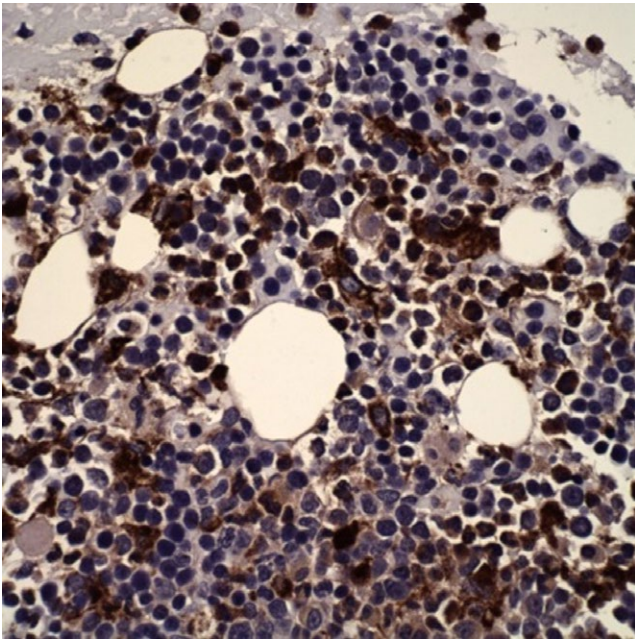


FIGURE 4 Bone marrow biopsy. The IHC stain was also positive for KP1 (CD68), highlighting the nuclei of engulfed cells within macrophages

a frequency of 8%-53%.^{9,12,13} The role of these chromosomal abnormalities is uncertain. It is thought that *i*[7q] is a driver chromosomal anomaly and that trisomy 8 is a probable secondary event.¹⁴

The constellation of fevers, splenomegaly, cytopenias, hyperferritinemia, elevated soluble IL-2, and hemophagocytes

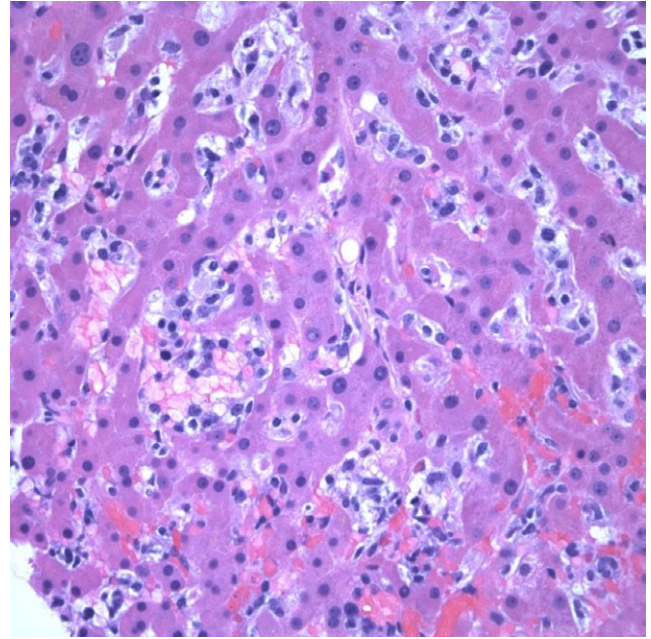


FIGURE 5 Liver biopsy. High power view. Sinusoidal infiltration of hepatic sinusoids by lymphocytes

bought the diagnosis of HLH. In light of the hepatomegaly, a liver biopsy was pursued which confirmed a diagnosis of HSTCL involvement in the liver (Figure 5). The lymphoma cells infiltrated the liver sinusoids (Figure 5), which is a typical finding with HSGDTL.^{1,7} IHC stains were positive for CD3 and CD56. They were negative for CD20, CD30, granzyme, TdT, and CD1a. There was aberrant loss of CD5. In situ hybridization for Epstein-Bar virus (EBER) was negative. EBV is commonly negative in HSTCL.⁹

Systemic therapy with chemotherapy was initiated; however, he was refractory to CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone), ICE (ifosfamide, carboplatin, etoposide), romidepsin, cladribine, and alemtuzumab. Interestingly his cytopenias responded to steroids. He was eventually readmitted with recurrent fevers and worsening hepatosplenomegaly and he died due to progressive disease.

3 | DISCUSSION

Hepatosplenic T-cell lymphomas are an uncommon extranodal and systemic malignancy derived from cytotoxic T-cells usually of gamma-delta ($\gamma\delta$) T-cell receptor type.² A lesser number of cases are of alpha-beta ($\alpha\beta$) type. The peak incidence of HSTCL is in young adults with a median age of 20 years and a male to female ratio of 9:1.² The normal-cell counterpart for HSTCL is a functionally immature cytotoxic $\gamma\delta$ T-cell of the splenic pool.¹⁵ The two main types of $\gamma\delta$ T-cell lymphomas recognized by the WHO classification are

HSTCL and primary cutaneous $\gamma\delta$ T-cell lymphoma (PCGD-TCL).³ The neoplastic cells tend to localize within sinusoidal regions of the splenic red pulp and in epithelial-rich tissues.¹ HLH is a well recognized but rare occurrence that can occur in patients with HSTCL.¹

The pathogenesis of HSTCL is not fully understood. Literature suggests an association with chronic immunosuppression including patients with Crohn's disease on immunotherapy.^{16,17} One hypothesis is that up-regulation of the JAK/STAT pathway or mutations in chromatin modifiers such as SETD2 induces a neoplastic clonal proliferation derived from a $\gamma\delta$ T-cell.¹ Additional transforming events including isochromosome (7q) and trisomy 8 may be involved in the commencement of the full clinical manifestation of HSGDTL.¹ Furthermore, other mutations reported to be common HSGDTL are STAT3 and STAT5B and mutations in chromatin-modifying genes including SETD2, ARID1B, and INO80.^{18,19} Less frequent mutations reported in HSTCL are PIK3CD, TP53, KRAS, and EZH2 mutations.¹⁹ The molecular findings in HSTCL seem to be discrete from other T-cell lymphomas. Isochromosome (7q) and trisomy 8, which are frequently observed in HSTCL are rarely appreciated in other types of T-cell lymphoma and leukemia.²⁰

The immunophenotype typical of HSTCL is the following: CD2+, CD3+, CD4-, CD8-, CD5-, CD7+, and TCR $\gamma\delta$ +.¹⁻³ At least one NK marker is regularly expressed, including CD56, CD57, or CD16.¹⁻³ A marginal number of cases are CD8+.² However, not infrequently, there is loss of CD3, CD5, and/or CD7 expression and irregular reactivity for killer immunoglobulin-like receptors (KIR) with a weak or absent CD94.^{9,11}

Long-term immunosuppression is a strong-risk factor for the development of HSTCL. Up to 20% of cases of HSTCL develop in patients with long-term immune suppression.¹ The common clinical scenarios are patients with immunodysregulatory disorders, most frequently Crohn's disease, who are on immunosuppressive agents and post-organ transplantation.¹ Azathioprine and TNF-alpha inhibitors such as infliximab have been involved in the pathogenesis of HSTCL.^{4,7} There is a fourfold increased risk of B- and T-cell lymphoma when TNF-alpha inhibitors are used to treat patients with Crohn's disease.^{17,21} Rates of $\gamma\delta$ T-cell frequencies are higher in patients with Crohn's disease.^{22,23} Interestingly, higher levels have been found in patients with active disease.^{22,23} Gamma-delta T-cell clones with a survival advantage are selected through a multistep process, resulting in malignant transformation of lymphocyte subsets.²⁴ There is conflicting data behind the degree of influence of TNF-alpha inhibitors in the development of HSTCL. Factors such as chronic antigenic stimulation and genetic predisposition may play a more vital role in the pathogenesis of HSTCL in patients with immunodysregulatory disorders.^{2,4,25}

The most frequent symptoms patients present with are B symptoms.^{4,7,9} The most common physical examination finding is splenomegaly.^{4,7,9} Hepatomegaly is reported in 40%-88% of patients and lymphadenopathy is reported in up to 25% of patients.^{4,7} Lymphadenopathy is uncommon, reported in less than 25% of patients.⁷ The most frequent laboratory abnormalities are cytopenias.^{2,4,7} Splenic sequestration may be a cause of the cytopenias; however, the severity of cytopenias tends to correlate with disease progression, even in patients who undergo a splenectomy. Hence the pathogenesis of cytopenias is unclear.^{2,4,9} Myelodysplasia has also been suggested as an etiology of the cytopenias; however, morphologic characteristics of dysplasia have not been found to correlate with the presence of severity of cytopenias.² Less than 10% of patients present with a lymphocytosis.² About 90% of patients present with an elevated beta-2 microglobulin level, 50%-60% of patients present with an elevated serum lactate dehydrogenase, and about 50% of patients have a transaminitis at diagnosis.⁷

Our patient was also diagnosed with HLH, thought to be secondary to the lymphoma. HLH is a well-recognized but rare entity that occurs in HSTCL. The reported incidence of HLH with a concurrent diagnosis of HSTCL is 5%.⁷ HLH is an inflammatory disorder driven by an unregulated activation of macrophages and lymphocytes.¹⁰ HLH tends to have a pediatric and young adult predominance.¹⁰ It is characterized by constitutional symptoms, splenomegaly, and cytopenias. HLH can be triggered by numerous conditions including viral infections, most commonly Epstein Barr virus (EBV), malignancies, and autoimmune disorders.¹⁰ Given the nonspecific symptoms of HLH there is often a delay in diagnosis. It remains vital that when a diagnosis of HLH is made in an adult, providers must investigate an underlying triggering disorder.

The prognosis of HSGDTL is dismal, with median survival less than one year from diagnosis.^{2,4} Poor prognosticators include an elevated serum bilirubin (>1.5 mg/dL), elevated serum LDH, and trisomy 8 at time of diagnosis.⁷ The presence of i(7q) or aberrations of chromosome 7 may also confer a poor prognosis however larger studies are required to confirm this statistically insignificant finding.⁷ One group demonstrated that only INO80 gene mutation showed a tendency toward improved survival and alternative gene mutations including STAT3 and STAT5B did not draw a parallel with survival.¹⁹ Other clinical, pathological, and laboratory factors studies in HSGDTL have not demonstrated any prognostic significance.^{2,7}

The refractory and rare nature of HSTCL poses an extreme challenge in treatment. There is no established standard treatment. Most studies in literature have excluded patients with HSTCL due to its rarity, hence the paucity of data. The median overall survival (OS) ranges 3-28 months with chemotherapy.^{7,9} Two thirds of patients have a response to anthracycline-based therapy however complete

remission (CR) is uncommon.^{7,9} Salvage treatments include alemtuzumab, antigamma delta T-cell receptor monoclonal antibodies, and anti-CD44 therapy.^{2,7,9} There are a handful of reports that suggest the addition of alemtuzumab and/or cladribine to anthracycline-based regimens (classically CHOP) as first-line chemotherapy may be of benefit, however this tactic needs further study.²⁶

The use of hematopoietic stem cell transplant (HCT) in patients with HSTCL has been of interest lately. A study by the European Bone Marrow Transplant (EBMT) Lymphoma Working Party included 25 patients with HSTCL who received a HCT and demonstrated a median survival of 36 months.²⁷ Of the 18 patients who received an allogeneic HCT (allo HCT), 2 eventually relapsed and of the 7 patients who received an autologous HCT (auto HCT), 5 eventually relapsed and died.²⁷ The investigators implied that the transplant benefit relies on the graft-versus-lymphoma (GVL) effect conferred by an allo HCT, conferring a long-term survival for some patients with HSGDTL.²⁷ A systematic review of reports of allo HCT in 44 HSTCL patients demonstrated that 35% of the patients relapsed, all of which occurred within 1.5 years post transplant and no patients relapsed after 1.5 years.²⁸ Again, the investigators suggested that the GVL effect presented by allo HCT can provide a long-term survival benefit in some HSTCL patients.²⁸ Yabe et al⁷ evaluated 12 patients with HSTCL who received HCTs at MD Anderson Cancer Center, and although the data was not statistically significant, it did suggest that long-term survival was feasible with allo HCT.

Unfortunately our patient did not have genetic studies performed. JAK1/2, STAT3, STAT5B, and PI3KCD have been identified as potential therapeutic targets by genetic studies.²⁹ There are ongoing studies utilizing chimeric antigen receptor (CAR) T-cell based immunotherapy in relapsed or refractory HSGDTL.

4 | CONCLUSION

Our case emphasizes the significance of investigating an underlying trigger such as lymphoma for secondary HLH. Due to its rarity and non-specific signs and symptoms, a delay in diagnosis of HSGDTL may occur. Recognition of this T-cell lymphoma is paramount in order to manage patients aggressively with systemic chemotherapy and consider early HCT. Furthermore, illustration of more cases with new biological features is required with a goal of developing novel therapeutic agents in the future. This field is in dire need of further research in the pathophysiology of the HSGDTL and treatment strategies.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

PHB: the first author, conceptualized the case report, collected the data included under Case Presentation and conducted a thorough literature review and drafted the manuscript. LTR: the second (corresponding) author collected the images included under Case Presentation, conducted a literature review and drafted and revised the manuscript with the other two co-authors. SSA: the third author supervised the conceptualization of the case report, helped acquire data and critically revised the manuscript and provided final approval for its publication.

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