CASE REPORTS

Hepatosplenic T cell lymphoma and hemophagocytic lymphohistiocytosis in an adult patient with Crohn's disease on immunosuppressive therapy

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ABSTRACT

Hepatosplenic T cell lymphoma (HSTCL) is an exceedingly uncommon, aggressive peripheral T cell lymphoma comprising < 1% non-Hodgkin's lymphomas (NHL). Despite treatments including allogeneic stem cell transplantation, median survival is < 2 years. In the majority of patients, the etiology of HSTCL is undetermined; although it has been associated with chronic immunosuppression which accounts for 20% of cases. HSTCL presents as a systemic illness, and sometimes in association with hemophagocytic lymphohistiocytosis syndrome (HLH). Our patient is a young male with a long-standing history of Crohn's disease on immunosuppressive medications, who presented with progressive bicytopenia. He was diagnosed with HSTCL on a bone marrow biopsy and met clinical diagnostic criteria for HLH. He was started on chemotherapy and dexamethasone per HLH treatment protocol and underwent allogeneic hematopoietic stem cell transplantation (HSCT).

Key Words: Hemophagocytic lymphohistiocytosis, Hepatosplenic T cell lymphoma, Crohn's disease, Ferritin

1. INTRODUCTION

HSTCL is a rare type of lymphoma that commonly presents with a systemic illness in association with HLH. Patients who are on immunosuppressive therapy for autoimmune diseases and antirejection regimens are at risk for developing HTSCL. Early diagnosis is important as both diseases are rapidly fatal without treatment.

2. CASE PRESENTATION

2.1 History

Our patient is a 30-year-old Caucasian male with a past medical history of Crohn's disease, appendiceal carcinoid tumor (diagnosed on appendix pathology following acute appendicitis), and post-operative isolated inferior mesenteric vein thrombosis (negative hypercoagulable workup), who was transferred to our facility for workup of acute bicytopenia (hemoglobin 5.8 gm/dl, platelets 41,000/ul). He was diagnosed with Crohn's disease when he was 13 years of age and has been on azathioprine since diagnosis (except for 2 years interruption) up until the onset of bicytopenia 12 weeks prior to this transfer. His other therapies for Crohn's disease included mesalamine (at age 17) and infliximab (6-12 months, at age 22). He developed acute bicytopenia (hemoglobin 4.9 gm/dl, platelets 74,000/ul) 3 months prior to this admission. His direct antigen test (DAT) was positive at that time, and he was started on prednisone and received mul-

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tiple units of packed red blood cells on an inpatient and outpatient basis. On admission, he had stable vital signs. Physical exam showed skin and conjunctival pallor, and hepatosplenomegaly. His medications at the time of admission included prednisone 120 mg. He never smoked, rarely consumed alcohol, and never used illicit drugs.

2.2 Hospital course

His initial blood work showed a corrected reticulocyte count of 1.5% (inappropriately normal), lactate dehydrogenase 925 u/l, haptoglobin < 30 mg/dl, alanine aminotransferase (ALT) 129 u/l, aspartate aminotransferase (AST) 50 u/l, total bilirubin 1.5 mg/dl with a direct bilirubin 0.4 mg/dl, creatinine 0.69 mg/dl, ferritin > 7500 ng/ml and triglycerides 256 mg/dl. A repeat DAT in our facility was negative. His peripheral smear did not reveal any qualitative morphologic abnormalities. Viral studies for Epstein-Barr virus, cytomegalovirus, hepatitis (A, B, C) and human immunodeficiency virus were negative. An ultrasound of the abdomen obtained on admission showed mild hepatomegaly and moderate-marked splenomegaly.

Based on the patient's progressive bicytopenia requiring transfusion of multiple blood products, lack of evidence for a brisk hemolytic process with a negative direct antigen test and an inappropriately low reticulocyte count, our clinical suspicion was of a primary bone marrow disorder. A bone marrow biopsy was performed and revealed an interstitial infiltrate of atypical T lymphocytes (50%) compatible with interstitial T cell lymphoma (see Figures 1-4). Very rare hemophagocytosis was identified (see Figure 5). Bone marrow flow cytometry reported atypical T cells with expression of CD3, CD8 and gamma/delta T-cell receptor, compatible with CD8+ T cell lymphoma.

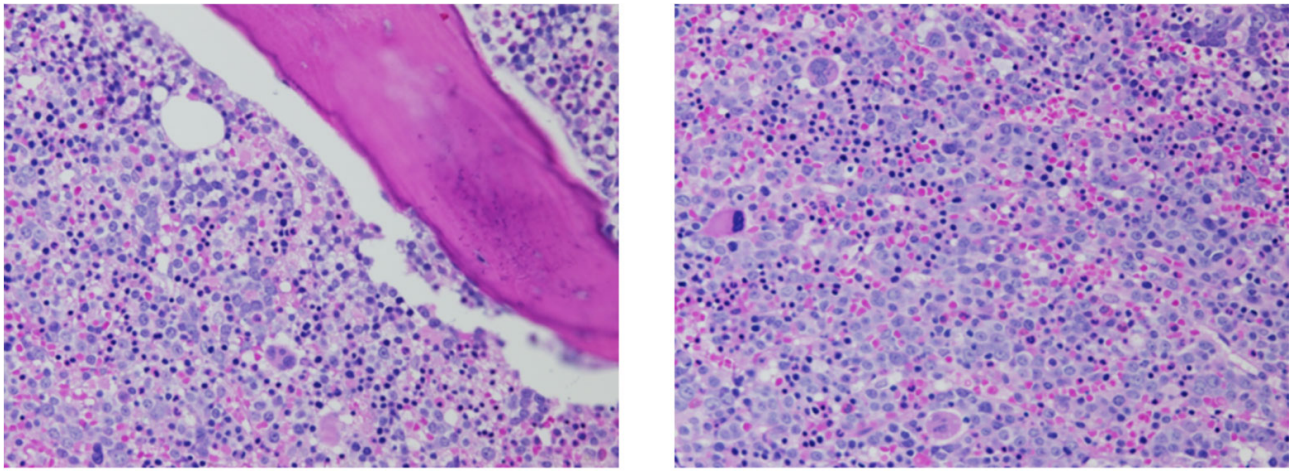

Figure 1. Bone marrow biopsy. The lymphoma cells infiltrated the bone marrow in a subtle, interstitial pattern, composed of medium size lymphoma cells with small nucleoli

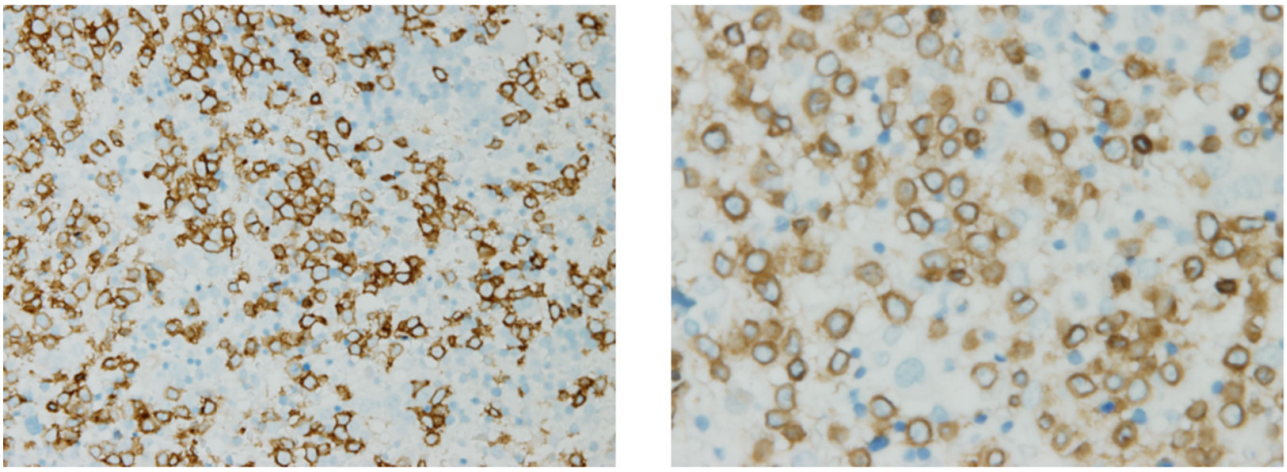

Figure 2. Bone marrow biopsy. Immunostains for CD3 (left photo) and CD8 (right photo) highlight the interstitial infiltrate of lymphoma cells in the bone marrow

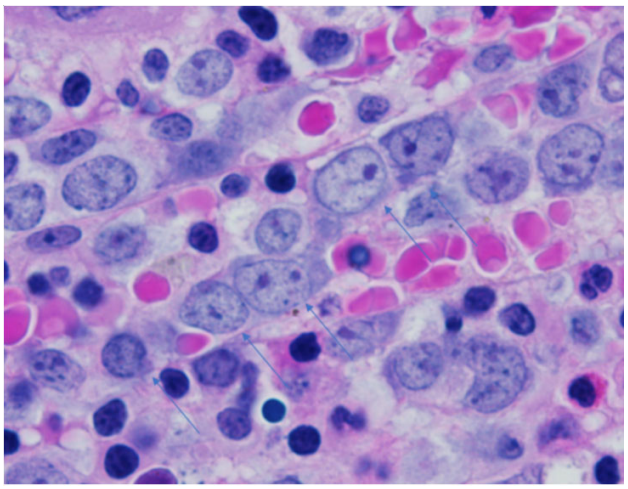

Figure 3. Bone marrow biopsy. Touch prep shows medium to large, atypical lymphoma cells

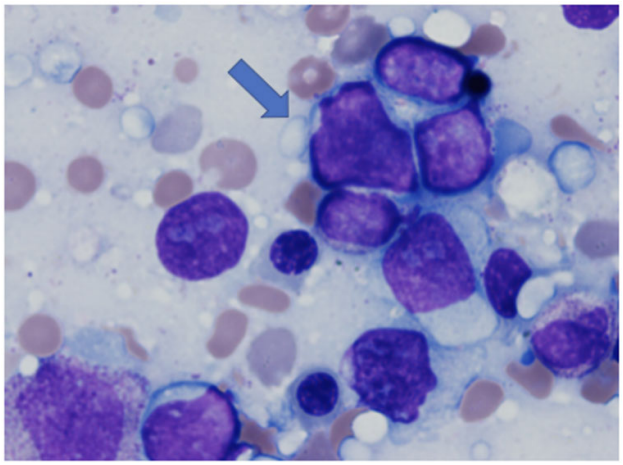

Figure 4. Bone marrow biopsy. Sinusoidal pattern of lymphoma cell infiltration

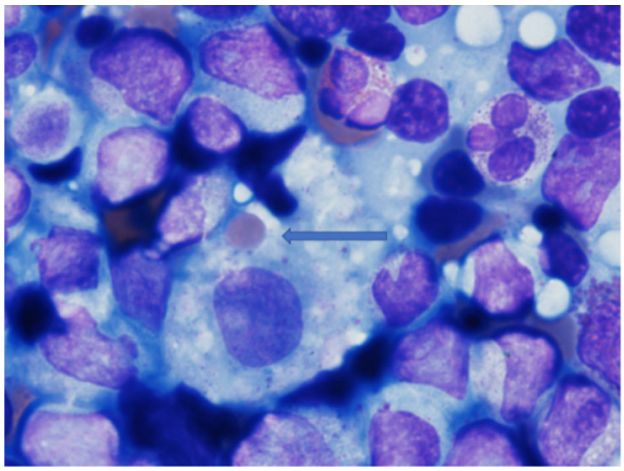

Figure 5. Bone marrow touch prep. Histocyte with hemophagocytosis

In addition to the above blood workup, serum interleukin-2 (IL-2) soluble receptor was 23,800 pg/ml (normal < 1,033). A positron emission tomography (PET) scan did not show hypermetabolic lymph nodes to suggest lymphoma but revealed diffuse marrow and spleen abnormal hypermetabolic uptake. The patient later developed sepsis with fever/tachycardia, and was started on empiric antimicrobials, but his infectious workup remained negative during his hospital stay.

2.3 Treatment plan

The patient was started on HyperCVAD-A (Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone) for HSTCL. Dexamethasone was started at 40 mg/day on day 1 to day 4 as part of the chemotherapy regimen and later on was switched to dosing per HLH-2004 protocol. He did not receive Etoposide/Cyclosporine. The patient continued to spike fevers and in light of the negative infectious workup, it was felt his fevers were secondary to progressive HSTCL/HLH. A repeat computed tomography (CT) scan of abdomen and pelvis showed persistent marked splenomegaly. With that, he was started on ICE (Ifosfamide, Carboplatin, Etoposide) regimen for progressive HSTCL, not responding to HyperCVAD. His fevers then subsided within 24-48 hours, and he was discharged home on dexamethasone taper per HLH protocol.

2.4 Response to therapy

The patient was discharged from the hospital on a slow taper of dexamethasone. A repeat CT scan of abdomen and pelvis 2 weeks following discharge showed decreased splenomegaly and stable mild hepatomegaly. A repeat PET scan 4 weeks after discharge showed resolution of spleen Fluorodeoxyglucose (FDG) uptake and decreased marrow FDG uptake. A repeat bone marrow biopsy 4 weeks after discharge showed hypercellular bone marrow with no morphologic evidence of lymphoma. Flow cytometry revealed 0.2% residual T cell lymphoma. Following that he received 2 cycles of ICE followed by HyperCVAD-B (Methotrexate/Leucovorin, Cytarabine, Methylprednisolone) to further lower disease burden prior to transplant and decrease risk of relapse. He was then referred to the bone marrow transplant clinic and underwent allogeneic HSCT, but he had poor graft function after transplant followed by disease relapse. He passed away 12 months after diagnoses.

3. Discussion

Our case is important for multiple reasons. First, the increased incidence of HSTCL in patients who are on immunosuppressant drugs should be noted especially in an era of increased use of biologic agents and advancements in solid organ transplantation and treatment of lymphoproliferative

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disorders. Second, this case represented a diagnostic challenge due to overlap in clinical presentation of HSTCL, HLH and partly Crohn'sdisease. The multiorgan involvement is characteristic of T cell lymphomas and HLH. Crohn's disease patients commonly present with sepsis which is also part of the manifestations of lymphomas and HLH and was present in our patient. Third, early recognition and treatment initiation in these two aggressive syndromes is critical.

3.1 Hepatosplenic T cell lymphoma

T cell lymphomas are uncommon, representing fewer than 15% of all NHL. HSTCL is a rare subset of the peripheral T-cell lymphomas accounting for < 1% of NHL. Although the pathogenesis of HSTCL is poorly understood, chronic immunosuppression contributes to 20% of HSTCL.[1] The two most common clinical settings for long-term immunosuppression associated with HSTCL are post organ transplantation and immune-dysregulatory disorders, most often Crohn disease and infrequently rheumatoid arthritis, psoriasis and other autoimmune diseases.[2] No proven association between infections and HSTCL has been found. Pathologically, HSTCL involves the liver and the spleen, but also frequently involves the bone marrow in 70% of cases. HSTCL is a mature T cell neoplasm with T cell markers expressed, like CD3. Whereas the majority of HSTCL cases are CD4-/CD8-, a less common immunophenotype of CD4-/CD8+ can occur such as our patient's case.[1,3]On staining, it has an interesting staining pattern of infiltration involving liver sinuses and bone marrow sinusoids in a linear fashion unlike most other lymphomas in which neoplastic cells form large lymphoid aggregates.[1]

The typical patient will be a young adult, more frequently males with a median age of 35 years. It presents as a systemic illness with B symptoms, hepatosplenomegaly and abnormal liver function tests. Cytopenias are common and often multifactorial due to bone marrow infiltration, autoimmune mediated hemolysis/thrombocytopenia or part of HLH syndrome.[4] Unlike other lymphomas, HSTCL usually presents with minimal or no detectable peripheral lymphadenopathy. LDH is commonly elevated in these patients. Peripheral lymphocytosis is uncommon in early stages but as the disease advances, a "leukemic" phase can be seen. Examination of peripheral smear is usually unremarkable, and diagnosis is made on biopsy specimens of liver, bone marrow or spleen.[1,5]

HSTCL is an aggressive disease with a dismal prognosis and a median survival of HSTCL patients ranges from 3 to 28 months.[2] While up to half of patients may achieve a complete remission (CR), this is usually short lived.[6] No standard therapy exists, though autologous or allogeneic transplantation should be considered in patients who achieve a CR.

3.2 Association of HSTCL and IBD treatment regimens

Our case highlights the association between HSTCL and the use of azathioprine and tumor necrosis factor-alpha (TNFa) inhibitors in patients with Crohn's disease. Treatment goal in Crohn's disease is to achieve deep mucosal healing rather than symptomatic improvement alone. With this, it's not uncommon to recommend early introduction of biologic agents or combination therapy with biologics and immunomodulators.[7]

The data about HSTCL in inflammatory bowel disease (IBD) patients receiving biologic agents is scarce due to rarity of disease. Long term use of azathioprine (> 2 years) in IBD patients is a risk factor for developing HSTCL.[7,8] A systematic review of 36 cases found the overall risk in IBD patients who receive thiopurines is exceedingly rare, at 1:45,000 patients, although this risk in men under the age of 35 who receive thiopurines is significantly higher, at 1:7500, (a roughly 4-fold increased risk).[8] The risk in patients receiving both thiopurines and TNFa inhibitors in patients who are younger than 35 is approximately 1:3500.[8] A more recent systematic review of 62 cases of HSTCL occurring among IBD patients who received biologic agents found that 57 cases had exposures to azathioprine previously however 5 cases were identified without any reported azathioprine exposure,[7] an estimated risk of fewer than 1:21,947 patients on TNFa inhibitors.[8]

Although the benefits of long-term biologic therapy in IBD patients may outweigh the very low risk of a devastating condition for most patients, guidelines and product labeling ensure that patients receiving these agents are adequately informed of the potential risk of HSTCL.[8] Another potential area of importance is exploring a step-down therapy approach to patients who have achieved remission on biologic therapy. This however must be balanced with the risks of IBD relapse following withdrawal of biologic agents[9] which can be as high as 44% for Crohn's disease and 38% for ulcerative colitis.

3.3 Hemophagocytic Lymphohistiocytosis (HLH)

HLH is a life-threatening syndrome involving excessive immune system activation and results in a febrile illness associated with multiple organ involvement (Liver, kidneys, and CNS) and markedly elevated inflammatory markers. Patients with HLH tend to present with fever, hepatosplenomegaly, bicytopenia 92%, elevated ferritin and soluble IL-2 receptors.[10] Events that activate the immune system are common triggers for HLH, such as infections, autoimmune diseases

(SLE, IBD) and hematological neoplasms, especially lymphoma.[11] It is reported that HLH affects 1% of adults with hematological cancer, but the prevalence rises to 20% in patients with some types of B-cell and T-cell lymphoma.[12] The diagnosis and management of HLH is based on the HLH-2004 protocol,[13] detailed discussion of this is beyond the scope of this article.

4. Conclusion

HSTCL is a rare but fatal disease, especially if unrecognized early. The use of biologic agents in treatment of immune dysregulation disorders is a known risk factor for development of HSTCL. Although the benefits of using biologic agents in patients outweigh the risks of HTSCL, patients should be informed about the possible risks. HLH is also a systemic hyperinflammatory disease that is often triggered by lymphomas. HLH specific therapies should be considered in addition to treating the triggering event.

Conflicts of Interest Disclosure

The authors have declared no conflicts of interest.

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