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CASE REPORT | INFLAMMATORY BOWEL DISEASE

A Rare Presentation of a Devastating Disease: Hepatosplenic T-Cell Lymphoma in Crohn's Disease Without Thiopurine Exposure

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ABSTRACT

Hepatosplenic T-cell lymphoma (HSTCL) is a rare, aggressive malignancy that has been associated with thiopurines during the treatment of inflammatory bowel disease (IBD). We present a case of a 26-year-old man with Crohn's disease on infliximab without prior thiopurine exposure who developed HSTCL. His diagnosis was confirmed through flow cytometry, fluorescence in situ hybridization, and bone marrow biopsy. This is the sixth case of HSTCL in patients with IBD without prior thiopurine exposure and highlights the need for a comprehensive risk-benefit discussion with patients on the various treatment modalities for IBD.

KEYWORDS: hepatosplenic T-cell lymphoma; inflammatory bowel disease; Crohn's; tumor necrosis factor alpha inhibitors, infliximab; thiopurines

INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive subtype of peripheral T-cell lymphoma, accounting for <1% of all non-Hodgkin lymphomas.[1,2] This devastating malignancy has been documented as a feared association of treatment in inflammatory bowel disease (IBD) with thiopurines or combination therapy with thiopurines and antitumor necrosis factor (TNF)-α agents.[3,4] Furthermore, almost all identified HSTCL cases among patients with IBD on biologic therapy had azathioprine/mercaptopurine exposure.[5] We present a rare case of HSTCL associated with IBD treatment without prior exposure to thiopurines.[5]

CASE REPORT

A 26-year-old man with a history of Crohn's disease presented after a recommendation from his outpatient hematologist for splenomegaly in the setting of abnormal labs.

One year before presentation, splenomegaly was incidentally noted on a computed tomography (CT) scan during a hospital admission for pneumonia, and our patient was referred to outpatient hematology. Further workup included a Fibroscan that had no evidence of chronic liver disease and flow cytometry that did not show proof of circulating lymphoma. Two months before presentation, labs were obtained, which were all within normal limits except for an elevated lactate dehydrogenase (LDH) of 665 IU/L. During routine follow-up, new lab work revealed a white blood count of 23.2 K/mcL, hemoglobin of 9.8 g/dL, platelets of 87 K/mcL, and LDH of 2,657 IU/L, prompting urgent referral to our hospital.

On admission, peripheral blood flow cytometry showed circulating gamma/delta (γδ) T cells consistent with HSTCL (Figure 1). Positron emission tomography (PET)/CT scan demonstrated marked hepatosplenomegaly with multiple cervical lymph nodes with increased fludeoxyglucose (FDG) uptake, which was consistent with the newly diagnosed HSTCL, hypermetabolic lesions in the sacral region, increased FDG uptake in the axial and appendicular skeleton, and multiple inguinal lymph nodes with mild FDG

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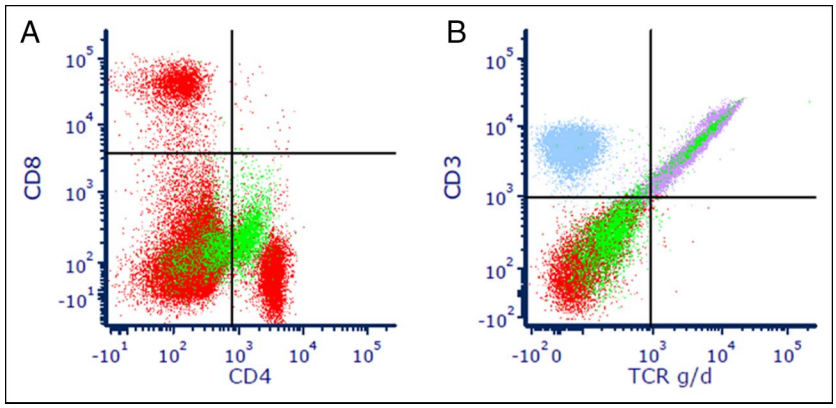

Figure 1. Flow cytometry on the pheripheral blood: (Lymphocytes highlighted in green). (A) T cells demonstrating negative cell surface makers for CD4 and CD8. (B) T cells reveal positive cell surface makers for T cell receptor (TCR) g/d and CD3.

uptake (Figure 2). Bone marrow biopsy confirmed that the diagnosis of HSTCL and fluorescence in situ hybridization studies showed isochromosome 7q and trisomy 8.

He was started on a regiment of cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HyperCVAD). After initiation of treatment, we saw improvement in his splenomegaly until 1 month after his fourth cycle of HyperCVAD when interval PET/CT revealed increased splenic size and metabolic activity. A planned haploidentical stem cell transplant was canceled due to declining blood counts and a worsening LDH, suggesting disease progression. He received one cycle of ifosfamide, carboplatin, and etoposide salvage therapy. Subsequent PET/CT imaging demonstrated worsening disease in the spleen and liver, prompting a switch to pentostatin and alemtuzumab. After receiving 6 cycles of pentostatin and alemtuzumab, he continued to have worsening splenomegaly and leukocytosis, and it was ultimately decided to transition to hospice care.

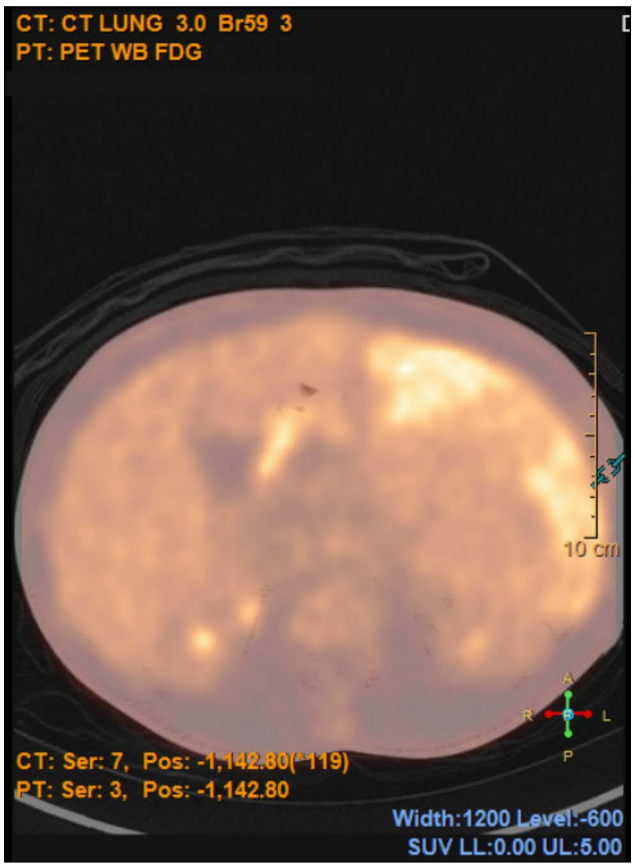

Figure 2. PET/CT scan revealing increased FDG uptake in anterior and posterior spleen. CT, computed tomography; PET, positron emission tomography.

DISCUSSION

Our patient was initially diagnosed with inflammatory ileocolonic Crohn's disease at age 11 and quickly achieved remission with mesalamine and steroids. He remained off therapy until age 21 when he developed hematochezia and was started on adalimumab. After a year on adalimumab, he developed abdominal pain with worsening inflammatory markers and he was transitioned to ustekinumab. Several months later, his course was complicated by perianal abscesses and developing fistula. He was changed to infliximab and methotrexate with significant improvement in his symptoms. The methotrexate was subsequently discontinued due to abnormal liver labs, and infliximab was escalated to every 4-week dosing. He remained on infliximab for 3 years until presentation to us.

HSTCL is an extremely rare disease and accounts for $<1\%$ of all non-Hodgkin lymphomas.[1] HSTCL has a median survival between 3 and 28 months and most commonly affects patients who are younger, males, and of black ethnicity.[2,5,6] Factors that can worsen survival rates include patients with thrombocytopenia, serum bilirubin level ≥ 1.5 mg/dL, HSTCL cells expressing $\alpha\beta$ T-cell receptors, trisomy 8, and patients with hemophagocytic syndrome.[7,8] Genetic risk factors include chromosomal abnormalities of isochromosome 7q and trisomy 8, which were also seen in our patient.[1,2] Kandiel et al showed a roughly fourfold increase in lymphoma with patients with IBD being treated with thiopurines.[9] Ten percent of HSTCL cases reported by Thai et al occurred in patients with IBD who have been treated with thiopurines or combination of

thiopurines and anti-TNF inhibitors.[10] Moreover, Sokol et al stated that there was not enough data linking the risk of lymphoproliferative disease to anti-TNF inhibitors alone because the patients were often cotreated with thiopurines.[11] Deepak et al analyzed over 3 million reports from the US Food and Drug Administration adverse event reporting system and reported the risk of T-cell non-Hodgkin lymphomas was higher in anti-TNF inhibitors and thiopurines or in thiopurines alone but did not see an increased risk with anti-TNF inhibitors alone.[12] In a review article by Shah et al also analyzing the adverse event reporting system, there were only 5 prior patients who developed HSTCL without prior exposure to thiopurines.[5]

Our literature review revealed no published cases detailing the clinical course of patients with IBD with HSTCL without prior thiopurine exposure. However, 3 young males with Crohn's disease and prior infliximab and thiopurine exposure have been reported to develop HSTCL. One patient received one cycle of HyperCVAD followed by one cycle of ifosfamide, carboplatin, and etoposide salvage therapy.[13] Although this patient had a sibling allogenic bone marrow transplant, disease recurrence was seen after 1 year, leading to a palliative approach. The 2 other patients had refractory disease to cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone.[14,15] One achieved remission after early cord blood transplantation, but the other passed 1 month after an unrelated allogeneic stem cell transplant. While anthracycline-based chemotherapy remains the standard, hematopoietic stem cell transplantation has demonstrated a more sustained remission.[2,6]

Although the pathophysiology of HSTCL is poorly understood, one theory involves the monoclonal proliferation of neoplastic γδ T cells via the Janus kinases/signal transducer and activator of transcription proteins pathway or mutations in chromatin modifiers.[1,2] Infliximab promotes the survival of and exacerbates the production of γδ T cells, predisposing patients to developing HSTCL.[11,16] Furthermore, infliximab inhibits TNF-α, a crucial cytokine that regulates cell growth and proliferation. With TNF-α inhibited, cancerous cells can proliferate unchecked. Our patient was also previously on adalimumab and ustekinumab, which have also been taken by patients who developed HSTCL.[1,5] The combination of these therapies can create a synergistic risk through immune-modulating pathways. Osterman et al. noted a 3-fold increase in the relative risk of malignancies with combination therapy with adalimumab and immunomodulators.[17] However, adalimumab has not been seen to cause a proliferation of γδ T cells, and ustekinumab was rarely mentioned in our literature review.[16] Males have more γδ T cells than females and may explain the increased risk of developing HSTCL in younger males.[18]

Anti-TNF medications are a mainstay treatment in IBD and can be used in the induction and maintenance of Crohn's disease.[19,20] In patients with all stages of Crohn's, anti-TNF agents are effective in achieving remission and are recommended as treatment in Crohn's resistant to corticosteroids, thiopurines, or methotrexate.[20] However, in patients who decide to stop anti-TNF medication after 1 year of remission, one-third of patients with IBD will relapse and the number will increase to up to one-half over time.[21] Therefore, it is recommended to continue treatment in the setting of endoscopic and clinical remission if the treatment is well tolerated.[20] The extremely low risk of HSTCL must be weighed against the risk of uncontrolled IBD, which severely hinders patients' quality of life. Understanding this, anti-TNF medications are quintessential for reducing morbidity and mortality and outweigh the remote risk of HSTCL.

Given the low incidence of HSTCL, we would not recommend regular screening tests for HSTCL. We recommend clinicians have a comprehensive discussion with all their patients before initiation of anti-TNF medications, detailing the benefits of anti-TNF medications and acknowledging the small risk of HSTCL. We recommend routine lab work and a thorough history and physical exam during every follow-up. This would allow practitioners to identify associated lab abnormalities such as lymphocytosis, anemia, and thrombocytopenia or exam findings such as hepatosplenomegaly for earlier diagnosis and treatment. It is especially important for clinicians to identify patients with high-risk demographics such as young males and understand the mortality benefit of stem cell transplant.

We present a case of an extremely rare disease that is rarely seen without thiopurine exposure in patients with IBD. Our case highlights that although unlikely, the risk of HSTCL should be discussed with all patients with IBD before the initiation of anti-TNF inhibitors. Ultimately, it should be noted that the benefits of treatment with anti-TNF therapy heavily outweigh the risks and that stopping anti-TNF therapy can often lead to disease recurrence.

DISCLOSURES

Author contributions: M. Chang: study and concept design, literature search, analysis and interpretation of data, drafting of manuscript, and is the article guarantor; N. Williams: analysis and interpretation of data, drafting of manuscript; M. Frohlinger: drafting of manuscript, study supervision; L. George: study supervision, critical revision of the manuscript for important intellectual content.

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