

The Risk of Hepatosplenic T-Cell Lymphoma (HSTCL) in Women with Inflammatory Bowel Disease (IBD) on Thiopurines

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Abstract

Hepatosplenic T-cell Lymphoma (HSTCL) is a rare and often fatal malignancy classically thought to affect males less than 35 years of age with Inflammatory Bowel Disease (IBD) on thiopurines. Even though HSTCL is thought to affect predominantly young males with IBD, it can occur in female patients as well. We report a case of HSTCL in a young female patient with ulcerative colitis (UC), the 6th female case of IBD-associated HSTCL reported in the literature. Although the risk of developing HSTCL may be lower in women, it remains a substantial concern given the aggressive nature of this disease.

Keywords: Lymphoma; Inflammatory bowel disease; Proctosigmoiditis; Splenomegaly; Hepatomegaly

Introduction

Hepatosplenic T-cell Lymphoma (HSTCL) is a rare and frequently fatal malignancy classically thought to affect males, less than 35 years of age, with Inflammatory Bowel Disease (IBD) and receiving thiopurines [1]. Prior review of the published medical literature reveals 100-200 cases of HSTCL, 37 with concomitant inflammatory Bowel Disease (IBD), more specifically Crohn's disease [2]. Although the risk of acquiring this malignancy is low, given its aggressive nature and high mortality [3], awareness of HSTCL is essential so patients and gastroenterologists can make informed decisions prior to starting thiopurines. Anecdotally, we have these conversations with young male patients, but what about female patients? We report a case of HSTCL in a young woman with Ulcerative Colitis (UC).

Case Report

Our patient initially presented at the age of 18 with complaints of 2 months of bloody diarrhea. She was diagnosed with ulcerative proctosigmoiditis and was initially treated with various oral and topical 5-aminosalicylic acids (5-ASAs); however, she failed to achieve clinical remission and was transitioned to prednisone and 6-mercaptopurine (6MP) with a clinical response. She continued to do well until just prior to her 23rd birthday when she developed fatigue, night sweats, and fever. She saw her primary physician who noted an unremarkable physical exam, but laboratory studies revealed pancytopenia. An abdominal ultrasound was performed and showed marked splenomegaly. A PET scan showed splenomegaly with increased FDV avidity (max SUV 3.1) without hepatomegaly (max liver SUV 2.6) (Figure 1).

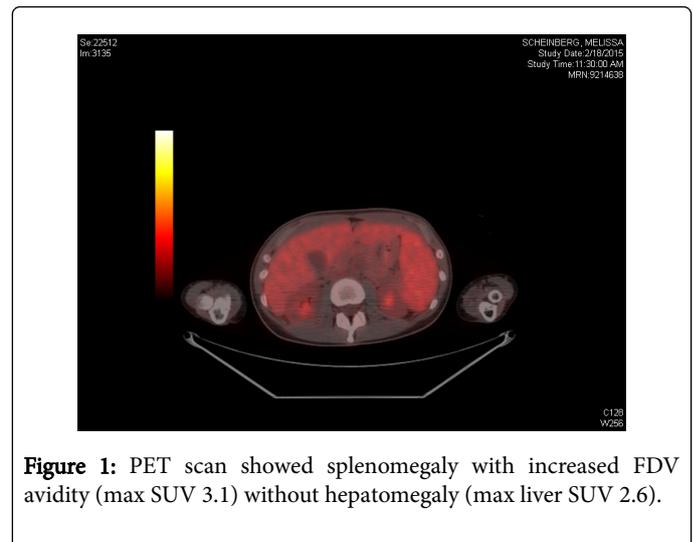
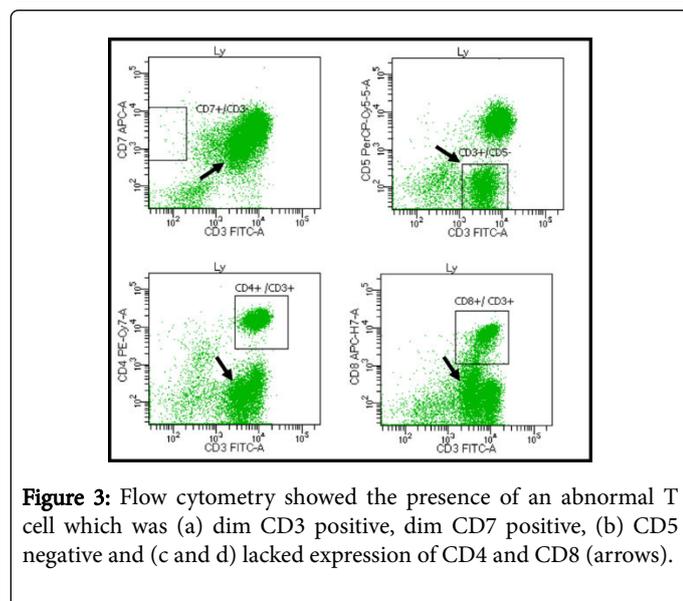
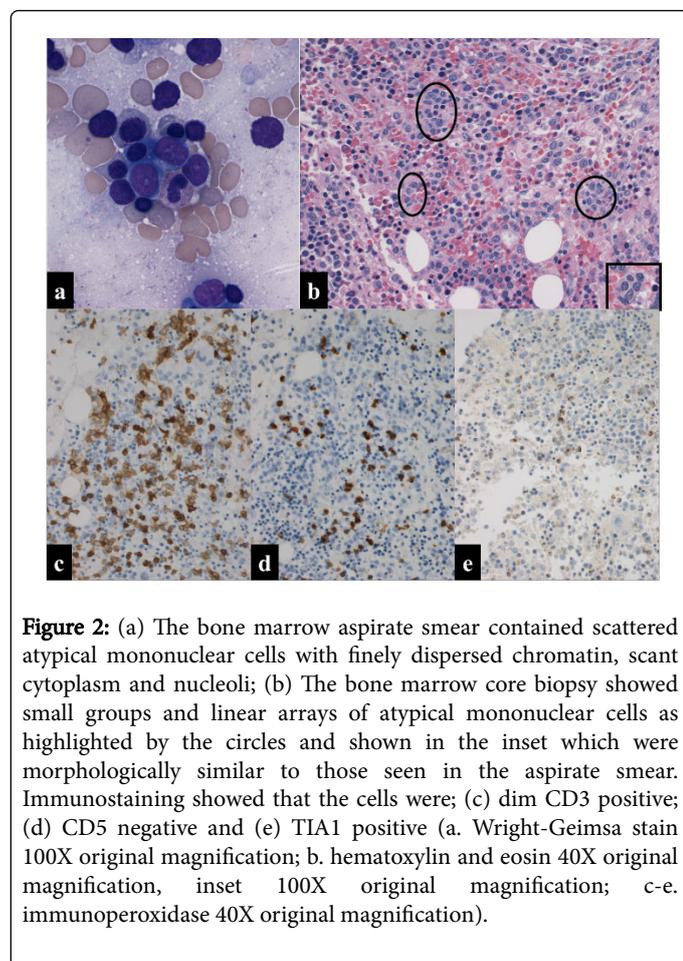


Figure 1: PET scan showed splenomegaly with increased FDV avidity (max SUV 3.1) without hepatomegaly (max liver SUV 2.6).

She was referred for a bone marrow biopsy and analysis showed scattered atypical mononuclear cells with finely dispersed chromatin, scant cytoplasm and nucleoli. Immunostaining showed that the cells were dim CD3 positive, CD5 negative and TIA1 positive (Figure 2). Flow cytometry showed a small abnormal T cell population which was CD5 negative, dim CD3 positive, CD56 positive, lacked expression of CD4 and CD8 and was gamma/delta positive (Figure 3). Pathology was consistent with HSTCL, but her anemia and leukopenia were out of proportion to her thrombocytopenia. Furthermore, her female sex and ulcerative colitis are not typically associated with HSTCL.



A discussion ensued regarding her underlying diagnosis. Cytogenetic analysis identified a gain of 7q (most consistent with isochromosome 7q) as well as trisomy 8 in a small number of cells, findings consistent with HSTCL. On further review of her clinical presentation, radiology and pathology, a diagnosis of HSTCL with

associated Hemophagocytic LymphoHistiocytosis (HLH) was made [4]. She underwent induction with etoposide, ifosfamide, and cytarabine (IVAC) followed by allogeneic bone marrow transplantation. She remains in oncologic remission and her UC is currently well-controlled on oral mesalamine alone.

Discussion

HSTCL is a rare type of lymphoma that accounts for 5% of all T cell lymphomas [5]. It presents with fevers, weight loss, night sweats and hepatosplenomegaly [3]. Laboratory results are significant for neutropenia, thrombocytopenia, anemia and lymphocytosis [6]. The diagnosis of HSTCL requires a high index of suspicion. Bone marrow biopsy with immunohistochemical staining and cytogenetic analysis leads to a diagnosis [5]. The treatment of HSTCL necessitates intensive induction chemotherapy followed by allogeneic bone marrow transplantation [7]. HSTCL is an extremely aggressive often fatal malignancy with a median survival of less than 2 years. Even with achievement of initial remission, patients often relapse [8].

An association between IBD and HSTCL has been reported, specifically in patients managed with thiopurines, and more specifically in young males [9]. In 2009, Kotlyar et al. performed a systematic review of HSTCL in IBD and revealed a 72% rate of Crohn's Disease (CD) amongst 36 reported cases of HSTCL in the IBD population [10]. The most recent review of the literature was performed by Selvaraj et al. in 2013, at which time a search of Pubmed, EMBASE and the FDA Adverse Event Reporting System (FDA AERS) identified 37 unique cases of CD with HSTCL; all were younger than 40 year of age and 86% were male. Around this time, Deepak et al. reported on HSTCL in the IBD population as part of a larger investigation of the incidence of T-cell non-Hodgkin lymphoma in IBD [11]. Using the AERS alone, they reported 30 cases [12-14] of HSTCL in patients taking anti-TNFs and/or immunomodulators and showed that there was an increased incidence of HSTCL in IBD patients on immunomodulators with or without anti-TNF ($p < 0.0001$) [11].

Of the thirty seven reported cases of HSTCL in IBD patients, five are female [11,12,15,16], making our case the 6th female case reported in the literature (Table 1). Of the five female patients, all carried a diagnosis of CD, unlike our patient who was diagnosed with UC. The age at HSTCL diagnosis varies and ranges from 17 to 79 years of age. All female patient except one were exposed to thiopurines. Fifty percent of female IBD patients with HSTCL died, which is lower than the mortality seen in male patients, although still very significant.

Even though HSTCL is typically thought to predominantly affect young males with IBD on thiopurines, this aggressive and often fatal malignancy can occur in female patients as well. Although the risk of developing HSTCL may be lower in women, it remains a substantial concern given the mortality and morbidity of this disease. When prescribing thiopurines, physicians and patients must have an informed conversation regarding the risks, benefits and alternatives of treatment. Our case highlights that this conversation should be with all patients, not just young males. Furthermore, a high index of suspicion for HSTCL is required when treating patients with IBD who are on thiopurines, whether the patient is male or female, so as not to delay diagnosis. In our case, the diagnosis of HSTCL was initially debated because women are not considered the "typical" population to develop HSTCL. Our patient was diagnosed soon after her symptoms began, which may have played a role in her successful outcome. It is

important to continue reporting these rare cases, particularly in lesser described patient populations such as women, in order to inform the medical community, and to determine possible risk factors in these specific populations.

Source	Age	Gender	Disease	Prior IBD treatment	Current IBD therapy	HSTCL treatment	Prognosis
Thayu [15]	17	F	Crohn's disease	mesalamin; steroids; 6MP ² for 4.5 y	IFX ³ (20 infusions)	Chemotherapy	Died
Humphrey [16]	27	F	Crohn's disease	steroids	AZA ⁴ for 5 y	Interferon alpha for 9 months	Alive, in remission (20 months)
Parakkal [12]	74	F	Crohn's disease	IFX ³ (12 infusions)		Chemotherapy	Died
Parakkal [12]	79	F	Crohn's disease	IFX ³ ; 6MP			Died
Deepak [11]	34	F	Crohn's disease	IFX ³ 3.56 y; AZA ⁴ 3.56 y		Splenectomy; chemotherapy	Alive
6 th case	22	F	Ulcerative colitis	5ASA ⁵ ; steroids;	6MP ² for 4 y	Chemotherapy; bone marrow transplant	Alive

Table 1: Inflammatory Bowel Disease (IBD)-Associated Hepatosplenic T-cell Lymphoma (HSTCL) in Women as Reported in the Literature(2-mercaptopurine (6MP), 3-infliximab (IFX), 4-azathioprine (AZA), 5-aminosalicylic acid (5ASA).

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