J Cases Obstet Gynecol, 2017;4(3):76-79

Case Report

T cell lymphoma associated with immunomodulator therapy in a pregnant patient with Crohn's disease

Adeola Awomolo[1,*], Theofano Orfanelli[1], Joshua Segal[1], Christina Duzyj[1]

[1]Rutgers Robert Wood Johnson Medical School, Department of Obstetrics and Gynecology and Reproductive Sciences, New Jersey, United States.

Abstract

Immunomodulatory agents have gained widespread use in the treatment of several disorders and so have the complications associated with their use. This is the first case to our knowledge in a pregnant woman with Crohn's disease and history of treatment with both agents who was diagnosed with a T-cell acute lymphoblastic lymphoma.

Key Words:

Lymphoma, pregnancy, Crohn's disease, immunomodulators

Introduction

Over the last few decades several immunomodulatory agents have been developed and introduced into clinical practice for the treatment of a variety of autoimmune diseases including inflammatory bowel disease (IBD). However, there is a growing body of evidence in regards to their use and association with lymphoproliferative disorders. Specifically, cases of non- Hodgkin hepatosplenic T cell lymphoma (HSTCL) have been reported in patients with Crohn's disease (CD) treated with an anti-tumor necrosis factor alpha (anti-TNF- alpha) agent in conjunction with thiopurines [1].

Article History:
Received: 13/03/2017
Accepted: 21/04/2017

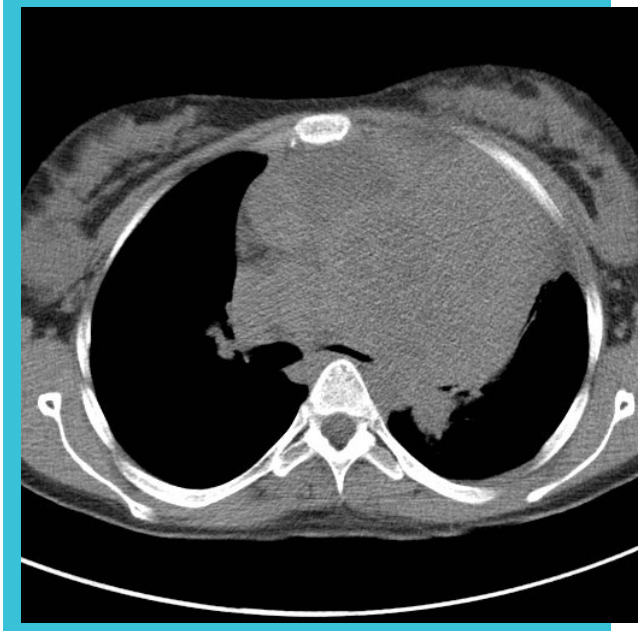
***Correspondence:** Adeola Awomolo
Address: 125 Paterson Street, New Brunswick, New Jersey, United States, 08902.
Tel: 718 909 4661
Fax: 732 235 9855
e-mail: aa1362@rwjms.rutgers.edu

Case Presentation

A 32-year-old G3P2002 at 27 weeks of gestation with diamniotic dichorionic twins and CD presented to the emergency department reporting worsening cough and dyspnea for 2 months and development of hemoptysis 2 days prior to presentation. Her CD was diagnosed 2 years prior to her presentation. She had been treated with a monoclonal antibody against TNF- alpha and 6- Mercatopurine since her diagnosis and her disease was well controlled. Her cough and dyspnea had been treated empirically twice with antibiotics for presumed bronchitis with minimal improvement. Her vital signs on arrival were all within normal limits. However, due to the above symptoms and the high risk of pulmonary embolism (PE) in pregnancy, a computed tomography angiography (CTA) scan of the chest was obtained. The CTA of the chest was negative for a PE but it revealed a 17.8cm x 10.8cm x 10.7cm anterior mediastinal mass with compression of the main and left

pulmonary arteries as well as the left main bronchus (Figure 1). Physical exam revealed no peripheral lymphadenopathy or hepatosplenomegaly. Her initial blood workup was unremarkable with the exception of an elevated lactate dehydrogenase of 1099 (125-220 IU/L normal range).

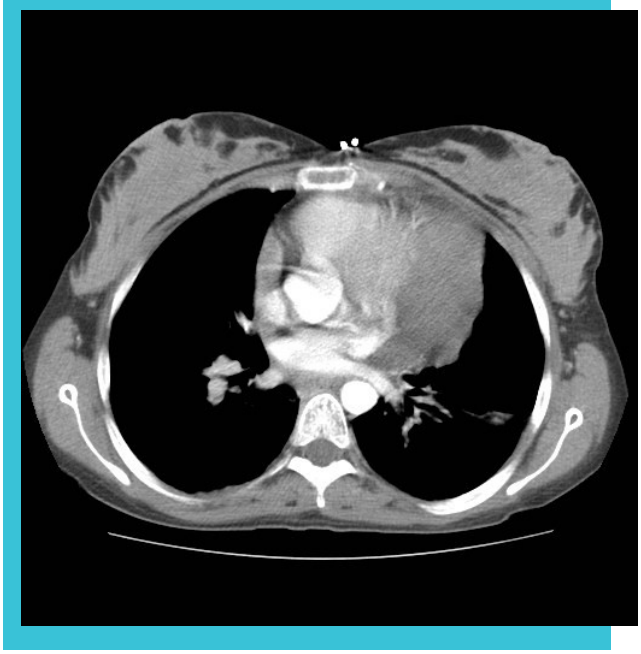
Figure 1.



Computed Tomography Angiography (CTA) of the chest revealing a 17.8cm x 10.8cm x 10.7cm anterior wall mediastinal mass with compression of the main and left pulmonary arteries as well as the left main bronchus

She underwent a fine needle aspiration and core biopsy of the mediastinal mass with results consistent with T-cell acute lymphoblastic lymphoma. Bone marrow biopsy and aspirate did not show evidence of involvement. Abdominal staging ultrasound showed no evidence of other lymphadenopathy or metastatic disease. She was treated as an inpatient with part 1A Cyclophosphamide, Vincristine, Adriamycin and Dexamethasone (Hyper- CVAD) for three weeks. Methylprednisolone was substituted for dexamethasone and mesna was held given concerns for fetal toxicity. After a 2-week break, she was treated with part 2A Hyper-CVAD for one week with the same substitution and omission as with the part 1A regimen. A repeat CT scan

Figure 2.



CTA of the chest after two cycles of chemotherapy revealing a significant reduction in the mass from a 17.8cm x 10.8cm x 10.7cm to 8.8 x 8.3x 5.1cm.

2 weeks after the second cycle of chemotherapy showed a significant decrease in the size of mass to 8.8 x 8.3x 5.1cm. Her obstetrical course was complicated by fetal growth restriction in both fetuses diagnosed at 32 weeks, monitored with standard fetal surveillance. She subsequently went into preterm labor at 35 weeks and had a normal vaginal delivery. Twin A was a male infant weighing 2295 grams with Apgars 8 at one minute and 9 at five minutes. Twin B was a female infant weighing 1635 grams with same Apgars as twin A. Both infants were admitted to the neonatal intensive care unit for prematurity. Twin B was found to be leukopenic with a white blood cell count (WBC) of 5.8 Thousand/ul which was monitored and normalized to 10.4 Thousand/ul by day three of life and was remained within normal limit until discharge on day fourteen of life. Twin A's WBC at birth was 9.2 Thousand/ul and remained normal upon discharge on day 2 of life. Twin B's significantly longer hospital stay was secondary to poor weight gain requiring tube feeds. Placental histopathology revealed no evidence of lymphoma. The mother was discharged without complications on postpartum day 2 and subsequently transferred her oncologic care to a different institution. At

6 months' postpartum patient is doing well, in remission and is in the process of getting a bone marrow transplant.

Discussion

Epidemiological data provide evidence of a steady rise in autoimmune disease throughout westernized societies over the last decades [2]. The introduction of immunomodulatory agents in the treatment of several autoimmune inflammatory diseases such as IBD, psoriasis, psoriatic arthritis, rheumatoid arthritis, multiple sclerosis, and ankylosing spondylitis has been revolutionary, nonetheless, controversial. Notably, the safety of immunomodulatory agents has been an area of considerable importance and on-going research over the last few decades. More specifically, there is a general concern regarding the use of the immunomodulatory agents and their association with malignancies. The biggest volume of evidence comes from cases reported in patients with IBD and some isolated cases of psoriasis. Within the IBDs, there is more of an association with CD than there is with ulcerative colitis (UC) and this association is strongest when treatment consists of a combination of both an anti-TNF-alpha agent and thiopurines rather than with single therapy. In addition to lymphomas other cancers such as non-melanoma skin cancers have been reported in patients with IBD treated with both thiopurines and anti-TNF-alpha [3, 4]. The duration of exposure to the agents in patients who subsequently developed the above malignancies is not consistently reported in all cases but some studies report months to 4 years after initiation of treatment [1, 5]. The pathogenesis of these malignancies is not completely understood but immunosuppression as a result of the treatment is thought to be a significant contributing factor [5] . Several studies have investigated the inherent risk of lymphoma based on a history of IBD without immunomodulatory treatments. One of the largest population based studies was conducted based on the General Practice Research Database. This study examined computerized medical records and identified 6000 cases of CD, 10000 cases of UC and 60, 000 matched controls. Based on the study the relative risk for lymphoma in the studied population was 1.20 (95% confidence interval 0.67-2.06) but this increase was not statistically significant [6]. However, two meta-analyses and a prospective cohort trial all show a four to sixfold increase in risk of lymphoma in IBD patients treated with thiopurines [4, 7, 8]. The specific subtype of lymphoma most associated with combined treatment in patients with IBD is HSTCL. While HSTCL is a rare and aggressive form of Non-Hodgkin lymphoma that can arise de novo, 10-20% incidence has been reported in patients with IBD receiving immunodulator therapy[9]. It has been primarily described in young male patients with IBD less than age 35 after therapy with anti-TNF-alpha agents and thiopurines. A case series reviewing 28 cases of HSTCL occurring in non-gender specific patients with CD showed a median survival of 8 months and only one patient achieved remission [10] . Literature is lacking in discussion of the incidences of lymphoma associated with immunomodulatory therapy in pregnancy. We identified one case report of diffuse large B cell lymphoma in a 35-year-old pregnant patient with a history of CD treated with long-term azathioprine therapy [11]. We report the first case to our knowledge of T-cell lymphoma in pregnancy in a patient with immunomodulatory therapy and CD. Our case is unique as it describes an unusual clinical presentation of T- cell lymphoma associated with immunomodulatory therapy. The overwhelming majority of lymphomas after treatment with these agents for patients with IBD is HSTCL as discussed above[1] . On the contrary, our patient presented with a large mediastinal mass consistent with T-cell acute lymphoblastic lymphoma without hepatic or splenic involvement. Lymphoma is the fourth most common malignancy in pregnancy. Highly aggressive lymphomas such as T-cell lymphomas and diffuse large B cell lymphomas have been reported to have 6-month mortality rates of 25% and 12.8% respectively[12]. Three quarters of the pregnant patients diagnosed with non- Hodgkin's lymphoma are diagnosed with stage IV disease which is a higher proportion compared to non-pregnant women of reproductive age. This is thought to be in part due to a delay in diagnosis as a result of overlapping lymphoma and pregnancy symptoms [12]. Despite the poor prognosis of lymphoma in pregnancy, our patient improved dramatically due to the prompt treatment with immediate initiation of chemotherapy. The presenting symptoms of pregnant patients with underlying lymphomas typically do not vary from that of non-pregnant patients. Lymphoma associated symptoms such as fatigue, dyspnea, sweating sometimes overlap with physiologic changes in pregnancy. This can create a scenario where diagnosis maybe very delayed or even missed entirely, leading to debilitating, if not deadly, sequelae. As the use of immunomodulatory agents continues to ex-

pand for treatment of chronic inflammatory diseases, we can anticipate an upward trend in pregnant patients being treated with those agents. Pregnant patients should be aware of the risk of lymphoproliferative disorders associated with these therapies and be counseled appropriately. Maintaining a keen awareness of risk factors in patient's non-obstetrical histories, recognizing when pregnancy related symptoms deviate from the norm in duration or intensity and taking a systematic approach for work-up and diagnosis might be key in optimizing the outcome of an insidious process.

Acknowledgement
None

Declaration of Interest
None

References

1. Deepak, P., et al., T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-alpha) inhibitors: results of the REFURBISH study. Am J Gastroenterol, 2013. 108(1): p. 99-105.
2. Lerner, A., P. Jeremias, and T. Matthias, The World Incidence and Prevalence of Autoimmune Diseases is Increasing. International Journal of Celiac Disease, 2015. 3(4): p. 151-155.
3. Sifuentes, H. and S. Kane, Monitoring for Extra-Intestinal Cancers in IBD. Curr Gastroenterol Rep, 2015. 17(11): p. 42.
4. Siegel, C.A., et al., Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. Clin Gastroenterol Hepatol, 2009. 7(8): p. 874-81.
5. Zeidan, A., et al., Hepatosplenic T-cell lymphoma in a patient with Crohn's disease who received infliximab therapy. Leuk Lymphoma, 2007. 48(7): p. 1410-3.
6. Lewis, J.D., et al., Inflammatory bowel disease is not associated with an increased risk of lymphoma. Gastroenterology, 2001. 121(5): p. 1080-7.
7. Beaugerie, L., et al., Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet, 2009. 374(9701): p. 1617-25.
8. Vos, A.C., et al., Risk of malignant lymphoma in patients with inflammatory bowel diseases: a Dutch nationwide study. Inflamm Bowel Dis, 2011. 17(9): p. 1837-45.
9. Kotlyar, D.S., et al., A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol, 2011. 9(1): p. 36-41 e1.
10. Ochenrider, M.G., D.J. Patterson, and D.M. Aboulafia, Hepatosplenic T-cell lymphoma in a young man with Crohn's disease: case report and literature review. Clin Lymphoma Myeloma Leuk, 2010. 10(2): p. 144-8.
11. Chen, G., et al., Placental involvement by non-Hodgkin lymphoma in a Crohn disease patient on long-term thiopurine therapy. Intern Med J, 2016. 46(1): p. 102-5.
12. Horowitz, N.A., et al., Reproductive organ involvement in non-Hodgkin lymphoma during pregnancy: a systematic review. Lancet Oncol, 2013. 14(7): p. e275-82.