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Case Report Open Access

Peripheral T-Cell Lymphoma in Adult Female with Rheumatoid Arthritis: Case Report

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Abstract

Introduction: Lymphoma association with Rheumatoid Arthritis (RA) is well established. The mechanisms behind this association remain a matter of controversy.

Objective: We here report a patient with rheumatoid arthritis who developed peripheral T-cell lymphoma not otherwise specified following etanercept (TNF-alpha inhibitor) and methotrexate therapy.

Clinical Presentation: A 38-year-old female presented to emergency with history of fever and cough for 2 weeks. The patient's medical history revealed that she had seronegative RA for 3 years. The patient had started initially on Methotrexate then she was switched to etanercept for 3 years. Initial workup done in emergency showed pancytopenia; right axillary inguinal lymphadenopathy and splenomegaly by computerized tomography scan. Lymph node excisional biopsy was consistent with peripheral T-cell lymphoma not otherwise specified stage IIIB.

Conclusion: Due to the pre-existent severe RA disease and prior methotrexate administration, it is difficult to establish a clear relationship between etanercept and the development of lymphoma in our case. Long term follow-up of patients with RA who are on anti TNF blockers is recommended.

Keywords: Lymphoma; PTCL; TNF-alpha antagonists; Rheumatoid arthritis

Introduction

Lymphoma association with Rheumatoid Arthritis (RA) is well established [1-3]. The mechanisms behind this association remain a matter of controversy. Thus, it is difficult to ascertain whether the development of a lymphoma is due to the disease activity or the immunosuppressive therapy [3,4]. For instance, it has been reported that patients with RA have an increased risk to develop lymphoma compared to the general population [3]. Furthermore, many reports have been published on malignant lymphomas that developed in patients with RA using Tumor necrosis α inhibitors (TNF-α) and methotrexate (MTX) [4-7].

The published literature and the WHO Classification of Tumors of Haematopoietic and Lymphoid tissues have identified an association between lymphomas arising in patients taking immunosuppressive agents for autoimmune conditions under "other iatrogenic immunodeficiency-associated lymphoproliferative disorders" [8]. Moreover, a 3-year prospective French RATIO registry demonstrated results of 38 cases of lymphoma, concluding that lymphomas associated with immunosuppression might occur in patients receiving anti-TNF therapy [9]. Furthermore, the Food and Drug administration Agency (FDA) announced a black box warning in September 2011 reporting that Lymphoma and other malignancies, some fatal, have been found in children and adolescent patients treated with TNF blockers. Still, the role of TNF blocker therapy in the development of malignancies is unknown, and no clear-cut associations have been established to whether lymphomas are a result of the underlying disease or only related to the patient's immunomodulatory drug therapy [9,10].

We here report the first case in Qatar for a patient with rheumatoid arthritis who developed peripheral T-cell lymphoma following etanercept and methotrexate therapy.

Clinical Presentation

A 38-year-old female was present at Hamad Hospital emergency department in Doha, Qatar with a history of fever and cough for 2 weeks. The patient's medical history revealed that she had seronegative RA for 3 years. The patient had started initially on MTX treatment for 6 months that was complicated with intolerance, which led to drug discontinuation. As her adherence to MTX had been quite poor, she was started on etanercept, a TNF-alpha inhibitor (Table 1). Laboratory tests upon clinical presentation revealed pancytopenia WBC: 1.3 cells/mm^3; absolute neutrophil count 0.6, hemoglobin level at 9.9 gr/dL; platelets 42 and elevated lactate dehydrogenase at 873 IU/L. Other laboratory results were within normal range; albumin: 40 g/L; Total protein 71 g/L Serum creatinine: 76 umol/L; urea nitrogen: 3.4

umol/L; Total bilirubin: 13.9 umol/L; alanine aminotransferase: 39 U/L; aspartate aminotransferase was slightly elevated: 82 U/L.

Blood cultures taken from the patient were negative for bacterial, fungal and mycobacterial pathogens. Furthermore, serologic tests for cytomegalovirus; herpes Simplex Virus; epstein-Barr virus; mumps; adeno virus; hepatitis C; hepatitis B and human immunodeficiency virus were negative.

Initial workup done in emergency by computerized tomography (CT) scan revealed right axillary inguinal lymphadenopathy and splenomegaly. Staging by PET/CT scan showed high uptake in the right axilla; left external iliac lymph nodes and diffuse splenic uptake with splenomegaly 11 cm. Both bone marrow aspiration and biopsy revealed normocellular marrow with multiple lymphoid aggregates of uncertain significance. Axillary lymph node excision was suggestive of T cell lymphoma not otherwise specified. Further molecular studies of T-cell gene rearrangement were performed at mayo clinic in Rochester, the results of which were positive for clonal T-cell receptor gene rearrangement in a polyclonal T-cell background. No Ebstein-Barr Virus (EBV) positive cells were identified by EBV in-situ hybridization or immunohistochemistry. All the findings were consistent with stage IIIB peripheral T-cell lymphoma not otherwise specified (NOS).

Medication	Regimen	Starting date	End date
Methotrexate	20 mg orally once weekly	Feb 26,2012	Jun 18,2012
Methotrexate	12.5 mg orally once weekly	Jun 18, 2012	Aug 18, 2012
Etanercept	50 mg subcutaneous once weekly	Apr 16,2012	Dec 23, 2013

Table 1: Rheumatoid arthritis medications.

Discussion

The risk of increasing hematological malignancies in patients with RA is well recognized in the literature. However, conflict evidence exist regarding the association between lymphoma and RA treatment. Many observational and interventional studies have looked into the association between anti-TNFs and the risk lymphoma development. A meta-analysis of nine randomized controlled trials (RCTs) of anti-TNF-alpha infliximab and adalimumab has shown a dose dependent increased risk of malignancies including lymphomas [10]. Seven of the trials co-administered MTX with the anti-TNFs, one of which included newly diagnosed RA patients (<3 years) and two trials administered anti-TNF alone in patients who had inadequate response to methotrexate. However, despite matching mechanisms of action, etanercept trials were not included in the meta-analysis. In addition, only two trials administered anti-TNF alone due to MTX inadequate response.

Additionally, based on an FDA analysis of 48 case reports of cancer in children and adolescents treated with TNF blockers, it was shown that malignancy-reporting rates for etanercept were higher compared to background rates for lymphomas [5]. On the other hand, observational studies underpin lack of increased lymphoma risk with etanercept. A registry-based study from France demonstrated an increased risk of lymphoma in patients receiving anti-TNF (standardized incidence rate (SIR) = 2.4, 95% CI 1.7-3.2) [9]. In this case control, Infliximab and adalimumab were associated with more risk of lymphoma compared to etanercept. Also, it was recognized that patients with severe rheumatic inflammatory diseases and not receiving TNF blockers exhibited increased lymphoma risk similar to patients receiving TNF blockers. However, patients included were receiving TNF blockers for any indication.

Furthermore, in a longitudinal study conducted by the National Data Bank for Rheumatic Diseases (NDB) for long-term outcomes of RA including 19562 patients, semi-annual questionnaires were administered to assess the lymphoma risk in patients on MTX, infliximab or etanercept [1]. Upon adjustment for age, sex, and disease duration, the study showed no difference in lymphoma development in patients receiving anti-TNF versus those not receiving anti-TNF, odds ratio (OR) = 1.0 (95% CI 0.6-1.8). In addition to conflicting evidence, rheumatoid arthritis alone is a risk factor for lymphoma and may confound the establishment of a clear relationship between anti-TNF-alpha and lymphoma risk [7-10]. Moreover, studies that have established increased lymphoma risk with anti-TNF-alpha included patients who were previously administered MTX. MTX has a U.S. box warning cautioning from malignant lymphoma [6]. Meanwhile, studies suggesting increased lymphoma risk with TNF blockers have high quality designs i.e. RCTs and meta-analyses, unlike studies in support of no lymphoma increased risk, which are mostly observational.

Conclusion

Due to the pre-existent severe RA disease and prior MTX administration, it is difficult to establish a clear relationship between etanercept and the development of lymphoma in our case. Nevertheless, etanercept may have contributed to the development of lymphoma. Long term follow-up of patients with RA who are on anti TNF blockers is recommended.

Ethical Considerations

A waiver of informed consent was obtained from Hamad Medical Research center.

Disclosure

The authors declare no conflict of interest.

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