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Hodgkin's lymphoma in a patient with ankylosing spondylitis following treatment with TNF inhibitors

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Abstract

Ankylosing Spondylitis (AS) is a chronic, systemic, inflammatory rheumatic disease affecting primarily axial skeleton. New treatment regimens such as Tumor Necrosis Factor inhibitors (anti-TNF) have been widely used. Patients with Rheumatoid Arthritis (RA) treated with anti-TNF agents might have increased risk of lymphoma occurrence. However, unlike RA, in AS an increased rate of lymphoma has not been reported. We present a patient with AS who developed Hodgkin's Lymphoma (HL) at the 5th year of golimumab therapy. However, he was previously treated with two other anti-TNF agents (infliximab and adalimumab). Although we report a single case it should be kept in mind that anti-TNF agents might predispose to lymphoma development in patients with AS and a close follow-up should be pursued in such patients.

Keywords

hodgkin's lymphoma; ankylosing spondylitis; tumor necrosis factor inhibitors; biopsy

Abbreviations

AS: Ankylosing spondylitis; HL: Hodgkin's lymphoma; NHL: Non-hodgkin's lymphoma; NSAIDs: Non-steroidal anti-inflammatory drugs; BASDAI: Bath ankylosing spondylitis disease activity index; TNF: Tumor necrosis factor; HLA: Human leucocyte antigen; MRI: Magnetic resonance imaging; RA: Rheumatoid arthritis; CTD: Connective tissue disease; EBV: Ebstein-barr virus; CMV: Cytomegalovirus

Introduction

AS is a chronic, inflammatory disease that predominantly affects axial skeleton and adversely affects quality of life. Some patients may also develop one or more articular, periarticular or non-articular features, sush as peripheral arthritis, enthesitis, daktylitis, uveitis or Inflammatory Bowel Disease (IBD) [1]. AS probably results from interaction of genetic predisposition involving HLA-B27 with environmental stimuli, such as bacterial infections [2]. In contrast, Hodgkin's lymphoma is a cancer of the lymphatic system characterized by a unique cellular composition developing in an inflammatory background.

Several autoimmune, systemic rheumatic diseases such as Rheumatoid arthritis and Sjögren's syndrome are associated with an increased risk of malignant lymphoma [3]. However, the association between spondyloarthropathies and Hodgkin lymphoma is uncommon. The exact mechanisms leading

from inflammation or autoimmunity to lymphoma remain unclear [4].

Tumor Necrosis Factor α (TNF-α) is a pleiotropic proinflammatory cytokine that plays a central role in pathogenesis of inflammatory rheumatic diseases. Baecklund et al reported that chronic inflammatory activity within the joints of patients with RA increased the risk of hematological malignancies [5]. Elevations of serum proinflammatory cytokines such as IL-1, TNF-α, IFN-γ in patients with AS have been postulated to induce $CD4^+$-T cells proliferation [6,7]. Anti-TNF medications commonly used to treat inflammatory rheumatic diseases, including AS, are highly effective in treating systemic inflammation. On the other hand these agents may cause various adverse effects such as increased tendency of infections, reactivation of latent tuberculosis, congestive heart failure, malignancies especially lymphoproliferative diseases (NHL or HL) and production of various autoantibodies [8]. There are few case reports describing the association of lymphoma with AS in cases receiving TNF inhibitors. We report a case of a 41-years old male patient with AS developing HL after a long time therapy with golimumab.

Case Report

A 41-year-old HLA-B27 positive caucasian male patient with a history of AS was admitted to our clinic for investigation of an acute swelling of left inguinal region, persisted over four weeks. The diagnosis of AS was made twelve years ago, based on inflammatory low back pain persisting for at least six months, limited spine and hip movements in physical examination, elevated acute phase reactants and bilateral grade IV sacroiliitis in Ferguson position. His baseline Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score was 4.9, initially he received Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for a short time and afterwards infliximab for a period of 4 years and discontinued because of secondary failure. Adalimumab was then administered for two years, which also secondary failed to induce adequate response. He receives golimumab for the last five years with adequate control of disease activity. However, at the 5th year of treatment an acute swelling of left inguinal region occurred.

During clinical evaluation, patient looked normal without any acute distress; also his vital signs were within normal range. Examination revealed an enlarged, painless and fixed left inguinal lymph node and hydrarthrosis of right knee which was aspirated. The rest of physical examination, regarding respiratory, cardiovascular, gastrointestinal and central nervous system was normal. Besides a monocytosis (10.10%), rest laboratories were normal. Viral serology showed positive EBV IgM, IgG and CMV IgG antibodies and synovial fluid analysis revealed a low-grade inflammation with lymphocytes predominance (Table 1). Ultrasonographic examination and magnetic resonance revealed a 5.2 x 3.5 cm sized mass that could be relevant to lymph node (Figure 1). Furthermore, computed tomography of thorax showed an axillary lymph node sized 1.9 x 1.7 cm.

Patient undergone surgical removal of inguinal lymph node and biopsy revealed Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL). Reed-Steinberg cells were CD30, CD15, CD23 positive and CD7, CMV, EBV, HHV-8, Cyclin D1 were negative in immunohistochemical analysis. Patient refused having B-symptoms and bone marrow biopsy was normal. Lymphoma was staged as IIIa and he received chemotherapy according to hematologist's instructions, while anti-TNF therapy was stopped. Our patient had no family cancer history and was not a smoker. Among environmental risk factors he had been exposed to EBV infection and previously received two different TNF inhibitors for a long period.

Discussion

Systemic autoimmune rheumatic diseases, especially RA, have an increased risk of lymphoma incidence [3]. However, this is not observed in AS. In literature, there are a few cases confirming a direct association of lymphoma with AS [9]. Furthermore a genetic linkage to HLA-B27 has been demonstrated to increase the risk of developing hematological malignancies in patients with AS. Au et al revealed that HLA-B27 carriers may have an increased risk of acute leukemia and those with concomitant AS may bepredisposed to malignant lymphoma [10].

Alternative risk factors for lymphomagenesis include exposure to infectious agents and environmental factors such as smoking. Infectious agents include Epstein-Barr virus (EBV), Human Immunodeficiency Virus (HIV), hepatitis C virus (HCV) and human T-cell lymphotropic virus 1 (HTLV-1). Among them, EBV and HCV are of particular interest. EBV infection might induce oncogenesis by persisting in B-cells and potentially transforms these cells leading to lymphoma development, including HL [11] . Patients with HL are reported to have increased EBV antibodies before or at the time of diagnosis [12]. Weiss et al observed EBV DNA existence in tissues obtained from patients with HL [13]. On the other hand smoking is an independent risk factor in both lymphomas and autoimmune/inflammatory arthritis. Various studies have linked smoking to specific variants of lymphomas, such as follicular, T-cell and Hodgkin's lymphoma [14].

Our patient was not a smoker and he had no family cancer history, so EBV infection and previous medication uptake (adalimumab, infliximab) should be considered as etiological factors. Immunosuppressive agents, such as TNF inhibitors and methotrexate, commonly used for treatment of rheumatic diseases might also act as risk factors predisposing to lymphoma. Anti-TNF therapy might contribute to and facilitate EBV infection.

In a Swedish case-control study Askling et al proposed that lymphoma risk in patients with AS in the absence of anti-TNFs was not increased [4]. Mariette et al observed a higher incidence of lymphoma occurrence when monoclonal antibody agents (adalimumab, infliximab) than soluble receptor agent (etanarcept) were used [15]. A recent large population study from Sweden and Denmark showed that treatment with TNFi was not associated with increased risk of cancer including lymphoma in patients with spondyloarthritis, when compared to TNFi-naïve patients [16].

According to the literature, the interval between the TNF inhibitor onset and development of lymphoma has been reported to be short (average 8 weeks), except one case that lymphoma's regression was observed following infliximab therapy (for 2 years) and switching to etanarcept [17]. Mariette et al revealed that in Connective Tissue diseases (CTDs) – including AS – the median time from onset of anti-TNF treatment and the first symptoms of lymphoma was 23.6 months. In five patients, receiving infliximab and adalimumab, lymphoma occurred while anti-TNF therapy had been discontinued 6.1 – 44.1 months before. Investigators observed an approximately linear relation between cumulative frequency of lymphoma and time from onset of anti-TNF therapy for the first or last anti-TNF agent received and did not differ among the medication that was received. In the same study, two factors were found to be independently associated with lymphoma development in patients receiving TNF inhibitors, 1) duration of anti-TNF therapy less than two years and 2) treatment with infliximab or adalimumab versus etanercept [15]. Our patient received infliximab and adalimumab for four and two years

respectively. The last five years therapy regimen was switched to golimumab. However, this interval seems to be incompatible with that one proposed by literature for lymphoma development.

In conclusion, the safety profile of TNF inhibitor therapy with respect to risk of lymphoma has been a concern. The majority of studies focusing the risk of lymphoma following exposure to TNF inhibitors, concerns RA. While in case of AS data are limited, making risk estimation difficult. Despite the fact that we present a single case, it should be kept in mind that anti-TNF medications may cause lymphoma in AS and physicians should be aware in order to facilitate early diagnosis and treatment. A genetic linkage to HLA-B27 has been demonstrated to increase the risk of developing hematological malignancies in patients with AS.

Figures

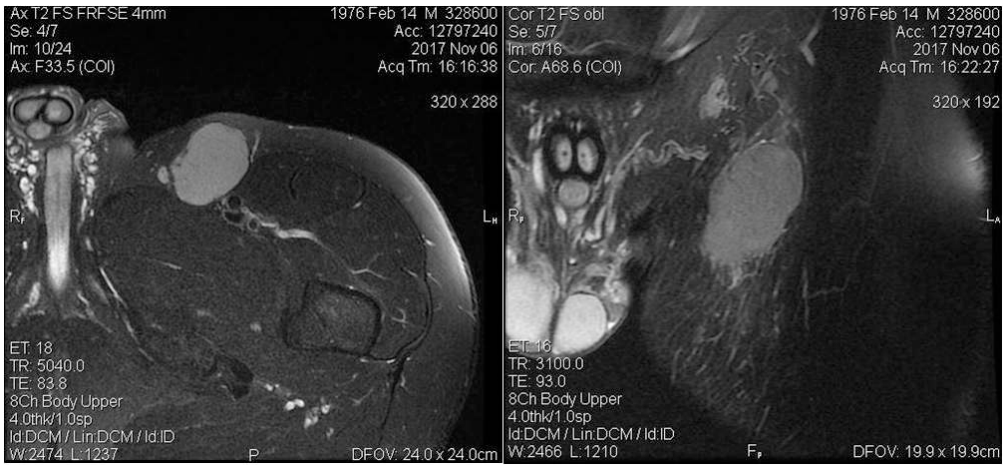

Figure 1: MRI showing the enlarged lymph node in left inguinal region

Tables

Table 1: Laboratory data

	Patient's values	Normal Values
HCT/Hbg	44.7/14.8	37-52%/12-18mg/dL
WBC (Monocytes)	8020 (1600)	4600-10500 (160-1000)
ESR	18	0-20 mm/h
CRP	0.33	0-0.5 mg/dL
EBV IgM	18.40	<13 IU/ml
EBV IgG	87.72	<10 IU/ml
CMV IgG	214.96	<25 IU/ml
HIV_Ag	Negative (0.10)	
HBsAg	Negative (0.25)	
Anti-HBc IgM	Negative (0.11)	
Anti-HCV	Negative (0.17)	
Synovial fluid/cells	1070 (N/L/M: 15/65/20%)	

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