Diffuse Large B Cell Lymphoma Secondary to Rheumatoid Artritis: Case Report

Romatoid Artrite Sekonder Difüz Büyük B Hücreli Lenfoma

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ABSTRACT Lymphoid malignancies are a heterogeneous group of neoplasms originating from B- and T-lymphocytes with an unexplained etiology. Several autoimmune conditions, especially Sjögren syndrome and rheumatoid arthritis (RA) are associated with lymphoma. Immunosuppressive agents like methotrexate may cause Epstein-Barr virus reactivation that can lead to development of lymphoma. The risk of lymphoma, especially Hodgkin lymphoma, is increased up to 2-3 times in RA patients compared to normal population. The cause of increased risk is independent from the immunosuppressive medication. We report here an unusual case of diffuse large B-cell lymphoma in a patient with RA receiving methotrexate treatment, after obtaining the approval of the informed consent of the patient.

Key Words: Lymphoma; arthritis, rheumatoid; methotrexate

ÖZET Lenfoid malignensiler B ve T lenfositlerden köken alan heterojen bir neoplazm grubudur ve etiyolojileri tam olarak açıklanmamıştır. Birkaç otoimmün hastalık, özellikle Sjögren sendromu ve romatoid artrit (RA) lenfoma ile ilişkilidir. Metotreksat gibi immünsüpresif ilaçlar lenfoma gelişimine yol açabilecek olan Epstein-Barr virüs reaktivasyonunu reaktive edebilir. Normal populasyonla kıyaslandığında, romatoid artrit hastalarında lenfoma riski, özellikle Hodgkin lenfoma riski 2-3 kat artmıştır. Artmış riskin nedeni immünsüpresif ilaçlardan bağımsızdır. Burada metotreksat tedavisi alan RA'lı bir hastada nadir görülen difüz büyük B-hücreli lenfoma olgusunu, hastanın aydınlatılmış onamını aldıktan sonra sunuyoruz.

Anahtar Kelimeler: Lenfoma; artrit, romatoid; metotreksat

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Lymphoid malignancies are a heterogeneous group of neoplasms originating from B- and T-lymphocytes. Although the etiology of lymphoid malignancies remains largely unexplained, immune deficiency is the strongest known risk factor, with human immunodeficiency virus (HIV) infection conferring more than 20-fold increased risk of non-Hodgkin lymphoma (NHL).[1] Several autoimmune conditions, including rheumatoid arthritis (RA), Sjögren syndrome and systemic lupus erythematosus have consistently been associated with NHL.[2] Immunosuppressive medications (e.g., methotrexate for RA) may cause reactivation of Epstein-Barr virus (EBV) which can lead to development of lymphoma especially in post-transplant patients.[3] The risk of lymphoma, especially Hodgkin lym-

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phoma (HL), is increased up to 2-3 times in RA patients compared to normal population. The cause of increased risk is independent from the immunosuppressive medication.[4] We report here an unusual case of diffuse large B-cell lymphoma (DL-BCL) in a patient with RA receiving methotrexate (MTX) treatment.

CASE REPORT

A 52-year-old man with a 7-year history of RA had been treated with 15 mg/week MTX and 5 mg oral prednisolone on alternate days for the last 6 years. Besides his new-onset symptoms, he also suffered from arthralgia in his hands and feet over one year. In December 2009, he presented with cough and dyspnea that had been present for 3 months. Night sweats and weight loss symptoms had been present for one month. Physical examination revealed rhonchi in upper right lung. Arthralgia was present on palpation of distal metacarpo-phalangeal joints of both hands. There was no peripheral lymphadenopathies or hepatosplenomegaly. Laboratory investigations showed no abnormalities except for a raised lactate dehydrogenase level (310 U/L). Plain chest X-ray showed widening of the mediastinal margins. Computed tomography of thorax revealed conglomerated, 3 x 3.5 cm in size, intense, well demarkated, hypodense lymphadenopathies located in the right paratracheal area. The patient underwent video-assisted thoracoscopy and biopsy. The biopsy showed a population of mainly medium-sized, uniform lymphoid cells with narrow cytoplasms and often multiple nucleoli. Immunohistochemical investigation was done; bcl-2 was positive, bcl-6 was negative and MUM-1 was not evaluated due to unavailability. Based on these clinical, histological and phenotypical data, the diagnosis of CD20 positive DL-BCL was made. At this point, the patient was evaluated with FDG-PET-CT for staging. FDG-PET-CT revealed increased metabolic activity in the right paratracheal and right hilar and right paraaortic thoracic cage (SUD max= 43.82). The patient was regarded as Stage II DL-BCL according to FDG-PET-CT. Previous to chemotherapy, the patient's serological markers for hepatitis B, C and HIV were checked and they were negative. MTX was discontinued and rituximab (375 mg/m^2 in day 1) together with cyclophosphamide, doxorubucin, oncovin and prednisolone (R-CHOP) as first line chemotherapy regimen was applied for 4 cycles. A complete remission was achieved. Involved field radiotherapy after four cycles of chemotherapy was added to treatment protocol of the patient as the consolidation therapy. During the chemotherapy the patient's symptoms related with RA were also improved.

DISCUSSION

RA is a chronic autoimmune disease that is also characterized by the presence of inflammation. It affects approximately more than 1% of the adult population worldwide. Epidemiological studies indicate that RA is associated with an increased risk of lymphoma compared to normal population.[5] Investigations that have focused on etiology of specific histologic subtypes of NHL revealed their differing incidence patterns, clinical features, gene profiles and associations with HIV infection. However, low prevalence of autoimmune conditions and the rarity of some NHL subtypes had limited the studies investigating associations between autoimmune conditions and NHL subtypes.[6] Hypothesized possible mechanisms for an increased risk of lymphoma in RA patients include the fact that persistent immunologic stimulation (which may lead to clonal selection and predispose CD5+ B cells to malignant transformation) of RA results in a decrease of the number and function of T-suppressor lymphocytes (including those directed against the pro-oncogenic EBV), and decreases the natural killer cell activity in the synovial fluid, tissues, blood, and lymph.[7]

MTX is a folate antagonist and it enables to lower the steroid dose significantly in treatment of autoimmune diseases like RA. An association between cancer and MTX, that is a commonly prescribed disease-modifying anti-rheumatic drug (DMARD) used to treat RA, has also been suggested. There have been numerous cases of cancer reports in patients with RA treated with MTX, particularly lymphoma. Additionally, in some cases

the tumors have regressed or disappeared when MTX was discontinued. Although these reports have prompted to concern that MTX itself is oncogenic in patients with RA, studies to date failed to prove this conclusion. Recent studies and meta-analyses evaluating the effect of MTX and anti–tumor necrosis factor therapy in lymphoma revealed that the results were unable to establish a causal relationship between the RA treatments and development of lymphoma. The authors have also postulated that the observed increased lymphoma incidence may reflect channeling bias that is, channeling of high risk patients to DMARD treatment.[8]

Rituximab is a genetically engineered chimeric monoclonal antibody that targets CD20 positive B cell. Food and Drug Administration (FDA) has approved it for the treatment of relapsed or refractory, low-grade or follicular CD20 positive B-cell NHL and for diffuse, large B-cell CD20 positive NHL in combination with approved chemotherapy. Clinical trials of rituximab have demonstrated significant efficacy and adequate safety in modifying the symptoms of RA and have provided further evidence of the role of B cells in the disease pathogenesis.[9] The current guidelines provide evidence-based advice on the use of rituximab either alone or in combinations for physicians and rheumatologists to treat RA especially in patients with active [disease activity score 28 (DAS-28) ≥3.2] rheumatoid factor-positive RA who have had an incomplete response or intolerance to an adequate course with TNF inhibitors.[10] We applied rituximab to our case as a part of standard chemotherapy protocol, besides its effects on lymphoma, rituximab alleviated symptoms of RA in our case. At the end of chemotherapy regimen, our patient's symptoms related to RA were improved. Radiotherapy was added to treatment protocol of the patient after 4 cycles of chemotherapy due to equal efficacy in remission and higher efficacy for consolidation of 4 cycles of chemotherapy plus radiotherapy when compared to 8 cycles of chemotherapy in the early stage of lymphoma (stage I or II) according to literature.[11,12]

Rheumatoid disease is associated with an increased risk of developing lymphoma, even in patients who are not treated with immunosuppressive therapy. Since spontaneous remission of lymphoma after immunosuppressive drug withdrawal has been documented, it has been speculated that immunosuppressive therapy is likely to be an additional factor for lymphoma development. A genetic predisposition has also been suggested as a possible factor in the development both of lymphoma and RA, but yet there is little evidence to support this hypothesis.[5]

In conclusion, the risk of a secondary malignancy should be kept in mind in patients with autoimmune diseases like RA, especially if the patient is previously treated with immune-modulator drugs like MTX. Patients should be closely followed-up for signs and symptoms of a lymphoid malignancy. If a secondary malignancy is detected and verified clinically and pathologically, MTX should be stopped. Rituximab has a possible important place in the treatment of CD 20 positive NHL, especially when it develops in symptomatic RA patients.

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