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

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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


Anahtar Kelimeler: Lenfoma; artrit, romatoid; metotreksat


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-
Lymphoma (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. 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 ronchi in upper right lung. Arthralgia was present on palpation of distal metacarpophalangeal 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 demarcated, 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 regarded as Stage II DL-BCL according to FDG-PET-CT. 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/m² in day 1) together with cyclophosphamide, doxorubicin, 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. 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. 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.

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 onco-
genic 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, chan-
neling 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 ap-
proved it for the treatment of relapsed or refrac-
tory, 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 patho-
genesis. 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 [dis-
 ease activity score 28 (DAS-28) ≥3.2] rheumatoid
factor-positive RA who have had an incomplete re-
 sponse or intolerance to an adequate course with
TNF inhibitors. 10 We applied rituximab to our case
as a part of standard chemotherapy protocol, be-
sides its effects on lymphoma, rituximab alleviated
symptoms of RA in our case. At the end of
chemotherapy regimen, our patient’s symptoms re-
lated to RA were improved. Radiotherapy was
added to treatment protocol of the patient after 4
cycles of chemotherapy due to equal efficacy in re-
mission 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 lit-
erature. 11,12

Rheumatoid disease is associated with an in-
creased risk of developing lymphoma, even in pa-
 tients who are not treated with immunosuppressive
therapy. Since spontaneous remission of lymphoma
after immunosuppressive drug withdrawal has
been documented, it has been speculated that im-
munosuppressive therapy is likely to be an addi-
tional 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 malig-
nancy should be kept in mind in patients with au-
toimmune diseases like RA, especially if the patient
is previously treated with immune-modulator
drugs like MTX. Patients should be closely fol-
lowed-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 im-
portant place in the treatment of CD 20 positive
NHL, especially when it develops in symptomatic
RA patients.

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