**MYC/BCL2 Double-hit Lymphoma in a Patient with Rheumatoid Arthritis Associated with Methotrexate Treatment**

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**Abstract**

Several reports have suggested an increased risk of malignant lymphoma in patients with rheumatoid arthritis treated with methotrexate (MTX). We herein describe the case of a 71-year-old woman with rheumatoid arthritis who developed MYC/BCL2 double-hit lymphoma associated with MTX therapy. She developed a fever and lymphadenopathies over a 2-week period and had elevated levels of soluble IL-2 receptor. Inguinal lymph node and bone marrow biopsies showed diffuse large B cell lymphoma. Fluorescent in situ hybridization revealed MYC and BCL2 gene rearrangements in her lymphoma cells. Accordingly, a diagnosis of MYC/BCL2 double-hit lymphoma was made. This is the first reported case of a double-hit lymphoma associated with MTX therapy.

**Key words:** double-hit lymphoma, MYC, BCL2, rheumatoid arthritis, methotrexate

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**Introduction**

The incidence of lymphoproliferative disorders (LPD) including lymphoma in patients with rheumatoid arthritis (RA) is 2.0-5.5 times higher than that in individuals without RA (1, 2), and methotrexate (MTX), one of the most widely used pharmacological agents for the treatment of RA, may contribute to the development of LPD.

Lymphomas with chromosomal rearrangements affecting the MYC/8q24 locus in combination with other genetic abnormalities, such as BCL2 or BCL6, are often referred to as double-hit lymphomas. Double-hit lymphomas are generally associated with a poor survival (median overall survival, 0.2-1.5 years) (3-9).

Various histological subtypes of lymphoma have been reported to be associated with MTX (10); however, there has been no report of double-hit lymphoma associated with MTX. We herein describe the case of a 71-year-old woman with RA who developed MYC/BCL2 double-hit lymphoma associated with MTX.

**Case Report**

A 71-year-old woman with RA was admitted to our hospital due to a persistent fever and lymphadenopathy. She experienced night sweats and fatigue for several weeks prior to admission; there was no history of weight loss. She had been diagnosed with arthritis 2 years previously, which was positive for rheumatoid factor. Initial treatment with bucillamine did not improve her RA, thus her primary physician prescribed MTX at 4 mg/week (22 months previously), gradually increasing the dose up to 16 mg/week due to her symptoms. Her RA then improved and remained stable without the requirement of other immunosuppressive or biological agents. The cumulative dose of MTX had become 1,232 mg. Bucillamine had been stopped 2 months previously. She also had a history of early stage gastric cancer, which had occurred 7 years previously.

On examination, the patient’s general condition was fair,
and her performance status was diagnosed as 1. Her body temperature was 38°C and pulse rate was 70 beats/min. Respiratory and abdominal examinations were unremarkable. Bilateral lymphadenopathy affecting the neck, axillary, and inguinal lymph nodes was observed. A neurological examination revealed no abnormalities. Slightly symmetrical polyarthritis affecting the proximal interphalangeal and metacarpophalangeal joints of the hands was noted. Laboratory examinations revealed serum levels of C-reactive protein at 5.4 mg/dL, lactate dehydrogenase (LD) at 1,446 IU/L, and soluble interleukin-2 receptor (sIL-2R) at 3,860 U/mL. Serum IgG reactions were positive (×160) for Epstein-Barr virus (EBV)-viral capsid antigen, EBV-EADR: EBV early antigen, EBNA: EBV nuclear antigen revealed a CD19+ CD20+ CD5 CD10 phenotype of pathological cells with clonal k light chain. EBV-encoded ribonucleic acid in situ hybridization (ISH) was negative. Cytogenetic and fluorescence ISH analyses demonstrated gene rearrangements of the IgH/MYC and IgH/BCL2 gene loci with a normal karyotype (Fig. 3). Iliac bone marrow biopsies demonstrated infiltration with lymphoma cells (Fig. 2E, F). The nucleated cell count was 9.5 × 10⁶/mm³ and the ratio of lymphoma cells was 42.8% in bone marrow aspiration. A diagnosis of clinical stage IV B double-hit lymphoma with a high-risk international prognostic index was accordingly made.

MTX therapy was stopped immediately. One week later, the serum LD levels decreased from 1,446 IU/L to 915 IU/L and the patient’s body temperature partially decreased. Her inguinal lymph node reduced from 28 mm to 20 mm in size on a physical examination. Because the clinical presentations were partially resolved following the withdrawal of MTX, she was diagnosed with double-hit lymphoma associated with MTX. However, the serum LD levels remained elevated (915-991 IU/L), and her fever and lymphadenopathy still remained after 2 weeks. Eight cycles of rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) were therefore initiated. Although double-hit lymphoma is known to have a poor prognosis, more intensive chemotherapy was judged unsuitable due to the age of the patient. The symptoms of lymphadenopathy, elevated LD and sIL-2R levels, and bone marrow in-
filtration improved and a complete remission (CR) was subsequently obtained from this treatment. However, 8 months later, the patient developed a temporal lobe tumor and epilepsy. A tumor biopsy showed DLBCL, thereby indicating relapse at the central nervous system (CNS). Second-line chemotherapy consisting of rituximab and high-dose cyclophosphamide was initiated for 2 courses, and subsequent whole brain irradiation for 30 Gray was undertaken without intrathecal chemotherapy. After these treatments, a second CR was obtained. There was no evidence of further recurrence at 3 years following her initial presentation. Through this clinical course, the patient’s RA remained stable, not necessitating the readministration of MTX, any anti-rheumatic drugs or other immunosuppressive drug therapies, including corticosteroid therapy.

Discussion

An increased incidence of LPD including malignant lymphoma has been reported in RA patients (1, 11-13), mainly in patients treated with MTX or antagonists of tumor necrosis factor-α; this has been categorized as “other iatrogenic immunodeficiency-associated lymphoproliferative disorders” in the WHO classification (14). Various histological subtypes of lymphoma have been reported in patients with RA, with DLBCL accounting for almost 40-70% of these cases (the present case being one of these) (10-13). Lymphoma development following the initiation of MTX therapy reportedly ranges between several weeks and several years (10-13). Niitsu et al. reported the median duration of
MTX treatment as being 56 months, with a median cumulative dose of 864 mg in RA patients with LPD (15). The present patient was treated with MTX for 22 months with a cumulative dose of 1,232 mg. In the present case, the resolution of symptoms and lymphadenopathy and the decreased serum LD levels following the withdrawal of MTX before chemotherapy initiation strongly indicated an association between the two distinct gene rearrangements, MYC and BCL2; however, a history of follicular lymphoma was absent in the present case. The recent concept of screening MYC/BCL2 double-hit lymphoma, by assessing the MYC and BCL2 protein expression by immunohistochemistry, may have prognostic significance. Hu et al. showed that DBCL patients with MYC/BCL2 coexpression, with or without MYC or BCL2 gene rearrangements, have a poorer prognosis (17). Thus, it would have been thought necessary to confirm the coexpression of the MYC and BCL2 proteins with the recent availability of anti-MYC antibodies suitable for immunohistochemistry staining in paraffin-embedded tissues.

In conclusion, we presented the first report of a case of MYC/BCL2 double-hit lymphoma associated with MTX treatment. The potential for aggressive lymphoma development should be considered when initiating MTX therapy, particularly given the widespread use of MTX in the treatment of RA.

The authors state that they have no Conflict of Interest (COI).

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