

Spontaneous Remission of Hodgkin's Lymphoma in a Patient with Systemic Lupus Erythematosus after Withdrawal of Methotrexate

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Methotrexate is often used in patients with systemic lupus erythematosus for effective disease control and steroid-sparing, and has been known to involve the development of lymphoproliferative disorders for patients with autoimmune diseases. We report a case of spontaneous regression of Epstein-Barr virus-positive methotrexate-associated Hodgkin's lymphoma in a 24-year-old woman with systemic lupus erythematosus. Following 6 months of treatment with low-dose methotrexate, the patient developed a neck mass in the right submandibular area. A computed tomography scan of the neck, chest and abdomen

revealed multiple enlarged lymph nodes. Excisional biopsy of the neck masses confirmed infiltrations of malignant lymphoid cells that were positive for CD15, CD30, and Epstein-Barr virus-encoded RNA. Reduction of the mass was observed 3 weeks after withdrawing from the methotrexate treatment. At 7 months after initial presentation, computed tomography revealed near-complete regression of lymphadenopathy. After 30 months, the patient was still in complete clinical remission.

Key Words. Hodgkin's lymphoma, Methotrexate, Systemic lupus erythematosus

Introduction

Methotrexate (MTX), an inhibitor of dihydrofolate reductase, is mainly administered to patients with autoimmune diseases such as rheumatoid arthritis to suppress the exaggerated immune response. Less commonly, MTX is used in patients with systemic lupus erythematosus (SLE) to reduce daily glucocorticoid dose and aid in controlling arthritis and skin manifestations (1,2). Recent reports have suggested that development of lymphoproliferative disorders or lymphomas in patients with autoimmune diseases is associated with receiving MTX (3,4). Although the true contribution of MTX to the pathogenesis of lymphoproliferative disorders remains unknown, its clinical relevance requires particular attention to the patients taking MTX and careful management of lymphoproliferative disorders or lymphomas when they occur.

Unlike in rheumatoid arthritis, few cases describe sponta-

neous remission of Hodgkin's lymphoma following withdrawal of methotrexate in a patient with SLE. Here we report a case of development of Hodgkin's lymphoma (HL) in a patient with SLE receiving MTX and spontaneous regression only after discontinuation of MTX.

Case Report

A 24-year-old female with SLE presented with a right submandibular mass, that had been gradually enlarging over since 3 months ago. The mass was fixed, firm and tender. The patient also complained of fever (measured up to 38.0°C), and night sweating, and weight loss of 2 kg over a month. A diagnosis of SLE had been made 9 years earlier on the basis of fever, malar rash, vasculitis of the central nervous system, leukopenia, thrombocytopenia, and positivity for anti-nuclear (ANA), anti-double strand DNA (dsDNA), and antiphospho-

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lipid antibodies. The patient had ever been treated for hemophagocytic lymphohistiocytosis, sepsis, lupus myositis, and vitreous hemorrhage, and her disease had been controlled readily by outpatient clinic visits since a hospitalization for herpes zoster infection 3 years ago. At the time of presentation, she re-

ceived prednisolone 7.5 mg, mycophenolate mofetil (MMF) 1,000 mg, aspirin 100 mg daily and MTX 10 mg weekly. MMF had been added to her drug regimen 35 months previously, and MTX was added 6 months previously for effective disease control and steroid-sparing.

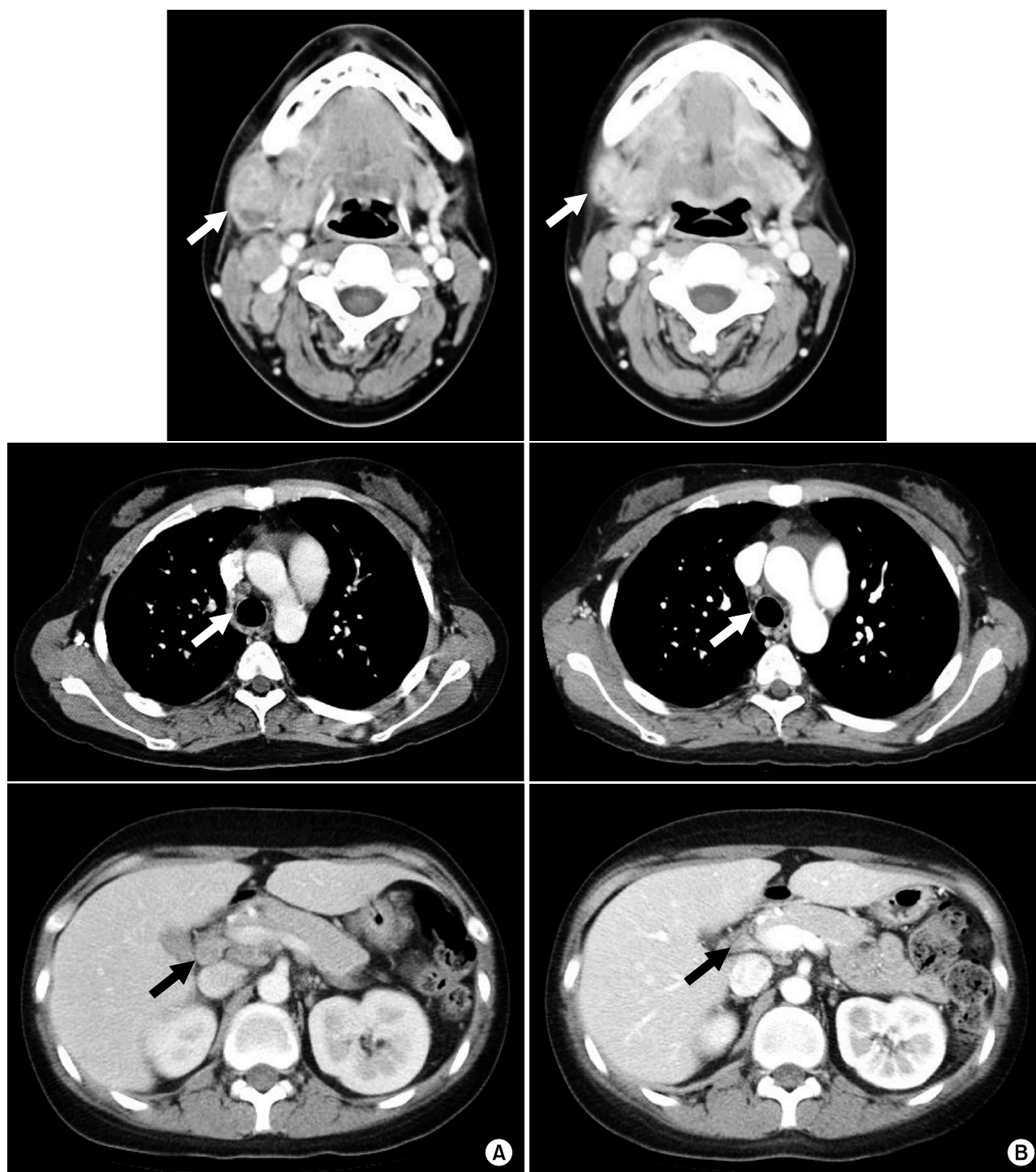


Figure 1. CT scan of neck, chest and abdomen. (A) Multiple enlarged lymph nodes are observed in the right submandibular, upper right paratracheal and the porta hepatis and portocaval space. (B) 7 months after withdrawal from MTX, near-complete regression of lymphadenopathies are noted.

On physical examination, the patient was normotensive (blood pressure, 110/70 mmHg), and had tachycardia (pulse, 102 beats/min), and a fever (38.2°C). She was found to have a normocytic normochromic anemia (hemoglobin, 9.3 g/dL, mean corpuscular volume, 91.0 fL). White blood cell (6,530/mm³) and platelet counts (227,000/mm³) were within normal range. Erythrocyte sedimentation rate was 78 mm/h and C-reactive protein (CRP) was 58.89 mg/L. Lactate dehydrogenase was 819 IU/L (reference, 200~400 IU/L). Serologic tests revealed a C3 complement of 73.6 mg/dL (reference, 90~180 mg/dL), a C4 complement of 11.1 mg/dL (reference, 12~40 mg/dL), total hemolytic complement activity of 41.2 U/mL (reference, 23~46 U/mL), ANA of 1 : 640 with a homogenous pattern, and an anti-dsDNA of titer 53.4 IU/mL (reference, <20 IU/mL).

A computed tomography (CT) scan of the neck revealed multiple enlarged lymph nodes along the right submandibular and internal jugular chain, measuring up to 3.1×2.3 cm, which were suspicious of lymphoma (Figure 1A). An excisional biopsy of

the neck mass was performed. Histopathological evaluation and immunohistochemistry revealed infiltration of malignant lymphoid cells that were positive for CD15 and CD30 but negative for CD20 (Figure 2). Histochemical stains for Epstein-Barr virus (EBV)-encoded RNA (EBER) were positive. A CT scan of the chest revealed several enlarged lymph nodes in the right upper paratracheal, prevascular, and paratracheal areas. On a CT scan of the abdomen, multiple homogeneously enhanced enlarged lymph nodes were noted in the porta hepatis and portocaval space; the largest one was located in the anterior aspect of the right common hepatic artery and was about 2.5 cm (Figure 2). Bone marrow examination showed no evidence of malignant cell infiltration. Additional serologic tests showed an EBNA IgG antibody titer of 34 U/mL and an EBV-DNA copy number of 16,250/mL. The patient was diagnosed with Ann Arbor Stage IIIB Hodgkin's lymphoma (5).

After completion of the lymphoma staging over two weeks of hospitalization, ABVD-based (Adriamycin, bleomycin, vin-

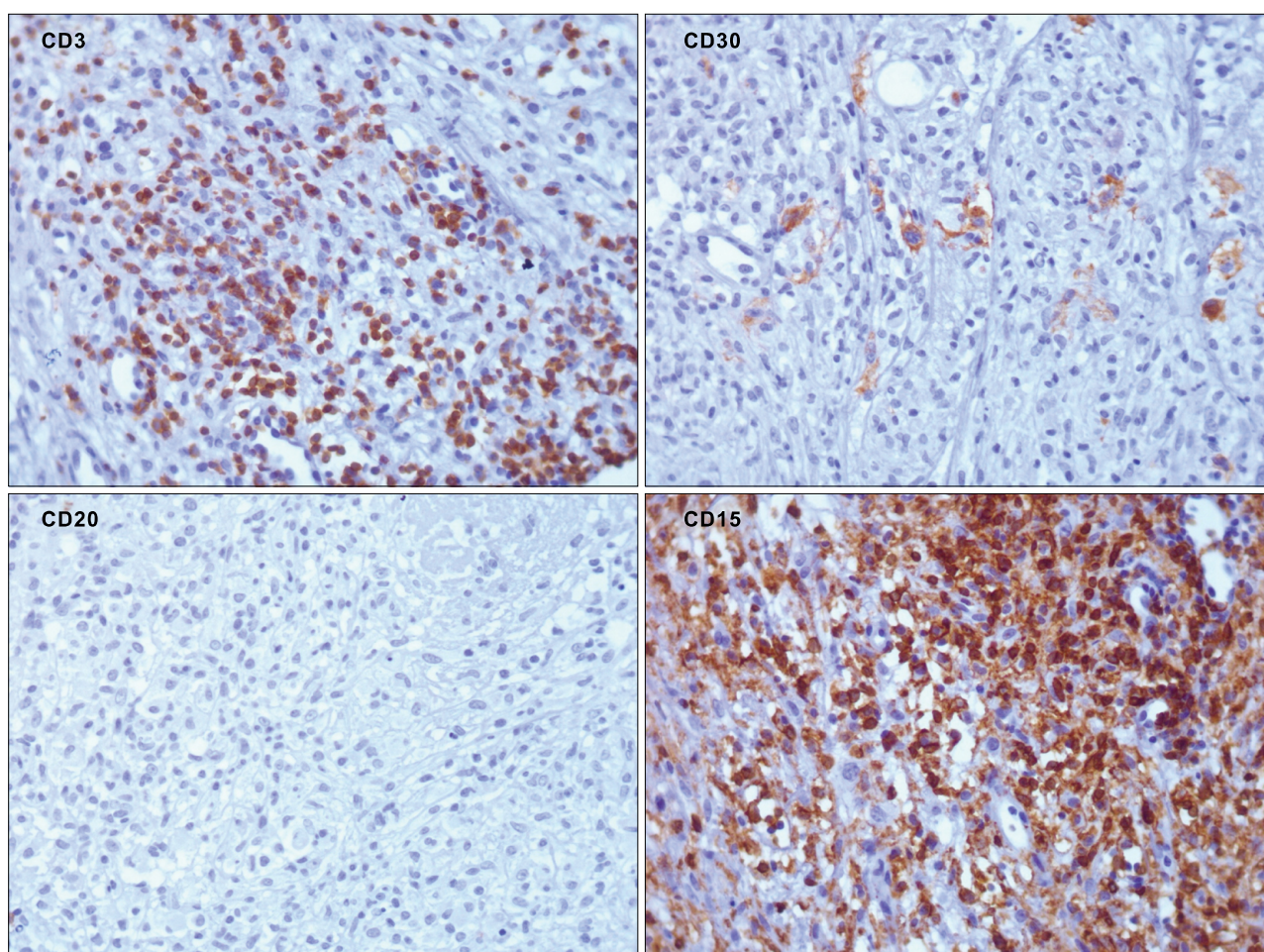


Figure 2. Immunohistochemical staining of the cervical lymph node biopsy specimen demonstrating positive for CD15, CD30 and negative for CD20 (×400).

blastine, dacarbazine) chemotherapy was planned. One week later after discharge, the patient was admitted again for chemotherapy. However, before beginning chemotherapy, around 3 weeks after the discontinuation of MTX, a reduction in the neck mass lesion was observed. A second round of CT scans of the neck, chest and abdomen showed regression of the mass lesions (Figure 1, 2). A lymphoma specialist advised that the lesion would not be overt lymphoma. After careful consideration with the specialist, we decided on close observation without starting chemotherapy. Afterward, only prednisolone 7.5 mg was prescribed for her disease control. At 7 months after the first CT scans, a third CT scan of the neck confirmed the complete disappearance of the lymphoma (Figure 1). To date, 30 months after initial presentation, the patient is still in complete clinical remission.

Discussion

The World Health Organization classification of 2001 recognizes the clinical setting of iatrogenic immunosuppression caused by MTX treatment to be associated with an increased incidence of lymphoproliferative disorders (6). MTX-induced lymphoid proliferation or lymphoma characteristically develops during the treatment of autoimmune disease, and the majority of reported cases have occurred in patients with rheumatoid arthritis (7). Fewer cases have affected patients with psoriasis, dermatomyositis, Sjögren's syndrome, or SLE (4,8). The described changes range from benign lymphoid hyperplasia to non-Hodgkin's lymphoma, most often large B-cell lymphoma, lymphoproliferation resembling Hodgkin's lymphoma, or Hodgkin's lymphoma (4).

A few previous reports documented development of lymphoproliferative disorders in patients with SLE that might be associated with use of methotrexate. Sliesoraitis et al (7) reported a case of mediastinal Hodgkin's lymphoma developed in a 48-year-old man, who had been taking a standard dose of MTX over 2 years. Nasr et al. (9) described diffuse large B-cell lymphoma involving the renal parenchyme in a 73-year-old woman, who had been treated with MTX 7.5 mg weekly for 3 years. In a case series of therapy-related lymphomas in patients with autoimmune diseases included a case of diffuse large B-cell lymphoma of the small intestine that developed in a 42-year-old woman with SLE, who had been prescribed with MTX for 10 years (8). The former two cases were negative for EBV and the latter was positive. All patients had received chemotherapy and/or anti-CD20 therapy and showed complete remission at a follow-up. In contrast, the case we report demonstrated complete remission only with withdrawal of MTX, suggesting a more direct association between use of

MTX and development of lymphoma in SLE patients.

EBV is associated with 30~50% of Hodgkin's lymphoma cases although the true contribution of EBV to the pathogenesis of Hodgkin's lymphoma remains unknown (10). EBV infection is more prevalent in individuals with SLE than in the general population (11) and the EBV load is abnormally elevated in the blood of SLE patients (12). SLE itself confers an increased risk for development of lymphoproliferative disorders including Hodgkin's lymphoma (13); this might be associated with the EBV seropositivity and its high load. The patient in this report was also seropositive for EBV and her plasma EBV copy number was high. Recent data suggest that MTX has a unique ability to stimulate the reactivation of latent EBV and encourage uninhibited expansion of EBV-infected B cells, possibly leading to promote EBV-positive lymphoproliferative disorders (14). Indeed, patients treated with MTX-containing regimens have statistically significantly higher mean EBV loads in their blood than patients treated with immunosuppressing regimens that do not include MTX (14). Moreover, a recent national prospective study comprising the entire French population studied over a period of 3 years suggested an increased risk for lymphoma, in rheumatoid arthritis patients treated with MTX (15). Thus, it is speculated that MTX makes EBV-seropositive SLE patients more vulnerable to development of lymphoproliferative disorders.

It is intriguing that lymphoma might regress only with MTX withdrawal. Some studies suggested that chronic iatrogenic immunosuppression by MTX leads to loss of immune surveillance, which is possibly restored by treatment discontinuation with subsequent control of the pathway of lymphomagenesis pathway (4). However, we cannot exclude that MTX-associated lymphoma is not overt lymphoma but simply lymphoproliferation. Significant numbers of MTX-associated lymphoproliferative disorders, that were diagnosed as non-Hodgkin's lymphoma or Hodgkin's lymphoma and spontaneously regressed after discontinuation of MTX, did not showed monoclonality (4). Finally, the development and spontaneous regression of MTX-associated lymphomas or lymphoproliferative disorders might depend on the interplay among EBV infection, iatrogenic immunosuppression and lymphoproliferation clonality.

The patient in this case report had also taken MMF, which is reported to be associated with development of non-Hodgkin's lymphoma in a transplant population (16). However, this association was not confirmed in a recent large-scale prospective study of renal transplant patients treated with MMF (17). The association has not been described clearly in patients with SLE taking MMF alone or in combination with corticosteroids. Three cases of lymphoma in SLE patients who had been taking

MMF for lupus nephritis have been reported to date (18-20). All were primary lymphomas of the central nervous system (PCNSL), which is known to be a complication of systemic immunosuppression following organ transplantation and HIV infection (20). After discontinuation of MMF, two patients underwent chemotherapy and one died from cerebellar hemorrhage complicated by brain biopsy. Therefore, MMF might foster an immunosuppressive environment that make a patient vulnerable to development of PCNSL. However, the association of MMF with PCNSL remains unclear in patients with lupus nephritis.

Summary

MTX is often used to lower the daily steroid dose in SLE patients with moderate disease activity, although it does not confer a significant advantage in decreasing disease activity (1,2). If lymphomas or lymphoproliferative disorders are developed in SLE patients receiving immunosuppressive regimens containing MTX, it is recommended that MTX withdrawal and closely monitoring for at least 4 weeks is recommended before the start of chemotherapy. Regression occurs within a time interval of 4 weeks after discontinuation of MTX in most of reported cases (4).

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