

[CASE REPORT]

Pulmonary Intravascular Large B-cell Lymphoma in a Patient Administered Methotrexate for Rheumatoid Arthritis

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Abstract:

A 70-year-old woman with rheumatoid arthritis undergoing methotrexate (MTX) treatment presented with dyspnea and a subfever. Computed tomography (CT) revealed a diffuse minimal ground-glass appearance in both lungs and splenomegaly. The gallium scintigram showed a diffuse, mild uptake in both lungs and the spleen. The lung biopsy specimen revealed the presence of CD20-positive atypical lymphocytes in the small pulmonary vessels. The patient was diagnosed with pulmonary intravascular diffuse large B-cell lymphoma (IVLBCL) and exhibited spontaneous regression after MTX was discontinued. This report describes a rare case of MTX-associated lymphoproliferative disorder expressing pulmonary IVLBCL.

Key words: diffuse large B-cell lymphoma, hypoxia, intravascular lymphoma, methotrexate, rheumatoid arthritis

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Introduction

Methotrexate (MTX) is a key drug for the treatment of rheumatoid arthritis (RA). The differential diagnosis of pulmonary diseases presenting as diffuse infiltration and hypoxia during treatment with MTX includes infection, interstitial pneumonia associated with RA, and MTX-associated interstitial pneumonia (1, 2). MTX is also known to induce lymphoproliferative disorders (MTX-LPDs), and diffuse large B-cell lymphoma (DLBCL) is the most common type (3-9).

Intravascular LBCL (IVLBCL) is a rare type of DLBCL, and tumor cells are seen only in the blood vessel lumen (10). There are some clinical challenges associated with IVLBCL, including the difficulty of making a diagnosis due to the non-specificity of the symptoms, such as a

persistent fever, as well as the aggressive and potentially fatal disease progression. Only three cases of MTX-associated IVLBCL have been reported (11-13).

We herein report an extremely rare case of pulmonary IVLBCL with hypoxia and dyspnea in a patient with RA receiving MTX. The diagnosis was confirmed using a lung specimen obtained by video-associated thoracic surgery (VATS).

Case Report

A 70-year-old woman with RA who had been treated with MTX (12-16 mg/week) for 7 years was referred to our hospital with complaints of progressive dyspnea on exertion and an intermittent subfever. The patient had a smoking history of 25 packs a year. Her body temperature was 37.3°C, respiratory rate was 16 breaths/min, and oxygen saturation

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was 90% on room air. There were no pain spots, skin eruptions, or lymphadenopathy. Physical and neurological examinations showed no abnormal findings.

An initial laboratory examination showed a white blood cell (WBC) count of 8,600 cells/ μ L (66.5% neutrophils, 17.1% lymphocytes), lactate dehydrogenase (LDH) level of 947 U/L, and C-reactive protein (CRP) level of 3.28 mg/dL. The serum levels of soluble interleukin-2 receptor (sIL-2R), KL-6, and matrix metalloproteinase (MMP)-3 were 5,280 U/mL (normal range, 121-613 U/mL), 308 U/mL (normal range <500 U/mL), and 42.9 ng/mL (normal range, 17.3-59.7 ng/mL), respectively. The beta-D-glucan level was 12 pg/mL (normal range <20 pg/mL). There was no marked increase in the level of antibody against *Trichosporon asahii*. The T-SPOT test for TB, which measures the number of interferon-gamma-secreting spot-forming T cells obtained from a patient stimulated by *Mycobacterium tuberculosis*-specific antigens, was negative. The chest radiograph findings were normal, whereas computed tomography (CT) revealed diffuse minimal nonspecific ground-glass appearance in the both lungs (Fig. 1) and splenomegaly. Bone marrow



Figure 1. Computed tomography (CT) showed a diffuse, minimal, nonspecific ground-glass appearance in both lungs.

aspiration revealed no malignancy. Bronchoscopy was non-diagnostic with normal findings in the bronchoalveolar lavage fluid (BALF), showing alveolar macrophages, 98.5%; neutrophils, 0.5%; and lymphocytes, 1%. A transbronchial lung biopsy was not performed. Pathogenic bacteria, mycobacteria, and fungi were not observed in the BALF culture. Staining of the BALF specimen did not show evidence of *Pneumocystis jirovecii* or cytomegalovirus infection. *P. jirovecii* DNA was also not detected in the BALF on a polymerase chain reaction (PCR) analysis.

Although MTX was discontinued on day 2 after hospitalization, the patient's respiratory failure gradually worsened. The clinical course of the patient is shown in Fig. 2. She needed supplemental oxygen therapy (1-4 L/min via a nasal cannula). A gallium scintigram showed a diffuse, mild uptake in both lungs and the spleen (Fig. 3). On day 17, a lung biopsy using VATS was performed, and a specimen was collected from S6 and S8 of the right lower lobe. A microscopic examination revealed the presence of moderate to large atypical lymphocytes in small pulmonary vessels (Fig. 4a). The neoplastic cells had large nuclei and moderate amounts of cytoplasm. Immunohistochemical staining showed that the tumor cells were positive for CD20 (Fig. 4b) and CD79a but negative for CD3, CD10, and Epstein-Barr virus (EBV)-encoded small RNA (EBER) using *in situ* hybridization. Based on these findings, the patient was diagnosed with pulmonary IVLBCL. A few weeks after discontinuation of MTX, her respiratory condition gradually improved, and oxygen therapy was withdrawn. The numbers of peripheral lymphocytes just before and 2 weeks after the cessation of MTX were 1,153 and 2,655 cells/ μ L, respectively.

She was discharged on day 35. She became afebrile, and her serum LDH, CRP, and sIL-2R values decreased to normal levels. On CT, the diffuse ground-glass opacities and splenomegaly were found to have disappeared. Because the patient showed spontaneous regression after the cessation of MTX and her symptoms completely disappeared, chemo-

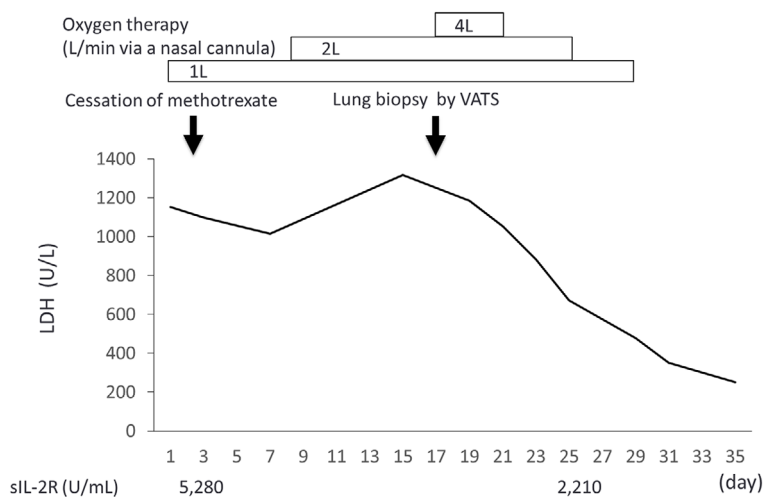


Figure 2. The clinical course of the patient. LDH: lactate dehydrogenase, sIL-2R: soluble interleukin-2 receptor, VATS: video-associated thoracic surgery

therapy was not administered, and she was only observed. 18-fluorodeoxyglucose positron-emission tomography (PET)/CT performed after discharge revealed no specific fluorodeoxyglucose uptake in the lungs, spleen, or lymphoid or extra-lymphoid organs. The patient is currently under careful observation and shows no signs of recurrence.

Discussion

This report describes a case of MTX-LPD in a patient expressed as pulmonary IVLBCL. The pulmonary IVLBCL regressed spontaneously after simple cessation of MTX, and there has been no recurrence.

According to the revised 4th edition of the World Health Organization (WHO) guidelines, LPDs that develop in a patient under treatment with an immunosuppressive drug are classified as “other iatrogenic immunodeficiency-associated LPDs” (14). Among them, cases of LPD in patients with RA who are treated with MTX have been called MTX-LPD. DLBCL is the common histologic type of MTX-LPD, and its typical clinical features have been reported to be lymphadenopathy or a mass lesion in an extranodal location (3-9),

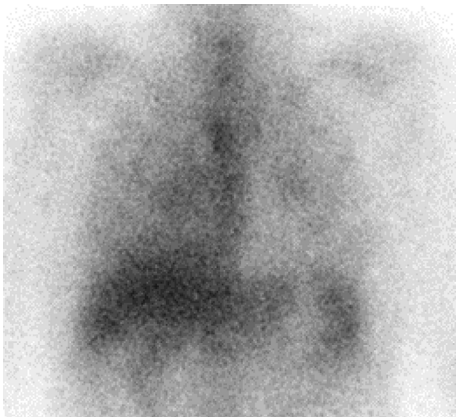


Figure 3. A gallium scintigram showed a diffuse, mild uptake in both lungs and the spleen.

including the skin, liver, spleen, lung, gastrointestinal tract, and bone marrow (3-8, 14). The patterns observed most frequently in the lungs of patients with DLBCL are consolidation, nodules and mass lesions (15-17). However, diffuse ground-glass opacity has been very rarely reported (17). This is a rare case of MTX-associated pulmonary DLBCL showing ground-glass opacity on CT with histopathological confirmation of the lesion as IVLBCL.

The initial differential diagnosis in our patient was opportunistic infections, interstitial pneumonia associated with RA, and MTX-induced pneumonitis. Hypersensitivity pneumonitis and sarcoidosis were also included as the differential diagnosis based on the symptoms, clinical course, and CT findings. No abnormalities were noted in the BALF, suggesting that the possibility of MTX-associated interstitial pneumonia, hypersensitivity pneumonitis, or sarcoidosis was low. Negative pathological findings and normal values of beta-D-glucan and serum KL-6 suggested that opportunistic infections, such as tuberculosis and pneumocystis pneumonia, were unlikely to be the cause of the pulmonary disease. According to a database search of papers published from 1990 to 2015, pulmonary complications seen in patients with RA under MTX treatment included LPD (42%), interstitial fibrosis (33%), and infections (25%) (2). In the cases of MTX-LPD, the median treatment period and cumulative dose of MTX were reported to be 4-10 years and 940-1,400 mg, respectively (3-8). The duration of 7 years and cumulative dose of 4,200 mg in our case suggested the possibility of MTX-LPD, which was further indicated by the findings of the gallium scintigram and elevated levels of sIL-2R. VATS was performed to identify the cause of pulmonary disease, confirm the pulmonary IVLBCL, and examine the contribution of interstitial pneumonia associated with RA. The findings of the VATS specimen confirmed the diagnosis of pulmonary IVLBCL.

The main sites of involvement in patients with IVLBCL are the central nervous system, skin, bone marrow, and lymph nodes, and involvement of the lungs has also been re-

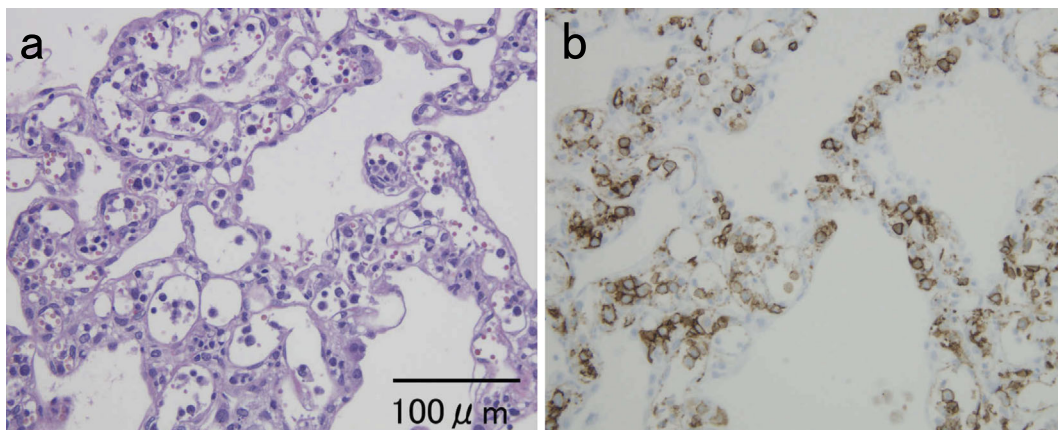


Figure 4. (a) A microscopic examination revealed the presence of atypical moderate to large lymphocytes in small pulmonary vessels. (b) Immunochemical staining showed that these cells were positive for CD20.

ported (10, 18, 19). Clinical manifestations of IVLBCL in the lungs have included a fever, cough, hypoxemia, and progressive dyspnea (18-23). The common patterns of parenchymal abnormality seen on CT images include bilateral diffuse ground-glass opacity, and in a few cases, peribronchovascular and interlobular septal thickening, nodules, and consolidation (19-23). These CT features have been reported to correlate with thickened alveolar septa owing to the distension of small vessels filled with neoplastic lymphoid cells (19). The clinical, radiological, and pathological findings seen in our case were consistent with those described in previous reports (19-22).

IVLBCL usually shows an aggressive clinical course with a poor prognosis (10). Chemotherapy has given a survival advantage to patients with IVLBCL (24). However, spontaneous regression has been reported to occur in 23-77% of patients with MTX-LPD after cessation of MTX (3-8). Previous studies showed that patients with spontaneous regression had a higher rate of EBV positivity than those without regression (3, 4). Another study reported that spontaneous regression occurred in 18 of 20 cases following MTX cessation alone and that the rate of lymphocyte recovery 2 weeks after MTX cessation was higher in cases with regression than in those without regression (5). This observation was confirmed by a study showing that an increase in the lymphocyte count of >220 cells/ μL at 2 weeks after MTX cessation may predict a favorable prognosis for spontaneous regression of LPD (25). Although EBER was negative in our case, the lymphocyte count rapidly recovered from 1,153 cells/ μL to 2,655 cells/ μL by 2 weeks after the cessation of MTX. Indeed, in our case, the patient demonstrated spontaneous regression of MTX-associated IVLBCL after the cessation of MTX. Close observation must be applied, as relapse is known to occur in a moderate number of patients whose LPD initially regresses after cessation of MTX (14).

This case report is important because pulmonary IVLBCL should be considered as a differential diagnosis in patients undergoing MTX treatment complicated with dyspnea and hypoxia.

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

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