**A case series of different courses of methotrexate-associated lymphoproliferative disease with pulmonary involvement**

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**Abstract**

Lymphoproliferative Disorder (LPD) is a complication of Methotrexate (MTX) therapy. Several cases of Methotrexate-Associated Lymphoproliferative Disorder (MTX-LPD) have been reported. However, pulmonary lesions in MTX-LPD are rare. Image findings of MTX-LPD show various patterns. Pneumocystis pneumonia and interstitial pneumonia, which have complex courses, have been reported in MTX-treated patients with lung diseases other than MTX-LPD. Furthermore, the treatment course of MTX-LPD differs from those of other lung diseases and could vary across patients. Herein, we discuss the importance of an accurate MTX-LPD diagnosis through detailed examination and treatment priority depending on the severity of underlying diseases and complications.

**Keywords:** Rheumatoid arthritis; Methotrexate; Lymphoproliferative disorder; Pulmonary lesion.

**Abbreviations:** LPD: Lymphoproliferative Disorder; MTX: Methotrexate; PCP: Pneumocystis Pneumonia; IP: Interstitial Pneumonia; RA: Rheumatoid Arthritis; OII-LPD: Other Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorders; WBC: White Blood Cell; Hb: Hemoglobin; LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein; B-D-G: 1,3-B-D-Glucan; KL-6: Krebs Von Den Lungen 6; Sil-2 R: Serum Soluble Interleukin-2 Receptor; HR-CT: High-Resolution Computed Tomography; TBLB: Transbronchial Lung Biopsy; BAL: Bronchoalveolar Lavage; HLH: Hemophagocytic Lymphohistiocytosis; RECIST: Response Evaluation Criteria In Solid Tumors.

**Introduction**

Methotrexate (MTX) is an anchor drug in rheumatoid arthritis treatment.

Lymphoproliferative Disorder (LPD) is a complication of low-dose MTX (frequency <0.1%). There are more reports in Asia (especially Japan) than in Europe and the USA, the reason for which is unknown [1,2]. The World Health Organization classifies MTX-associated LPD (MTX-LPD) under “Other Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorders (OII-LPDs), with MTX-LPD accounting for most OII-LPDs. In 40%-50% of cases, MTX-LPD develops at extranodal sites (the skin,
oral cavity, salivary glands, digestive tract, liver, spleen, and spine) and pulmonary lesions are rare [3]. The pulmonary complications of MTX include infections and Interstitial Pneumonia (IP), besides LPD. The first intervention in MTX-LPD treatment is MTX discontinuation, and in most cases, the disease spontaneously regresses after MTX has been stopped. When MTX-LPD does not regress spontaneously, chemotherapy or radiotherapy is needed, depending on the malignant lymphoma type. Here, we report three cases of MTX-LPD of pulmonary involvement with differing courses.

Case series

Case 1

A 76-year-old woman presented with a 1-day history of general malaise and high fever. She had RA and was taking MTX regularly (4 mg/week, 12 years). Laboratory tests revealed White Blood Cell (WBC) and platelet counts of 6600 (/μL) and 7.7 (×10⁴ /μL), respectively, and hemoglobin (Hb), Lactate Dehydrogenase (LDH), C-Reactive Protein (CRP), Serum 1,3-β-D-Glucan (β-D-G), Krebs von den Lungen 6 (KL-6), Serum-Soluble Interleukin-2 Receptor (sIL-2 R) levels of 7.9 g/dL, 625 (IU/L), 10.00 (mg/dL), <11.0 pg/mL, 361 U/mL, 6140 U/mL, respectively. High-Resolution Computed Tomography (HR-CT) showed cervical, supraclavicular and mediastinal lymphadenopathies, multiple nodules, and ground-glass opacities in both lungs (Figure 1Aa). Histological examination of a biopsied sample of the right submandibular lymph node revealed extensive necrosis. Immunohistology showed CD20 and CD79a expression (Figure 2A). The systemic lymph nodes that were swollen shrank after MTX discontinuation, and sIL-2 R decreased. However, the bilateral ground-glass opacities worsened after chemotherapy (a→b). Bronchoscopy (Transbronchial Lung Biopsy [TBLB] and Bronchoalveolar Lavage [BAL]) was performed. TBLB revealed no significant findings; however, lymphocytes were predominant and CD4 /CD8 ratio was 0.4. On the other hand, BAL fluid was positive for Pneumocystis jirovecii DNA, and the β-D-G level was elevated (30.4 pg/mL). Therefore, the patient was diagnosed with Pneumocystis Pneumonia (PCP). Her respiratory condition was good, and she was followed up without antibiotics therapy. Her lung shadow improved (Figure 1Ac), and the β-D-G level decreased gradually.

Case 2

A 72-year-old man presented with a 1-week history of general malaise and high fever. He had RA and was taking MTX regularly (16 mg/week, 2 years). Laboratory findings revealed WBC and platelet counts of 31900 (/μL) and 4.4 (×10⁴ /μL), respectively; Prothrombin Time-International Normalized Ration (PT-INR) of 1.4; and Hb, LDH, CRP, blood urea nitrogen, creatinine, D-dimer, β-D-G, KL-6, and sIL-2 R levels of 9.7 g/dL, 586 (IU/L), 13.19 (mg/dL), 44 (mg/dL), 2.11 (mg/dL), 41.3 (μg/mL), <11.0 pg/mL, 242 U/mL, and 58100, U/mL respectively. HR-CT showed cervical, supraclavicular, mediastinal lymphadenopathies; multiple granular shadows; infiltration shadows; bilateral bronchial wall thickening, predominantly distributed in the lower lung fields; hepatomegaly; and splenomegaly (Figure 1Ba). Histological examination of a biopsied sample of the right submandibular lymph node revealed extensive necrosis. Immunohistology showed CD20 and CD79a expression (Figure 2A). The systemic lymph nodes that were swollen shrank after MTX discontinuation, and sIL-2 R decreased. However, the bilateral ground-glass opacities worsened after chemotherapy (a→b). Lymph node biopsy was performed on the right inguinal lymph node. Histologic tests showed the normal lymph node structure was destroyed. Immunohistology showed CD3, CD4, CD5 and CD7 expression (Figure 2B). He was diagnosed with Peripheral T-cell lymphoma,
not otherwise specified. Therefore, systemic chemotherapy with pirarubicin (Tetrahydropyranyladriamycin [THP]), cyclophosphamide, vincristine, and prednisolone (THP-COP regimen) was initiated, and six cycles were administered in all. Partial response in the form of shrinking of systemic lymphadenopathy was noted after six cycles (Response Evaluation Criteria in Solid Tumors: RECIST version 1.1) (Figure 1Bb).

MTX-LPD was first reported as lymphoma in an MTX-treated RA patient [4]. RA alone increases the risk of developing LPD by 2- to 4-fold [5]. Antirheumatic drugs further increase this risk (MTX, 1.7-fold; infliximab, 2.6-fold; etanercept, 3.8-fold) [6]. Per its clinical course, MTX-LPD is classified into three groups: regressive LPD without relapse/regrowth, regressive LPD with relapse/regrowth event, and persistent LPD [7]. Case 1 fell under the regressive LPD without relapse/regrowth group, however Case 2 and Case 3 fell under persistent LPD. The ration of the three groups was similar. Approximately 50% of cases show spontaneous regression with only MTX discontinuation [8]. CT of pulmonary lesions in MTX-LPD has shown various patterns; however, no specific shadows have been reported [9]. MTX-LPD can cause various complications; therefore, it may not have characteristic shadows. The histologic patterns of MTX-LPD are heterogeneous; however, diffuse large B-cell lymphomas are the most common histologic type (58%), followed by classical Hodgkin’s lymphoma (15.3%) [3]. Some cases (25%, particularly the regressive group) could not be classified into a particular histologic type, because in these cases, MTX had already been discontinued and MTX-LPD was regressing at the time of biopsy [10]. Although it may be clinically difficult, a biopsy should be performed before MTX discontinuation, if possible. MTX-associated pulmonary complications include infections and IP, besides LPD. The percentages of patients with LPD, infection, and IP were 42%, 25%, and 33%, respectively, among MTX-treated RA patients [2]. In Case 1, MTX-LPD and PCP developed simultaneously. In this case, PCP was detected very early and improved only by follow-up. No detailed mechanism has been found, however changes in the immune status due to underlying diseases or administration of immunosuppressive drugs might affect the inflammatory process of PCP [11]. In Case 1, immune status seems to have changed rapidly after discontinuation of MTX.

There are many reports of MTX-LPD being associated with a high prevalence of Epstein-Barr Virus (EBV) infection, and EBV reactivation contributes to MTX-LPD development. MTX-LPD with EBV positivity is more spontaneously remissive compared to that with EBV negativity [12]. Among our cases, EBV positivity was the highest in case 1, as determined by EBV-encoded small RNA in situ hybridization staining. In case 1, multiple lymphadenopathies shrank after only MTX discontinuation; on the other hand, chemotherapy was required in case 2 and 3.

**Conclusion**

In conclusion, we described three cases of MTX-LPD with pulmonary involvement, and the disease course was different in each case. MTX-LPD with pulmonary lesions can show various shadows on imaging and cause complications. Therefore, careful attention is required for diagnosis and treatment in cases of suspected MTX-LPD with pulmonary lesions.

**Disclosure statement**

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References


