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【 CASE REPORT 】

Angioimmunoblastic T-cell Lymphoma Presenting as a Methotrexate-associated Lymphoproliferative Disorder with Extreme Peripheral Blood Plasmacytosis

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Abstract:
A 74-year-old man was admitted to our hospital because of systemic lymphadenopathy, weight loss, and a fever at night that had persisted for approximately 1 month. Blood tests revealed extreme peripheral blood plasmacytosis and hypergammaglobulinemia. A lymph node biopsy showed angioimmunoblastic T-cell lymphoma (AITL). Based on the history of methotrexate (MTX) administration, the established diagnosis was MTX-associated lymphoproliferative disorder (MTX-LPD). After MTX was discontinued, the lymphadenopathy spontaneously regressed and the plasmacytosis disappeared. He had no disease progression for three years. We found that AITL as an MTX-LPD can cause plasmacytosis, and the prognosis of this disease may not be poor.

Key words: methotrexate, angioimmunoblastic T-cell lymphoma, MTX-associated lymphoproliferative disorder, plasmacytosis

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Introduction

Methotrexate-associated lymphoproliferative disorders (MTX-LPDs) are associated with immunosuppressive therapy for autoimmune diseases, such as rheumatoid arthritis (RA). The World Health Organization considers MTX-LPDs to fall in the category of the other iatrogenic subgroup of immunodeficiency-associated LPDs (OIIA-LPDs) (1). Diffuse large B-cell lymphoma and classical Hodgkin lymphoma account for most MTX-LPDs, whereas T-cell lymphomas are rare (2, 3).

Angioimmunoblastic T-cell lymphoma (AITL) is one of the four major subtypes of peripheral T-cell lymphoma (PTCL), accounting for approximately 1-2% of non-Hodgkin lymphomas and 15-27% of PTCLs (4-6). AITL occurs mainly in older individuals, and most patients have aggressive systemic symptoms, such as systemic lymphadenopathy, a fever, and weight loss (7, 8). The cellular origin of AITL is follicular helper T-cells, which are known to produce various cytokines, such as interleukin (IL)-6, IL-10, and platelet-derived growth factor; or chemokines, such as C-X-C motif chemokine ligand 13 (CXCL13). The follicular helper T-cells also stimulate B-cells to cause a variety of autoimmune pathologies, such as autoimmune hemolytic anemia, immune thrombocytopenic purpura, plasmacytosis, and hypergammaglobulinemia (9-12). To our knowledge, there have been no reports on T-cell lymphoma presenting as an MTX-LPD with plasmacytosis.

We herein report the clinical course of a rare case of MTX-LPD mimicking AITL with extreme peripheral blood (PB) plasmacytosis and hypergammaglobulinemia in detail.

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Table. Laboratory Data on Admission.

Complete blood count		Serum tumor marker	
WBC (×10^9/L)	73.3	sIL-2R (U/mL)	12,059
Stab neutrophils (%)	3		
Segmented neutrophils (%)	12	Serological test	
Metamyelocytes (%)	1	IgG (mg/dL)	1,639
Eosinophils (%)	1	IgA (mg/dL)	439
Basophils (%)	0	IgM (mg/dL)	187
Monocytes (%)	8		
Lymphocytes (%)	8	Free light chain	
Plasma cells (%)	67	κ (mg/L)	337
Hemoglobin (g/dL)	10.3	λ (mg/L)	514
Platelet (×10^9/L)	178	κ/λ ratio	0.66

Serum biochemistry		Other immunologic tests	
LDH (IU/L)	1,093	Anti-nuclear antibody	<×40
AST (IU/L)	94	Direct Coombs test	Negative
ALT (IU/L)	37		
Total bilirubin (mg/dL)	1.3		
BUN (mg/dL)	16		
Creatinine (mg/dL)	1.69		
Total protein (g/dL)	7.1		
Albumin (g/dL)	3.5		
C-reactive protein (mg/dL)	13.64		
Beta-2-microglobulin (mg/dL)	11.4		

WBC: white blood cell, LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, sIL-2R: soluble interleukin-2 receptor

Case Report

A 74-year-old man had received MTX for RA treatment for 6 years. He was not taking any drug for RA other than MTX. He presented with systemic lymphadenopathy, a fever at night, and prolonged weight loss lasting for one month and was admitted to our hospital in September of year X.

His performance status score was 3 on admission. Laboratory findings showed an increased white blood cell count (73.3×10^9/L), 67% of which were plasma cells. Elevated lactate dehydrogenase (LDH, 1,093 U/L) and soluble IL-2 receptor (sIL-2R, 12,000 U/mL) levels and hypergammaglobulinemia were also observed (Table). The direct Coombs test and antinuclear antibody test results were negative. The monoclonal protein was identified as IgM lambda by immunofixation electrophoresis (IFE), but the M spike was not observed on serum protein electrophoresis. These plasma cells were analyzed by PB flow cytometry (FCM), where the expression of CD19, CD38, and CD138 was observed, but the expression of CD20 and CD56 and light-chain restriction was not. Computed tomography showed bilateral cervical, axillary, and inguinal lymphadenopathy ranging in size from 1.5 to 2.5 cm. There were no signs of hepatosplenomegaly.

A right inguinal lymph node biopsy was performed. Pathological findings showed that small- to medium-sized lymphocytes had proliferated with effacement of lymph nodes and high endothelial venules. Immunohistochemical findings showed that these lymphocytes expressed CD3, CD 4, CD5, PD-1, and CXCL13 but did not express CD8, CD 10, BCL-6, CD19, or CD20. Epstein-Barr virus-encoded small RNA in situ hybridization (EBER-ISH) was positive for peri-tumor B-cells but negative for tumor cells (Fig. 1 not shown in part). These pathological findings were deemed consistent with those of AITL. A bone marrow (BM) analysis showed that the total nucleated cell number was 40×10^9/L, and 18% of the cells were plasma cells, but there were no abnormal lymphoid cells; therefore, we judged that there was no AITL invasion in BM. In these plasma cells analyzed by FCM, the expression of CD38, CD 138, and CD19 was observed, but light-chain restriction was not observed. A biopsy of the BM revealed the same findings (Fig. 2). Based on the above pathological findings and the history of MTX administration, the patient was diagnosed with OIIA-LPD (AITL with plasmacytosis, MTX-LPD stage IIIB).

He was rehydrated, and MTX was discontinued. His LDH levels, sIL-2R levels, plasmacytosis, leukocytosis, and hypergammaglobulinemia gradually improved (Fig. 3). The constitutional symptoms and enlarged lymphadenopathy spontaneously regressed without chemotherapy (Fig. 4). He

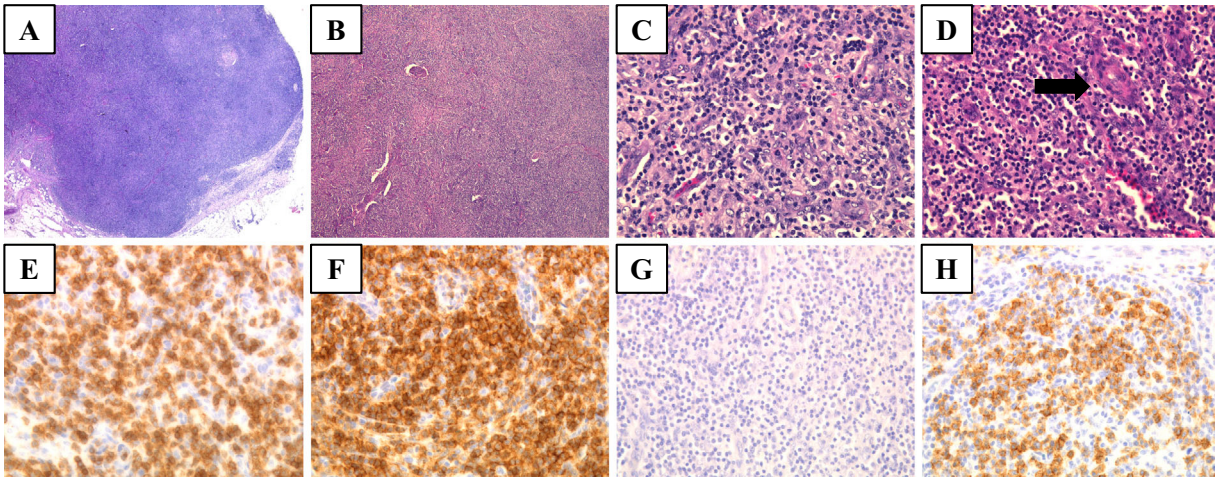

Figure 1. **An inguinal lymph node biopsy. (A-D) Polymorphic lymphocytes infiltrate with effacement of the lymph node architecture and high endothelial venules (arrow). These lymphocytes are composed of small- to medium-sized lymphocytes with clear cytoplasm. (A) Hematoxylin and Eosin (H&E) staining ×40 and (B) H&E staining ×100 and (C, D) H&E staining ×200. Polymorphic lymphocytes were positive for CD3 (E) CD4 (F) PD-1 (H). These lymphocytes were negative for Epstein-Barr virus-encoded small RNA *in situ* hybridization (G). (E-H) ×200.**

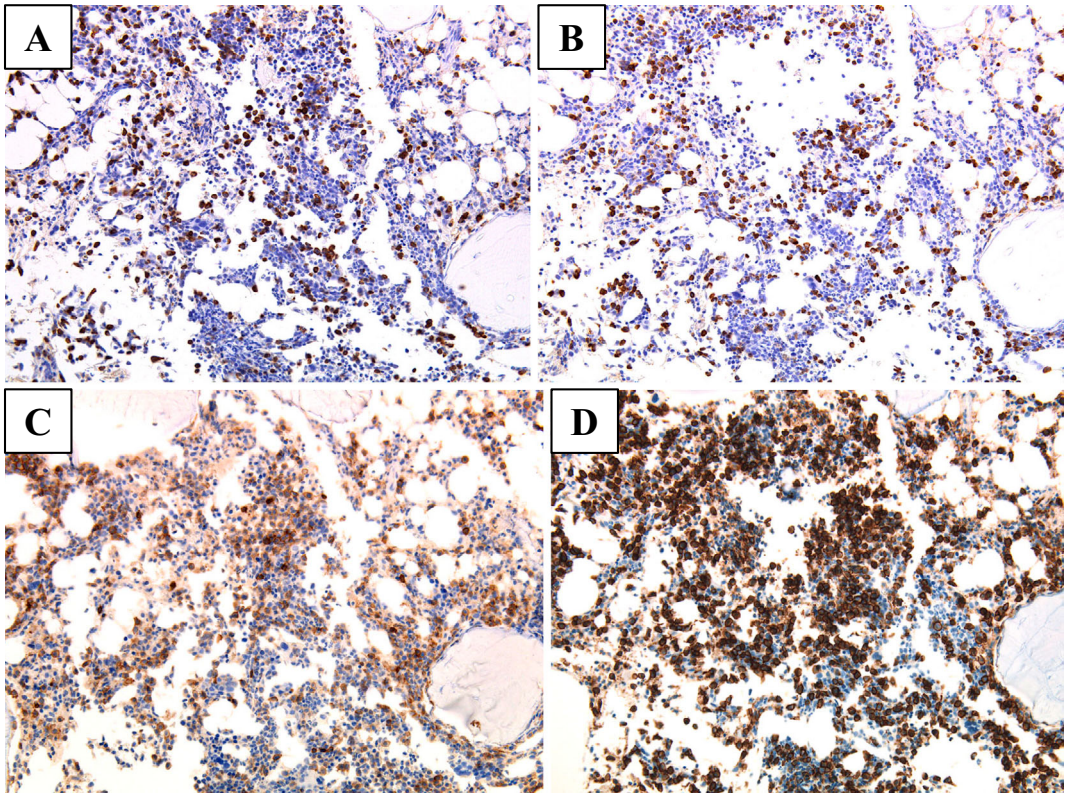

Figure 2. **A bone marrow biopsy performed the time of the diagnosis. Abnormal lymphocytes were not observed in the bone marrow biopsy. (A) IgGκ, (B) IgGλ, (C) CD19, (D) CD138. (A-D) ×20.**

was discharged on the 14th day after admission, and the M-protein loss was confirmed by IFE. As of March of year X+3, there has been no recurrence of the disease, and he is undergoing treatment-free follow-up in an outpatient clinic.

Discussion

T-cell lymphoma, including AITL, is rare in MTX-LPDs. Hatanaka et al. reported three similar cases in 2010 (13). In all cases, remission was achieved by discontinuation of

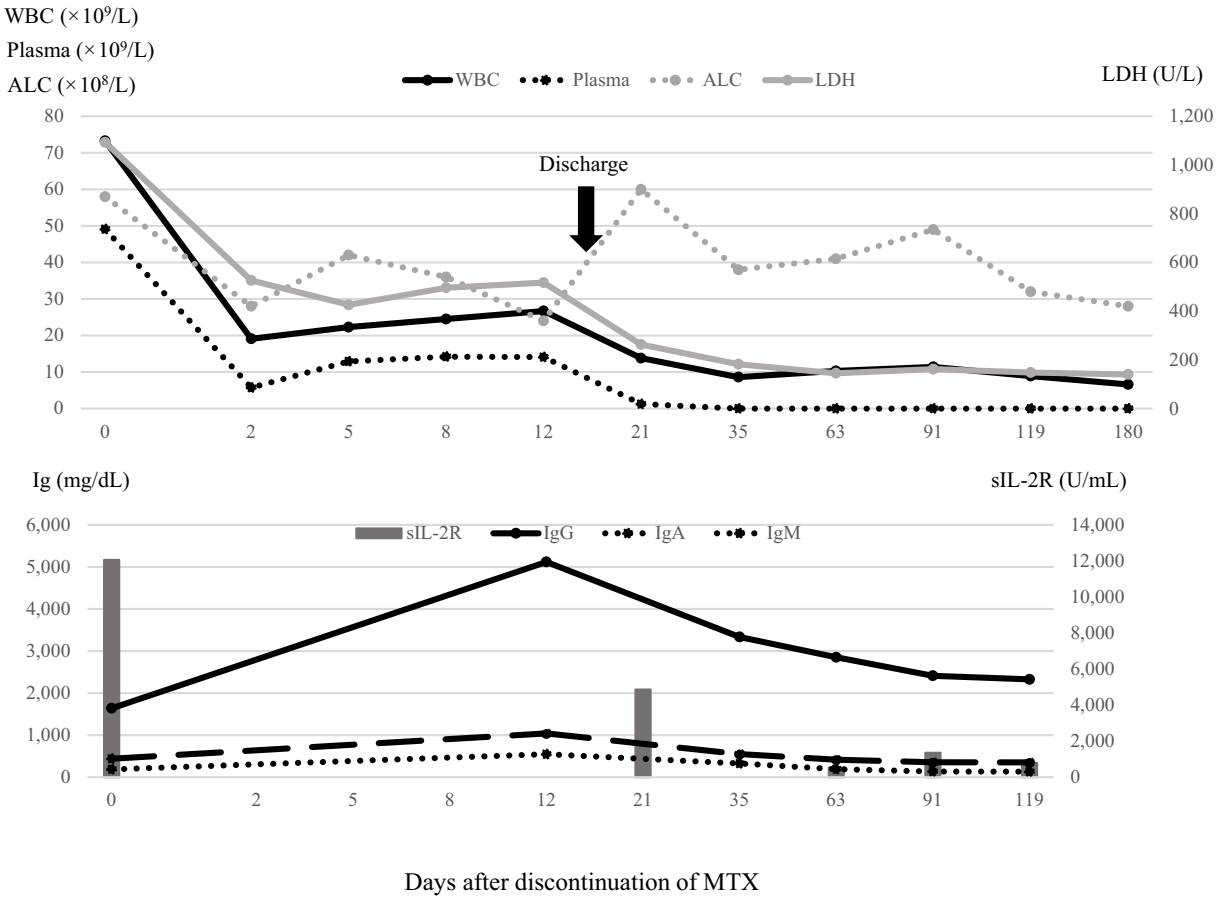

Figure 3. **Clinical course after the discontinuation of methotrexate (MTX). White blood cell (WBC) count, plasmacytosis, lactate dehydrogenase (LDH) level, and hypergammaglobulinemia improved over time after the discontinuation of MTX. Changes in the absolute lymphocytic count (ALC) are observed after the discontinuation of MTX.**

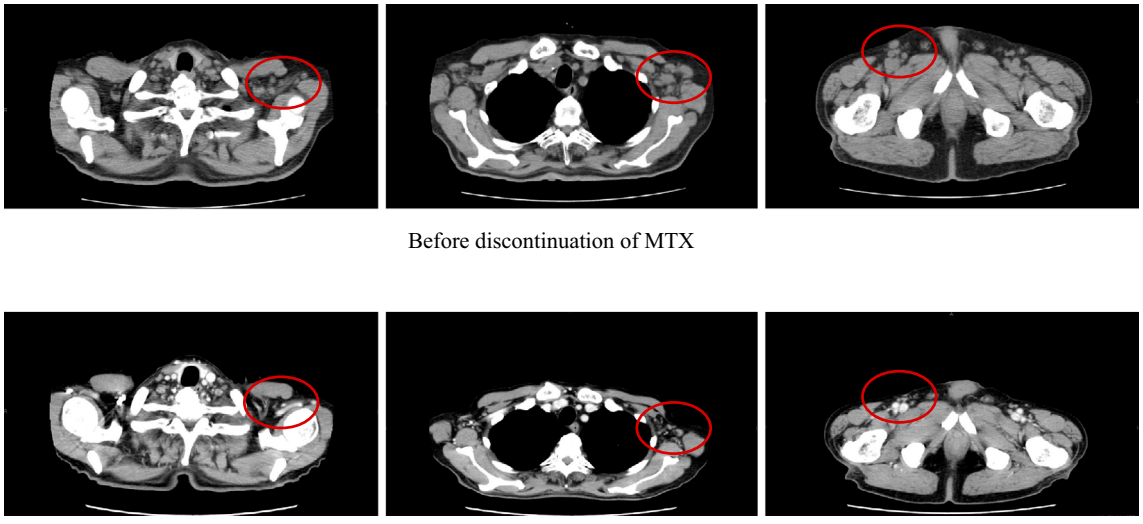

Figure 4. **Improvement in systemic lymphadenopathy after the discontinuation of methotrexate (MTX). Upper red circles indicate lymphadenopathy before the discontinuation of MTX. Lower red circles indicate the regression of lymphadenopathy after the discontinuation of MTX.**

MTX, but one of the patients showed relapse and received standard cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) therapy. The patient achieved a complete response (CR) and maintained it for six months.

Epstein-Barr virus is known to be the pathogenic cause of MTX-LPDs. Satou et al. reported 28 cases of T-cell lymphoma as MTX-LPDs, wherein only 1 (4%) was positive for EBER-ISH in the tumor cells, and spontaneous regression was observed after the discontinuation of MTX in 20 (77%) (14). As these cases were negative for EBER-ISH on tumor cells, the etiology of AITL as MTX-LPDs was not associated with Epstein-Barr virus. Therefore, this disease may have developed through another mechanism. Although the number of reported cases is small, based on these previous reports, T-cell lymphomas as MTX-LPDs may not be a disease entity with a poor prognosis.

Two reports of AITL with plasmacytosis have been published (15, 16). In both reports, no light-chain restriction was noted in the increased number of plasma cells, and these cells exhibited reactive proliferation. Nagoshi et al. compared clinical manifestations and the prognosis between AITL patients with plasmacytosis (n=3) and those without plasmacytosis (n=12) (16). The ECOG-performance status in AITL patients with plasmacytosis was extremely poor, and serum immunoglobulin levels were significantly higher than those without plasmacytosis. However, other parameters, such as B symptoms, levels of LDH, C-reactive protein, and sIL-2R showed no significant differences. Treatment outcomes with conventional chemotherapy or immunosuppressive therapy were favorable. The authors concluded that the prognosis of AITL with plasmacytosis may not be poorer than that of patients without plasmacytosis. In the present case, plasma cells had polyclonal proliferation, but the M-protein was identified on IFE. In AITL, tumor cells and reactive histiocytes produce inflammatory cytokines, such as IL-6, which induce the proliferation of each B-cell polyclonally to differentiate into plasma cells responsible for antibody production (9-12). In this case, polyclonal plasma cells differentiated from B-cells may have been found in the PB and BM. The detection of M-protein may have involved a small clone that produced M-protein temporarily.

We believe that our patient developed AITL as an LPD based on the history of MTX administration, and the mechanism described above induced an increase in the plasma cell count in the PB and BM. The response rate of MTX-LPDs after MTX discontinuation varies from report to report. Tokuhira et al. reported that the response rate was approximately 70%, and one-third of patients showed relapse (17). The response rate for T-cell lymphomas has been reported to be 77% (14). In the present case, CR was achieved by MTX discontinuation, but it is important to conduct follow-up of the patient, considering the possibility of relapse in the future. Recently, Tokuhira et al. reported that the absolute lymphocyte count (ALC) can be a useful predictor for the therapy-free survival (TFS) and overall survival (OS) in patients with MTX-LPD after regression. According to this report, an ALC ≥ 1,000/mL at 0 and 6 months and at 6 months after the discontinuation of MTX is a significant predictor for a favorable TFS and OS, respectively (18). In the present case, the ALC remained higher than this criterion during follow-up, suggesting a favorable prognosis (Fig. 3). AITL is associated with a variety of abnormal laboratory findings, and plasma cell leukemia was initially considered in this case. However, based on the history of MTX administration and the results of a lymph node biopsy, we were able to diagnose an MTX-LPD comprehensively and take appropriate action.

In conclusion, this case suggests that, similar to *de novo* AITL, AITL presenting as an MTX-LPD may also cause plasmacytosis. Considering previous reports on T-cell lymphomas as MTX-LPD and AITL with plasmacytosis, the prognosis of this disease may not be poor. The further accumulation of data and investigation of cases are needed.

Author's disclosure of potential Conflicts of Interest (COI).
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