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Case Report

Cutaneous methotrexate-related T-cell lymphoproliferative disorder with CD4, CD30, CD56, EBV-positive tumor cell infiltration: a case illustration and a brief review

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Abstract: Methotrexate (MTX) is a commonly used anti-metabolite agent. Long-term MTX treatment can cause MTX-related lymphoproliferative disorder (MTX-LPD). T-cell LPDs comprise a small fraction of MTX-LPDs. Epstein-Barr virus (EBV)$^+$ tumor cells are rarely detected in MTX-related T-cell LPDs (MTX T-LPDs). Therefore, there have been very few reports of EBV$^+$ MTX T-LPD. We encountered a case of cutaneous MTX T-LPD with a unique cellular phenotype. The patient was a 71-year-old Japanese man with rheumatoid arthritis treated with MTX for 6 years. He was referred to our department with a 6-month history of red plaques and ulcerated lesions in both lower legs and a 2-week history of high fever and fatigue. Cutaneous specimens showed that medium-sized atypical lymphocytes were positive for CD3, CD4, CD30, CD56, and in situ hybridization for EBV-encoded RNA. The patient was diagnosed with cutaneous MTX T-LPD. Four months after discontinuation of MTX, the skin lesions had disappeared. This is the first report of cutaneous MTX T-LPD with CD4$^+$CD30$^+$CD56$^+$EBV$^+$ tumor cells.

Keywords: Methotrexate, lymphoproliferative disorder, methotrexate-related T-cell lymphoproliferative disorder

Introduction

Lymphoproliferative disorder (LPD) is strongly associated with immunodeficiency, which is caused by aging, primary immune disorders, HIV infection, and immunosuppressive drugs, such as methotrexate (MTX) [1]. According to the World Health Organization classification (2017), lymphoid proliferations or lymphomas that develop in patients receiving immunosuppressive drugs for an autoimmune disease or conditions other than post-transplantation is defined as "other iatrogenic immunodeficiency-associated LPD". Among them, LPD in patients treated with MTX is referred to as "MTX-related lymphoproliferative disorder (MTX-LPD)". MTX is the current first-line treatment for rheumatoid arthritis (RA) [2]. Long-term MTX treatment may result in MTX-LPD in RA patients [3, 4]. The majority of MTX-LPD cases involve B-cell LPD, and T-cell LPDs are rare [1]. Only 43 cases of MTX-related T-cell lymphoproliferative disorder (MTX T-LPD) have been reported to date. Herein, we report a case of an elderly Japanese man with RA, who was treated with MTX, and a diagnosis of cutaneous MTX T-LPD with a unique cellular phenotype. All skin lesions disappeared within 4 months of discontinuing MTX treatment. This is the first report of cutaneous CD4$^+$CD30$^+$CD56$^+$EBV$^+$ MTX T-LPD.

Case report

A 71-year-old Japanese man with a 6-month history of red plaques with ulcers on both lower legs and a 2-week history of high fever and fatigue was referred to our department. He had been diagnosed with RA 7 years ago, and was

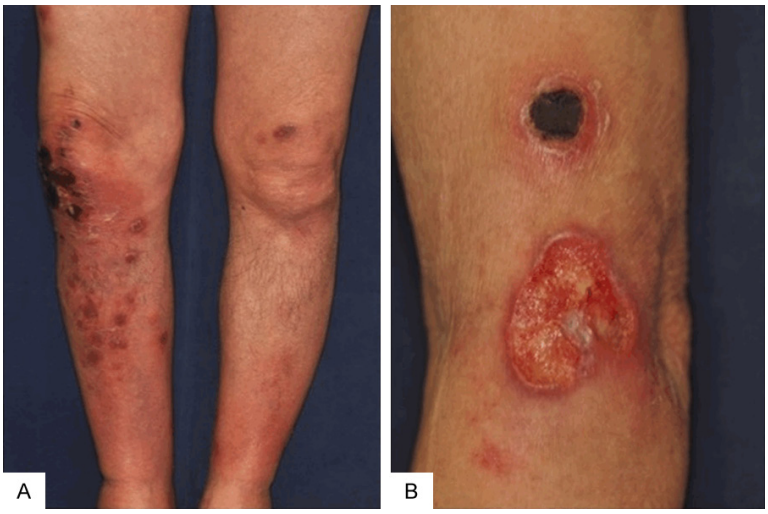

Figure 1. Erythematous lesions containing ulcerated lesions on (A) legs and (B) arms.

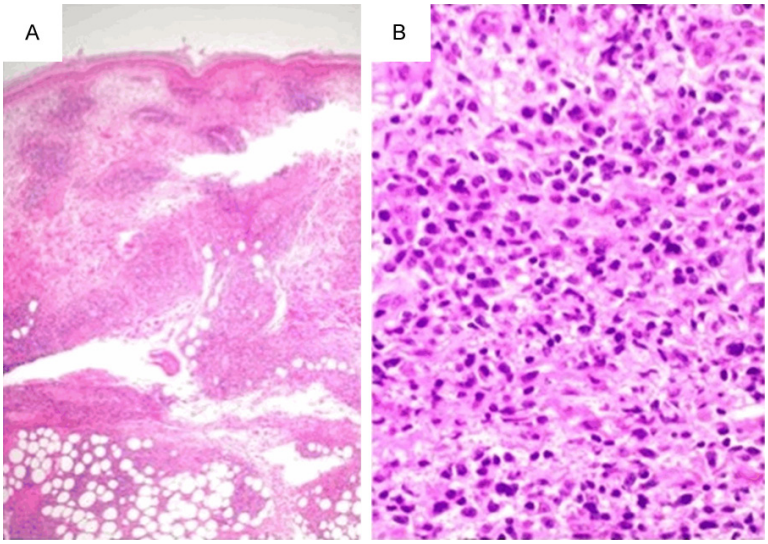

Figure 2. Histopathology of biopsy specimens showing infiltration of medium-sized lymphocytes with atypical nuclei throughout the dermis (hematoxylin-eosin, (A) ×40, (B) ×400).

treated with MTX (16 mg per week) for the past 6 years. Oral prednisolone was also administered. On admission, his temperature was 39.0°C. Physical examination revealed multiple indurated red plaques with ulcers and crusts on his upper and lower extremities (**Figure 1**). No swollen superficial lymph nodes were detected. Laboratory tests showed elevated C-reactive protein (12.0 mg/dL), white cell count (9.9*×10^9/L) (with a differential count of 88.5% neutrophils, 8.6% lymphocytes, 2.5% monocytes, 0.3% eosinophils, and 0.1% basophils), lactate dehydrogenase (585 IU/L), blood urea nitrogen (45.9 mg/dL), creatinine (1.78 mg/mL), and soluble interleukin-2 receptor (1830 IU/mL).

Blood cultures were negative. Serological tests for anti-EBV antibodies were consistent with previous infetions. Skin biopsy of the left-arm red plaque revealed infiltration of medium-sized lymphocytes with atypical nuclei throughout the dermis (**Figure 2A**, **2B**). Immunohistochemical staining showed that most of the atypical lymphocytes were positive for CD3, CD4, CD30, CD56, and Granzyme B, but negative for CD8, CD20, anaplastic lymphoma kinase (ALK) (**Figure 3A-H**). In situ hybridization for EBV-encoded RNA was positive for tumor cells (**Figure 3I**). Computed tomography of the chest, abdomen, and pelvis showed no evidence of lymphadenopathy or visceral involvement. Gallium-67-citrate scanning and single-photon emission computed tomography showed an abnormally increased uptake of the nasal cavity due to fungal infection, but no other lesions. Bone marrow aspiration findings were also normal. Based on these findings, the patient was diagnosed with cutaneous MTX T-LPD. Immediately after the cessation of MTX, his fever subsided and cutaneous lesions started to regress. At four months after discontinuation of MTX, the skin lesions disappeared completely. For six months, no recurrence has been observed.

Discussion

RA is associated with increased risk for LPD. Patients with RA have a 2 to 20-fold increase risk for lymphoma, even without MTX therapy

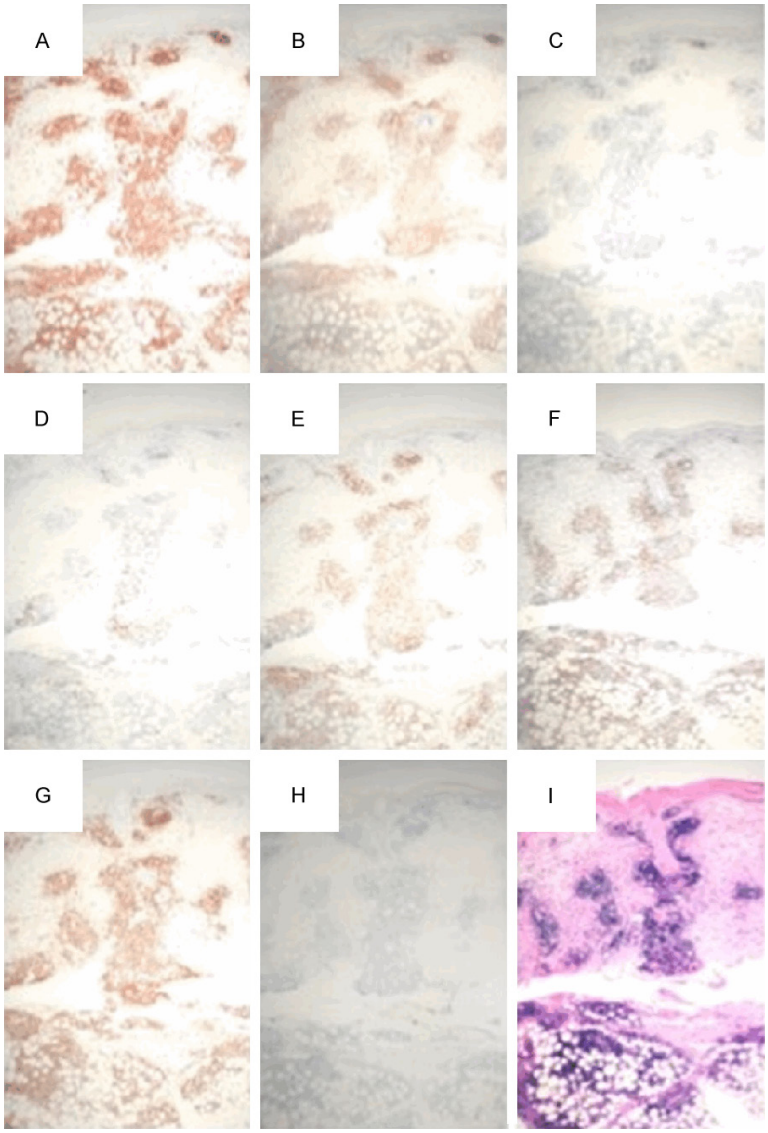

Figure 3. Immunostaining of (A) CD3, (B) CD4, (C) CD8, (D) CD20, (E) CD30, (F) CD56, (G) granzyme B, (H) ALK, and in situ hybridization for (I) EBV-encoded small RNA (×40).

[1]. Furthermore, the use of immunosuppressive drugs, including MTX, is an independent risk factor for LPD. Therefore, the impact of MTX on the development of LPD in RA patients is sometimes unclear. However, spontaneous remission of MTX-LPD after MTX withdrawal occurs in 50% of RA patients [5]. This is strong evidence for the potential tumorigenic role of MTX. We believe that, in our case, LPD was induced by MTX since complete remission was observed after MTX withdrawal without any additional treatments.

MTX-LPD manifests as a benign lymphoid proliferation or malignant lymphoma. Many characteristics of MTX-LPD have been clarified. Approximately 50% of the cases are positive for EBV^+ [6], and 40%-50% of all cases occur at extranodal sites, such as the skin, salivary glands, lungs, digestive tract, liver, and spine [7]. MTX-LPD originates from many cell types, including B, T, and natural killer cells. The majority of MTX-LPDs consist of B-cell LPD (75.5%), while T-cell LPD (3.6%) is rare [1]. In 2019, Satou et al. summarized the 43 MTX T-LPD cases that had been reported until that time [8]. To the best of our knowledge, no other MTX T-LPD case report has been reported since. These cases were classified as follows: 25 cases of angioimmunoblastic T-cell lymphoma, 6 peripheral T-cell lymphoma, not otherwise specified, 4 EBV^-CD8^+ T-LPD, 2 EBV^+CD8^+ T-LPD, and one case of anaplastic large cell lymphoma, EBV^+ $CD30^+$ cutaneous T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma (SPTCL), EBV^+ SPTCL, EBV^+ $CD30^+$ T-LPD, and adult T-cell leukemia/lymphoma. Only five cases had EBV^+ tumor cells, all positive for CD8. Patients with MTX T-LPD have a significantly lower proportion of EBV^+ tumor cells than those with MTX-related B-cell LPD. Therefore, MTX T-LPD with EBV^+ is relatively rare, and our patient is actually the first case of MTX T-LPD with $CD4^+CD8^-EBV^+$ tumor cells. Another striking point is that only three MTX T-LPD cases have been reported; their lesions were limited to the cutaneous area (2: skin lesion, 1: subcutis lesion). Claudino et al. [9] reported a case of MTX T-LPD that was similar to our case. The patient was a 66-year-old African American woman with RA treated with MTX. She had ulcerated lesions over her left leg for two months. However, complete remission was achieved two months after discontinuation of MTX. Pathologically, tumor cells from her skin

were positive for CD3, CD8, CD30, Granzyme B, and EBER-ISH, but negative for CD20, CD56, ALK. In comparison, our case showed a different staining pattern of CD8 and CD56, the location of skin lesions, and the term of complete response after the withdrawal of MTX. Co-expression of CD30 and CD56 in primary cutaneous T-cell lymphoma is rarely observed [10]. As described above, $CD4^+EBV^+$ tumor cells have not been observed in MTX T-LPD patients until now. It is still unclear whether this characteristic may influence disease activity and prognosis, but the phenotype ($CD3^+CD4^+CD30^+CD56^+EBV^+$) observed in the tumor cells of our patient is unique.

Although severe systemic symptoms and multiple skin lesions were observed in our patient, all of them regressed spontaneously with the cessation of MTX. Rizzi et al. [11] have shown that most case, patients with EBV^+ MTX-LPD achieve spontaneous complete remission of LPD within 4 weeks of discontinuing immunosuppressants. Other studies have shown that a high prevalence of spontaneous remission is associated with EBV-positivity and non-diffuse large B-cell lymphoma (DLBCL) histologic type. Older age (> 70 years) and DLBCL histologic type are predictive factors of shorter survival [12]. Our case was classified as having a high rate of spontaneous remission and passive characteristics because of non-DLBCL histologic type and EBV-positivity, except for the patient's advanced age. In our case, however, it took four months to achieve complete remission. Since the patient had untreated skin lesions for six months, there was a number of eruptions at the initial visit. Presumably, delaying MTX cessation might prolong the disease's duration. It was difficult to decipher, and the decision was made not to treat further as no new lesions appeared and the eruptions continued to regress. At the time of LPD diagnosis of a patient receiving immunosuppressive treatment for an autoimmune disease, it is advisable to withdraw the treatment and monitor for some weeks.

We present a rare case of cutaneous MTX T-LPD with a unique phenotype. This is the first report of cutaneous MTX T-LPD with $CD4^+CD30^+CD56^+EBV^+$ tumor cells. Since there have been few reports of cutaneous MTX T-LPD, further studies are needed to clarify the biological behavior and identify effective treatments for cutaneous MTX T-LPD.

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Disclosure of conflict of interest

None.

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