Grade 3 Lymphomatoid Granulomatosis in a Patient Receiving Methotrexate Therapy for Rheumatoid Arthritis

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Abstract

Lymphomatoid granulomatosis (LyG) is a rare, B-cell derived, lymphoproliferative disorder that often presents as pulmonary nodular lesions with a histopathology of lymphatic invasion of the vascular wall. The development of LyG may be associated with reactivation of the Epstein-Barr virus under an immunosuppressive state. We herein report a case of Grade 3 LyG that developed during methotrexate therapy for rheumatoid arthritis and regressed following the withdrawal of the drug.

Key words: lymphomatoid granulomatosis, methotrexate (MTX), rheumatoid arthritis

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Introduction

Lymphomatoid granulomatosis (LyG) is a rare, B-cell derived, lymphoproliferative disorder that often presents as pulmonary nodular lesions with a histopathology of lymphatic invasion of the vascular wall (1, 2). The development of LyG may be associated with reactivation of the Epstein-Barr (EB) virus under an immunosuppressive state (1, 2). When treated with methotrexate (MTX), rheumatoid arthritis (RA) patients rarely develop LyG, which regresses following the discontinuation of the drug (3-5). We herein report a case of Grade 3 LyG, which was likely associated with aseptic meningitis, that developed during MTX therapy in an RA patient and regressed following the withdrawal of MTX.

Case Report

A 65-year-old woman with a 27-year history of RA was referred to us for an evaluation of skin lesions and pulmonary nodulosis. Four months previously, she had noticed areas of pruritic eruption on her legs, which became red and subsequently brownish. Computed tomography (CT) of the chest showed multiple pulmonary nodules two months prior to her visit. She had experienced appetite loss and lost 4 kg in body weight over the previous five months. Her medical history included gastric ulcers, osteoporosis and hypertension. She had taken MTX (6 mg weekly) for 17 years. Other medications included prednisolone (5 mg/day), folic acid (5 mg/week), diclofenac sodium, lansoprazole, candesartan and risdownate. A physical examination showed no abnormal findings, except for areas of eruption on both lower legs. The lesions were firm and appeared similar to subcutaneous nodules. The patient’s laboratory data were as follows: WBC count, 8,730/μL; hemoglobin, 11.9 mg/dL; platelet count, 199,000/μL; aspartate aminotransferase (AST), 30 IU/L; alanine aminotransferase (ALT), 32 IU/L; lactate dehydrogenase (LDH), 280 IU/L; alkaline phosphatase (ALP), 371 IU/L; blood urea nitrogen (BUN), 30.5 mg/dL; creatinine, 1.11 mg/dL; and C-reactive protein (CRP), 3.59 mg/dL. Chest CT (Fig. 1) revealed multiple pulmonary nodules, which had increased in size and number compared to those noted on the previous scan. In addition, a skin biopsy demonstrated dense infiltration of large atypical lymphoid cells surrounded by small lymphocytes around the small vessels of the dermis and subcutaneous tissue that had led to the destruction of the vascular wall. Additional labo-
ratory data showed a soluble IL-2 receptor level of 3,448 U/mL and a ferritin concentration of 169.1 ng/mL. The serum antibody titers for the EB virus were negative for EB virus-associated nuclear antigen antibodies and viral capsid antigen (VCA)-IgM. Meanwhile, the VCA-IgG ratio was 1:640, and the early antigen-DR component-IgG ratio was 1:20. Positive EB virus DNA was found at 300 copies/1,000,000 leukocytes. Furthermore, the immunohistological findings of the skin biopsy showed the large atypical lymphoid cells to be positive for CD20, CD79α and EB-encoded small RNA (EBER), whereas the small lymphocytes surrounding the areas of dense infiltration of large atypical lymphoid cells stained positive for CD3. These findings led to a diagnosis of Grade 3 LyG based on the high number of EBER-positive lymphocytes (>50/high-power field) (1). A polymerase chain reaction (PCR) analysis of the specimen to elucidate the rearrangement of the immunoglobulin heavy chain gene was negative.

Three weeks after her initial visit, the patient was taken to the hospital by ambulance due to generalized tonic-clonic convulsions. Her body temperature was 38°C, and she exhibited neck stiffness. The convulsions subsided with the administration of benzodiazepine. The findings of brain magnetic resonance imaging were normal; however, an examination of the cerebrospinal fluid (CSF) revealed an increased cell number (41/μL; mononuclear cells, 36/μL, polynuclear cells, 5/μL) and an elevated protein level (43 mg/dL), with a glucose level of 56 mg/dL. The results of a microbacterial culture were negative, and cytology showed small lymphocytes without atypia. In addition, the findings of a PCR analysis for tuberculosis and Cryptococcus antigens in the CSF were negative. Although no tests for viral replication or a flow cytometric analysis were performed, we could not deny the possibility of aseptic meningitis due to MTX-induced LyG and decided to stop the drug. Empiric therapy with ceftriaxone and acyclovir was also commenced. Following the discontinuation of MTX and the antibiotics, the patient experienced no further convulsions, and the skin lesions disappeared within a few months. A bronchoscopic examination for pulmonary nodulosis was considered; however, it was canceled because chest CT three weeks performed after the cessation of MTX showed a marked decrease in the lesions of pulmonary nodulosis (Fig. 2). The patient has remained well for two years under the administration of sulfasalazine and prednisolone (2.5 mg/day), and chest CT performed two years after the discontinuation of MTX showed no pulmonary nodules.

Discussion

LyG cases often involve the lungs (>90%), skin (25-50%), kidneys (32%), liver (29%) and brain (32%) (1). The present patient demonstrated skin involvement of LyG due to MTX. In addition, the lung lesions were also considered to be caused by the drug, although the etiology of the aseptic meningitis remains unknown. However, we consider that LyG likely caused the patient’s aseptic meningitis, as the two conditions developed simultaneously, and convulsions are a neurological manifestation of LyG (2).

The association between the administration of MTX and the development of non-Hodgkin lymphoproliferative disorders is unclear. A prospective cohort study showed that the incidence of Hodgkin lymphoma, but not non-Hodgkin lymphoma, is significantly higher in RA patients treated with MTX compared to that observed in the general population (6). On the other hand, reports of lymphoma regression following MTX discontinuation suggest a causative role in select cases (6, 7). In a retrospective series of MTX-associated lymphoma in Japan, diffuse large B-cell lymphoma (DLBCL) was identified to be the most commonly reported type (60.4%, 29 of 48 cases) (7). In that study, a regression of lymphoma following the withdrawal of MTX was observed in 11 of 48 cases. Six patients, including one with DLBCL, experienced sustained remission, while the remaining five developed recurrence (7). LyG is a less aggressive lymphoproliferative disorder, with regression of LyG following the discontinuation of MTX having also been reported (3-5). Interestingly, LyG occasionally progresses to DLBCL (1), and the coexistence of LyG and DLBCL has been documented (3). Therefore, LyG may be a prodromal
condition of DLBCL.

Six previously reported cases demonstrated an association between the onset of LyG and the use of MTX (Table). The mean patient age and MTX exposure was 68.5 and 7.5 years, respectively. The patients exhibited involvement of the lungs (5/6), skin (2/6), liver (3/6) and spleen (3/6). In four of the six cases, LyG regression was observed within 3-12 weeks after the discontinuation of MTX. The current report presents the first case of MTX-induced Grade 3 LyG, and the patient’s condition improved with the discontinuation of MTX treatment. These findings suggest that MTX-induced LyG can display spontaneous regression following the discontinuation of drug therapy, even if the LyG demonstrated a high grade.

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

References


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