Methotrexate-associated Intravascular Large B-cell Lymphoma in a Patient with Rheumatoid Arthritis

Jun Kikuchi¹, Yuko Kaneko¹, Hidenori Kasahara², Katsura Emoto³, Akiharu Kubo⁴, Shinichiro Okamoto² and Tsutomu Takeuchi¹

Abstract

Intravascular large B-cell lymphoma (IVLBCL) is a rare and clinically aggressive lymphoma with an unfavorable prognosis. We report the case of a 50-year-old woman who was diagnosed with IVLBCL during treatment with methotrexate (MTX) and biologic agents for rheumatoid arthritis. The symptoms showed partial improvement only after the cessation of both treatments. She subsequently received chemotherapy and achieved a complete remission and has remained free of recurrence for 2 years without any further treatment. We herein describe a rare case of IVLBCL which presented with the features of an MTX-associated lymphoproliferative disorder.

Key words: rheumatoid arthritis, intravascular lymphoma, methotrexate, spontaneous regression

(Intern Med 55: 1661-1665, 2016)
(DOI: 10.2169/internalmedicine.55.6943)

Introduction

Patients with rheumatoid arthritis (RA) are at a high risk of developing malignant lymphoma, and the association is indicated not only with RA itself but also anti-rheumatic drugs (1). In 2008, methotrexate-associated lymphoproliferative disorders (MTX-LPDs) were recognized as iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPDs) by the World Health Organization (WHO) (2). Diffuse large B-cell lymphoma is the most common MTX-LPD, followed by Hodgkin lymphoma and peripheral T cell lymphoma. The spontaneous regression of MTX-LPDs with the cessation of MTX and without the need for chemotherapy has recently attracted attention (3).

Intravascular large B-cell lymphoma (IVLBCL), which is characterized by restricted growth in the lumina of vessels is a rare and aggressive malignant lymphoma that was also defined by the WHO in 2008 (4). The prognosis of IVLBCL is poor because it is often difficult to diagnose and due to its rapid progression. There are no previously reported cases of MTX-associated IVLBCL.

We herein report the case of a patient with RA who developed MTX-associated IVLBCL that partially regressed with the discontinuation of MTX.

Case Report

A 50-year-old woman with RA was admitted to our hospital complaining of persistent fever and painful red induration on her right leg. Her RA had been treated with MTX (8 mg/week) for 3 years and etanercept [50 mg/week; etanercept is a tumor necrosis factor inhibitor (TNFi)], for 1.4 years after 8-months of treatment with adalimumab (her treatment was switched due to a loss of efficacy). Although her RA activity was stable, she had had low-grade fever. One month later, she started complaining of high-grade fever together with transient painful erythema on her right thigh. MTX and subsequently etanercept were discontinued, and levofloxacin was administered. The symptoms showed slight improvement but she was admitted to our hospital because the painful skin erythematous induration spread over both lower legs (Fig. 1). Neither superficial adenopathy nor hepatosplenomegaly were observed. A neurological exami-
nation revealed normal findings, and she did not complain about any neurological symptoms, including headache or dizziness. Her blood test results were as follows: white blood cell count, 3,900/μL; hemoglobin, 11.2 mg/dL; platelet count, 30.6 × 10⁹/μL; serum lactate dehydrogenase (LDH), 519 IU/L (normal, 115-245); aspartate transaminase, 38 IU/L (normal, 5-40); alanine transaminase, 38 IU/L (normal, 0.70 mg/dL; normal, 0.47-0.79); C-reactive protein (CRP), 7.24 mg/dL (normal, ≤0.30); ferritin, 177 ng/mL (normal, 3.6-114); and soluble interleukin-2 receptor (sIL-2R), 1,373 U/mL (normal, 145-519). Tests for anti-neutrophil cytoplasmic antigens, immunoglobulin (Ig) G type rheumatoid factor, antigen of hepatitis B virus, antibody against hepatitis C virus and interferon gamma releasing assay for tuberculosis were all negative. Serum antigen tests with an enzyme immunoassay for Epstein-Barr virus (EBV) showed a previous infection [anti-viral-capsid antigen (VCA) IgG antibody, 7.9 IU/mL; anti-VCA IgM, 0.8 IU/mL; anti-EBNA IgG, 3.6 IU/mL; and anti-EA IgG, 1.4 IU/mL]; EBV-DNA was undetectable in the patient’s whole blood. A blood culture failed to grow any bacteria. Transthoracic echocardiography showed no vegetation on the valves and the whole body computed tomography findings were normal.

Biopsies of the skin and subcutaneous tissue in her left lower leg revealed atypical lymphoid cell proliferation within the small vessels of the adipose tissue; there were no significant findings in the superficial dermal tissue (Fig. 2a and b). The atypical lymphoid cells were positive for CD3, CD79α, CD5, and MIB-1 (KI-67), but were negative for CD20, CD34, and EBER in situ hybridization (Fig. 2c and d). Fluoroodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) showed uptake in the medias tinum, the dura mater in the right forehead, and the bones (including the bilateral zygoma, ethmoid, mandible, clavicle, scapula, sternum, spine, ribs, pelvic bones, bilateral humerus, radius, femur, tibia, and tarsal bones), which implied bone marrow uptake (Fig. 3a). A cytological examination of the patient’s spinal fluid was negative for atypical lymphocytes, but magnetic resonance imaging (MRI) of her head showed hypertrophy with contrast enhancement of the dura mater in the frontal and parietal head as well as FDG-PET/CT, which showed the same maximum standardized uptake value as other accumulating sites. This implied the infiltration of lymphoma cells in the dura mater (Fig. 3b and c). A bone marrow biopsy showed slightly hypercellular marrow with a few atypical cells that were positive for CD20 and CD79α. No lesion that could have been considered as the primary extravascular origin of lymphoma was evident.

Based upon these findings, she was diagnosed with IVLBCL. Within a few weeks after stopping MTX and etanercept, she gradually became afebrile and her serum LDH, CRP, and sIL-2R values decreased (Fig. 4). However, considering the unfavorable prognosis of IVLBCL and the involvement of her tumor with the central nervous system and bone marrow, we started 8 courses of R-CHOP chemotherapy [Rituximab (375 mg/m²), cyclophosphamide (750 mg/m²), Vincristine (1.4 mg/m²), Adriamycin (50 mg/m²), and prednisolone (100 mg/day) for 5 days every three weeks). She also received 4 courses of intrathecal chemotherapy prednisolone (50 mg), methotrexate (12 mg), and cytarabine (20 mg) per course]. After the treatment she achieved a complete remission and has remained free of recurrence for 2 years (Fig. 3d). In terms of the RA activity, her clinical disease activity index was less than that at the time of the diagnosis of LPD and remained in remission throughout and after chemotherapy. The rheumatoid factor titer was around 30 IU/mL at the onset of LPD and before R-CHOP chemotherapy, and decreased to 5 IU/mL after chemotherapy.

Discussion

To the best of our knowledge, this is the first report of an IVLBCL occurring as an OIIA-LPD in a patient with RA. Although IVLBCL usually shows an aggressive clinical course with a considerably poor prognosis (5), our patient demonstrated that IVLBCL as an MTX-LPD can regress with the cessation of MTX. IVLBCL is an aggressive type of lymphoma that is associated with a poor prognosis; its spontaneous regression has never been reported. While the distribution of the involved organs and the pathological findings in our patient were distinctive; the clinical presentation was atypical. Cases in which central nervous system involvement is restricted to the dura mater without neurological symptoms are rare (5-7). In Asian patients with IVLBCL, skin lesions are an infrequent initial symptom. Hemophagocytic syndrome, which is common in Asian patients, was not seen in the clinical course of our patient. She had no splenomegaly, cytopenia, hyperferritinemia of >500 ng/mL, and a bone marrow biopsy showed no hemophagocytosis. Such lukewarm presentations might have been attributable to her LPD being associated with MTX. This might have led to the partial regression of her IVLBCL after the cessation of MTX, despite
the multiple organ involvement.

In Japanese patients, MTX-LPDs are often associated with EBV. It has been reported that 60% of patients with MTX-LPDs are regarded as EBV-positive in Japan, which is higher than the rate reported in Western studies (3, 8, 9). The ratio of spontaneous LPD regression with the cessation of MTX alone is reported to be higher in EBV-positive patients than in EBV-negative patients. The patient of the present case was EBV negative, but LPD regressed with the cessation of MTX. There is one case report of RA with MTX-LPD that presented with vascular involvement (10). However, in that case, polymorphic or Hodgkin-like LPD with EBER-positive large B-cells in the destructed arteries and veins and extensive infiltration into the subcutaneous tissue.

It is not clear whether etanercept was responsible for the patient’s LPD. Her fever and skin lesions began to regress soon after the cessation of MTX. Although there are some reports of LPDs occurring in patients treated with TNFi, the suggestion that etanercept is associated with an increased risk of OHLA-LPDs remains controversial (11, 12). We therefore diagnosed the patient with MTX-induced IVLBCL.

Complete remission can be expected in MTX-LPDs that regress in less than 4 weeks (13). Since our case started showing spontaneous regression soon after the withdrawal of MTX, it was unclear whether additional chemotherapy was necessary. There is a growing interest in MTX-LPD regression without chemotherapy. The maximum shrinkage was obtained at approximately 8 weeks after the cessation of MTX (14). However, her FDG-PET/CT revealed extended involvement, which forced us administer R-CHOP because early chemotherapy has been reported to lead to a favorable outcome in IVLBCL (7, 15). At present, the patient has been in complete remission for 2 years. The 2-year relapse rate of IVLBCL with rituximab-contained chemotherapy is reported to be approximately 40% (15), thus further careful follow-up is warranted.

In conclusion, physicians should be aware of IVLBCL as an MTX-LPD, and the further accumulation of similar cases could enable us to understand the characteristics of IVLBCL as an MTX-LPD.

Author’s disclosure of potential Conflicts of Interest (COI). Tsutomu Takeuchi: Advisory role, Astra Zeneca, Eli Lilly Japan, Novartis Pharma, Mitsubishi Tanabe Pharma, Asahi Kasei Medical, AbbVie, Daiichi Sankyo, and Bristol-Myers; Honoraria, AbbVie, Bristol-Myers, Chugai Pharmaceutical, Eisai, Janssen Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer Japan, Takeda Pharmaceutical, Astellas Pharma and Daiichi Sankyo; Research funding, Astellas Pharma, Bristol-Myers, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, Mitsubishi Tanabe Pharma, Pfizer Japan, Santen Pharmaceutical, Takeda Pharmaceutical, Teijin Pharma.
Figure 3. Fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) of the whole body and head and T2-weighted magnetic resonance imaging (MRI) of the head. (a) Whole body FDG-PET/CT showed increased FDG uptake in the bones. (b) T2-weighted MRI showed hypertrophy of the dura mater in the right frontal head (white arrow). (c) FDG-PET/CT showed increased FDG uptake with a high titer of the maximum standardized uptake value in the dura mater of the right frontal head (white arrow). (d) The whole body FDG uptake decreased after chemotherapy.

Figure 4. The clinical course. The clinical symptoms, lactate dehydrogenase (LDH) level, C reactive protein (CRP) level and treatments are shown.
AbbVie, Asahi Kasei Pharma, Taisho Toyama Pharmaceutical, and SymBio Pharmaceuticals. Yuko Kaneko: Honoraria, Abbvie, Eisai Pharmaceutical, Chugai Pharmaceutical, Bristol Myers Squibb, Astellas Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer, Janssen, and UCB.

References


© 2016 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imonline/index.html