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Case Study

Successful Treatment of Immunodeficiency-Associated EBV-Negative Lymphoproliferative Disorders in Rheumatoid Arthritis by Methotrexate Withdrawal and Prevention of its Relapse by Rituximab Administration

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Immunodeficiency-associated lymphoproliferative disorders (LPD) in rheumatoid arthritis are a rare, aggressive, and life-threatening clinical entity. We describe a 60-year-old man who had rheumatoid arthritis that was treated with methotrexate. Eight months after the treatment, the case was diagnosed as Epstein-Barr virus-negative LPD (diffuse large B-cell lymphoma) with abdominal bulky mass and clinical stage IVB at high risk in the international prognostic index. Immediate withdrawal of methotrexate led the patient to achieve complete remission, and 8 subsequent courses of rituximab treatment for the prevention of relapse kept the patient disease-free for 29 months. Our case suggests that these treatments may be an effective, safe, and feasible strategy for immunodeficiency-associated LPD in rheumatoid arthritis. 〔*J Clin Exp Hematopathol 52(3) : 193-198, 2012*〕

Keywords: immunodeficiency-associated lymphoproliferative disorders, rheumatoid arthritis, methotrexate withdrawal, rituximab

INTRODUCTION

Rheumatoid arthritis (RA) is a progressive, chronic autoimmune inflammatory disease that is currently treated with various immunosuppressive agents such as prednisolone, methotrexate (MTX), rituximab, anti-tumor necrosis factor-α inhibitors, and anti-interleukin (IL)-6 receptor inhibitors.[1-4] Among these drugs, MTX is generally considered the mainstay for RA treatment.[5,6]

The incidence of malignant lymphoma (ML) was reported to be higher in RA patients than in the healthy population.[7-9] Moreover, immunosuppressive agents such as MTX have been reported to increase the risk of developing ML.[7-9] Immunodeficiency-associated lymphoproliferative disorders (LPD) are a clinical entity characterized by LPD, according to the WHO classification, that develop following administration of MTX for autoimmune diseases such as RA.[10-13]

Rituximab is a chimeric human/mouse anti-CD20 monoclonal antibody. Rituximab treatment is effective in patients with $CD20^+$ B-cell lymphoma, Waldenström's macroglobulinemia, and RA.[3,14]

Here, we report a case of immunodeficiency-associated LPD during the treatment of RA.

CASE REPORT

A 60-year-old man presenting with fever and an abdominal mass was referred to our hospital on November 9, 2009. The patient was previously diagnosed with RA on the basis of findings of symmetric polyarthritis of peripheral joints with pain, joint deformities, elevation of rheumatoid factor, and anti-cyclic citrullinated peptide on March 2, 2009. Initially, MTX was administered at a dose of 6 mg/week on May 7, 2009. Although MTX was administered, the symptoms of the patient were not resolved. Subsequently, the dose of MTX was increased to 8 mg/week on June 4 and 12 mg/week on September 7, 2009. His condition regarding RA was controlled by the administration of MTX in a dose-dependent manner. However, he was examined because of his fever and

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elevated C-reactive protein level on October 2, 2009. According to the examination of fever, he was diagnosed with nontubercular mycobacteria (NTM) by bronchial fiberscopy findings and treated with rifampicin, ethambutol, levofloxacin, and clarithromycin for NTM. Furthermore, computed tomography (CT) of the abdominal mass and elevation of lactate dehydrogenase (LDH) and soluble IL-2 receptor levels suggested the possibility of ML. The patient was admitted to our hospital for further examination on November 9, 2009.

On admission, the patient was normotensive (122/68 mmHg) with a heart rate of 72 beats/min. Physical examination revealed him to have 2 finger-breadths of splenomegaly and abdominal mass. His extremities presented a marked swan neck deformity. The laboratory findings are summarized in Table 1. Positron emission tomography/CT showed uptake in abdominal lymph nodes, splenomegaly, and a large lower-abdominal mass involving urinary bladder, colon, and aorta (Fig. 1a). The gastrointestinal endoscopy (GIS) findings of the stomach revealed chronic atrophic gastritis and swelling of the upper portion of the gastric body and ulcer with reddish swelling on the gastric fundus (Fig. 1b & 1c). These findings were compatible with ML. Chest CT showed lesions of the right lower lung cavity. Moreover, abdominal CT showed swelling of the abdominal lymph nodes, a large lower-abdominal mass, and splenomegaly.

The histological findings of the stomach revealed diffuse proliferation of atypical large lymphocytes (Fig. 1d). Immunohistochemical findings showed that these abnormal lymphocytes exhibited CD20, CD79a, CD10, and BCL6 (Fig. 1e). Epstein-Barr virus (EBV)-encoded RNA *in situ* hybridization was negative. MIB-1 index was 86.9%. These findings led to the histological diagnosis of diffuse large B-cell lymphoma (DLBCL). Infiltration of abnormal lymphocytes was not detected in the bone marrow.

Taking these findings together, we made a diagnosis of non-Hodgkin's lymphoma, DLBCL, with clinical stage IVB, at high risk in the international prognostic index (IPI), following MTX administration for RA. The total dose of MTX for RA was 210 mg during the 8 months from initiation to withdrawal of MTX.

Initially, the patient was examined for several complications, such as the possibilities of perforation of the upper colon, NTM activity, RA activity, and abdominal aneurysm. We also immediately withdrew the MTX therapy on November 9, 2009. Subsequent serial examination by LDH and abdominal ultrasound showed the gradual regression of LDH and abdominal mass (data not shown). Four weeks later, the stomach, abdominal, and lower-abdominal mass markedly regressed, except for the lesions of NTM in the left lung (Fig. 2a). Thus, the patient was assessed to have attained complete response on the basis of the findings of the resolution of positron emission tomography/CT uptake and normal findings on GIS on December 12, 2009 (Fig. 2a & 2b). Despite the excellent control of immunodeficiency-associated LPD, the activity of RA was progressive after MTX withdrawal. On the basis of the bulky mass and the high risk of IPI, we subsequently treated the patient with weekly rituximab at a dose of 375 mg/m^2 according to various

Table 1. Laboratory findings on admission

Urinalysis	
Protein	2+
Sugar	−
Occult blood	−
Peripheral blood cell count	
White blood cell count	8,450/μL
Band	5.0 %
Segmented	18.0 %
Lymphocyte	21.0 %
Atypical lymphocyte	1.0 %
Monocyte	10.0 %
Red blood cell count	384 × 10^4/μL
Hemoglobin	11.3 g/dL
Hematocrit	34.9 %
Mean corpuscular volume	90.9 fl
MCH	29.4 pg
MCHC	32.4 %
Platelet count	56.9 × 10^4/μL

Coagulation	
Prothrombin time	12.4 sec
APTT	31.2 sec
Fibrinogen	213.5 mg/dL
FDP	2.4 mg/dL
Serum chemistry	
Total bilirubin	0.54 mg/dL
Aspartate aminotransferase	29 IU/L
Alanine aminotransferase	9 IU/L
Lactate dehydrogenase	1,692 IU/L
γ-glutamyl transpeptidase	69 IU/L
Serum amylase	36 IU/L
Glucose	104 mg/dL
Na	137 mmol/L
K	5.03 mmol/L
Ca	9.2 mg/dL
Blood urea nitrogen	13.2 mg/dL
Creatinine	0.8 mg/dL
Uric acid	10.6 mg/dL
Total protein	6.8 g/dL
Serum albumin	2.8 g/dL

Serology	
C-reactive protein	10.46 mg/dL
IgG	1,946 mg/dL
IgA	434 mg/dL
IgM	713 mg/dL
Anti-nuclear antibody	x 640
Rheumatoid factor	5,850 IU/mL
CCP	45.0 IU/mL
Matrix metalloproteinase-3	85.8 ng/mL
Anti-cardiolipin antibody	(−)
Soluble interleukin-2 receptor	4,160 IU/L
Human T-cell leukemia virus type I	(−)
EBV VCA-IgM	1.1
EBV VCA-IgG	10.3
EBV EBNA IgG	4.1
EBV EA-DR IgG	< 10

MCH, mean corpuscular hemoglobin concentration ; MCHC, mean corpuscular hemoglobin concentration ; APTT, activated partial thromboplastin time ; FDP, fibrin/fibrinogen degradation products ; CCP, anti-cyclic citrullinated peptide antibody ; EBV, Epstein-Barr virus

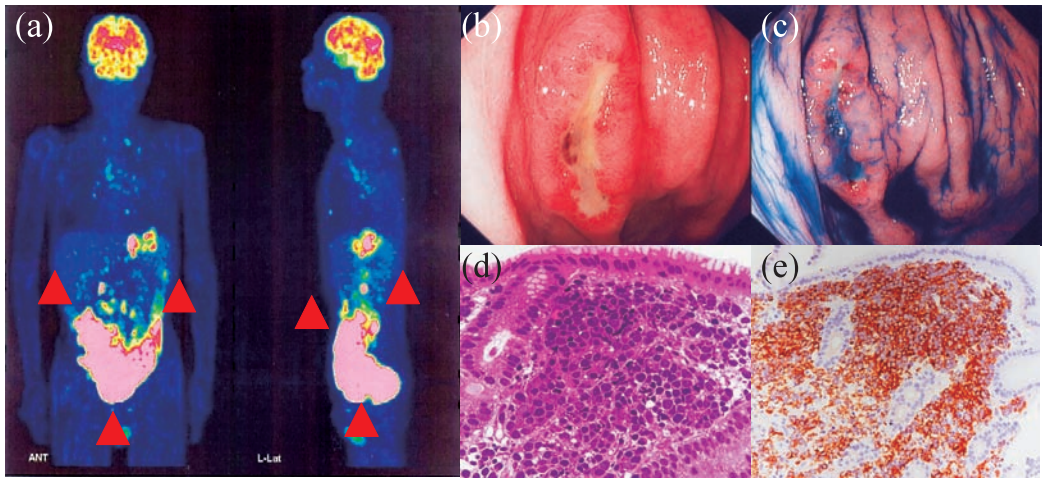

Fig. 1. Positron emission tomography/computed tomography (PET/CT), gastrointestinal endoscopy (GIS), and histological findings at diagnosis. (***1a***) PET/CT showing the uptake in abdominal lymph nodes, splenomegaly, and a large lower-abdominal mass involving urinary bladder, colon, and aorta. (***1b*** & ***1c***) GIS findings of the stomach revealing chronic atrophic gastritis and swelling of the upper portion of the gastric body and ulcer with reddish swelling on the gastric fundus. (***1d*** & ***1e***) Histological findings of the diffuse proliferation of abnormal lymphocytes with the expression of $CD20^{+}$ are consistent with non-Hodgkin's lymphoma (diffuse large B-cell lymphoma).

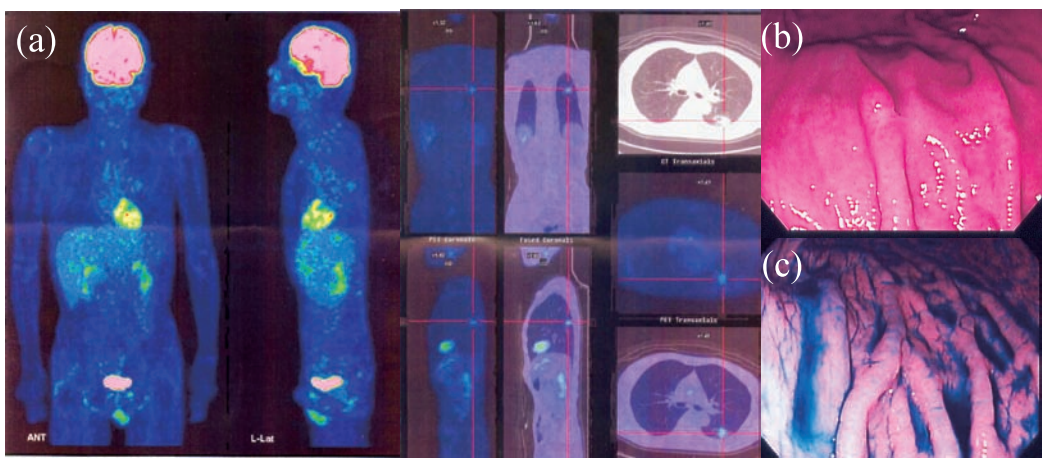

Fig. 2. Positron emission tomography/computed tomography (PET/CT) and gastrointestinal endoscopy (GIS) findings after methotrexate withdrawal. (***2a***) PET/CT showing nonuptake in previously uptaking lesions except for the lesions of nontubercular mycobacteria in left lung. (***2b*** & ***2c***) GIS findings of the stomach revealing resolution of the swelling in the upper portion of the gastric body and ulcer with reddish swelling on the gastric fundus.

complications and his performance status on December 14, 2010. After 4 courses of weekly scheduled rituximab therapy, the patient maintained a complete response. Rituximab was also effective for control of RA. The score of disease activity score-C-reactive protein for RA was improved from 6.3 to 2.2. Moreover, we additionally administered 4 courses of weekly scheduled rituximab therapy on June 14, 2010 (Fig. 3). After these treatments, the patient was disease-free and underwent pulmonary resection of the lesions due to NTM on July 11, 2011. However, the control of RA was exacerbated on December 20, 2011, and was controlled by the administration of tacrolimus at 2 mg and prednisolone at 5 mg. Twenty-nine months after diagnosis, he no longer needs further treatment for immunodeficiency-associated LPD.

DISCUSSION

Spontaneous remission of ML is reported to be an ex-

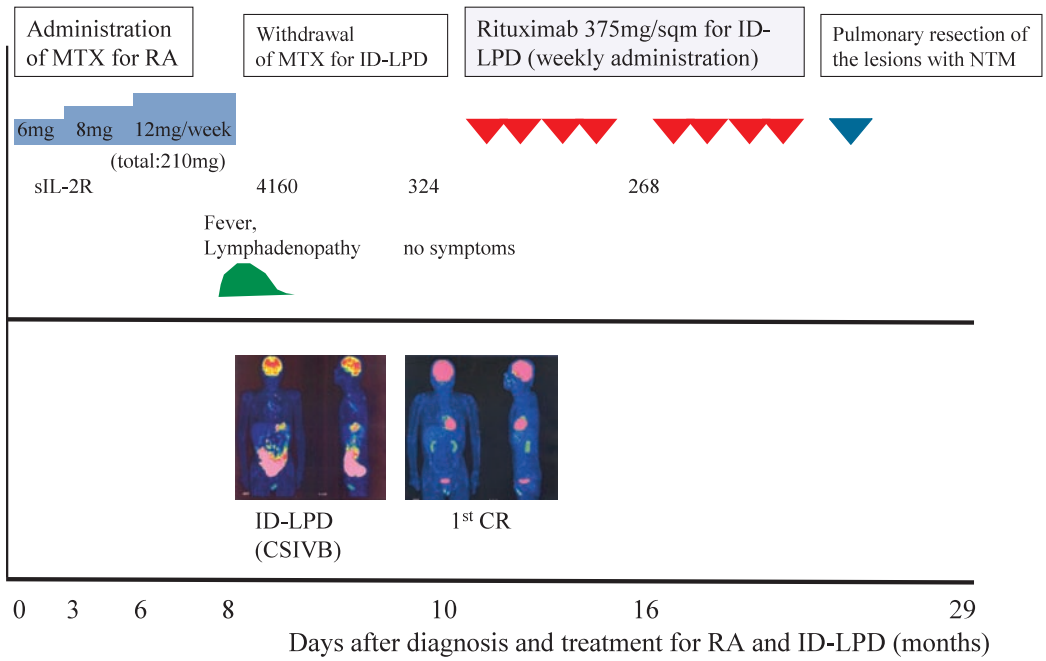

Fig. 3. Clinical course of immunodeficiency-associated lymphoproliferative disorder (ID-LPD). The patient was treated with methotrexate (MTX) for rheumatoid arthritis (RA). Eight months after the treatment, he was diagnosed with Epstein-Barr virus-negative LPD (diffuse large B-cell lymphoma) with abdominal bulky mass and clinical stage IVB (CSIVB). Immediate withdrawal of methotrexate led the patient to achieve complete remission (CR), and 8 subsequent courses of rituximab treatment for the prevention of relapse kept the patient disease-free for 29 months NTM, nontubercular mycobacteria ; sIL-2R, soluble interleukin-2 receptor.

tremely rare event.[15,16] However, regression of ML following withdrawal of MTX is a characteristic feature of immunodeficiency-associated LPD.[7-13] Hoshida *et al*. reported that the rate of immunodeficiency-associated LPD regression was approximately 30% following withdrawal of MTX.[13] Therefore, for treatment of immunodeficiency-associated LPD, immediate withdrawal of MTX is necessary.[7-13]

To the best of our knowledge, our case was the first to show onset of EBV-negative immunodeficiency-associated LPD under the condition of short-duration administration of MTX, and spontaneous remission of ML with a bulky mass after withdrawal of MTX. Subsequent treatment with rituximab also successfully led to a disease-free status. The onset of immunodeficiency-associated LPD in our case may be related to the administration of MTX and the high activity of RA.

First, marked regression of ML occurred after withdrawal of MTX, although the case was diagnosed as DLBCL with clinical stage IVB, with a large tumor (more than 10 cm) and high-risk IPI. Histological findings of immunodeficiency-associated LPD vary among DLBCL, follicular lymphoma, and Hodgkin's lymphoma.[7-13] One of the mechanisms of immunodeficiency-associated LPD was suggested to be the activation of EBV.[7-13] Wolfe *et al*. reported that 30−40% of all immunodeficiency-associated LPD cases were related to EBV activation.[8] Feng *et al*. reported that one of the direct mechanisms of ML due to MTX was the direct stimulation of EBV-infected B cells by MTX.[17] In our case, histological findings of EBV-encoded RNA-negativity confirmed the negative relationship between immunodeficiency-associated LPD and EBV. Other suggested mechanisms of immunodeficiency-associated LPD are the hyperimmune state of RA and immunosuppression by MTX.[7-13] We previously reported the disease progression of ML, such as adult T-cell lymphoma (ATL), in living-donor liver transplant recipients undergoing immunosuppressive treatment.[18] Moreover, we also described the development of 3 cases of ATL in 8 HTLV-I carriers among 164 living-donor liver transplant recipients undergoing immunosuppressive treatment.[18] Indeed, the cessation of immunosuppressive drugs suppressed the proliferation of ATL cells in one case.[18] These reports suggest that the immunosuppressive state of the host may play a major role in the development of ML. Niitsu *et al*. reported that the median duration of immunodeficiency-associated LPD in 29 RA patients was 96 months, and the median duration of MTX treatment was 56 months with a median cumulative dose of 864 mg.[19] Spontaneous remission oc-

curred in six of 29 patients, and the four EBV-positive patients achieved complete response.[19] In our case, the duration of MTX treatment for RA was only 8 months, and the total dose of MTX administered was 210 mg, given in a dose-escalated manner. Therefore, in our case, the development of immunodeficiency-associated LPD after MTX therapy may have been due to the hyperimmune state of RA and immunosuppression by MTX.

Second, to prevent the relapse of immunodeficiency-associated LPD, we administered 4 courses of weekly rituximab at 375 mg/m^2 every 6 months (a total of 8 courses) according to the performance status and various complications such as NTM and abdominal aneurysm. The major concern about immunodeficiency-associated LPD is the relapse of ML following regression.[7-13,19] Therefore, chemotherapy is needed to prevent relapse.[7-13,19] However, no standard treatment for immunodeficiency-associated LPD has been established to date because of the lack of randomized controlled trials. Currently, the appropriate chemotherapy for immunodeficiency-associated LPD is determined according to histological findings, IPI, performance status, organ dysfunction status, or immunological status of RA.[7-13,19] According to the bulky mass, the high risk of the IPI, various complications, and his performance status, we subsequently treated the patient with rituximab. Our results suggest that rituximab treatment is effective in patients with CD20$^+$ B-cell lymphoma and RA, and that the 4 weekly scheduled courses of rituximab consisting of 375 mg/m^2 every 6 months (a total of 8 courses) may be one of the reasonable treatment options for immunodeficiency-associated LPD and RA. However, in our case, the activity of RA was transiently controlled during only one year following the administration of 8 courses of rituximab. Therefore, further rituximab administration may be needed to control the activity of RA.

In conclusion, our case indicates that MTX withdrawal and rituximab treatment are safe, feasible, and effective for treating immunodeficiency-associated LPD in patients with RA. A randomized study and longer follow-up periods will be necessary to assess this therapeutic modality.

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Conflict of interest statement

The authors have no conflict of interest.

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