Lymphoproliferative disorder with pathological fracture of the femur in a patient with rheumatoid arthritis treated with methotrexate: A case report

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Abstract. Methotrexate (MTX) is the key drug for the treatment of rheumatoid arthritis (RA). MTX-treated RA has been associated with the development of lymphoproliferative disorders (LPDs). Notably, the hyperimmune state of RA itself or the immunosuppressive state induced by MTX administration may contribute to development of LPD. Furthermore, Epstein-Barr virus (EBV) has been indicated to contribute to the development of MTX-LPD. MTX-associated LPD (MTX-LPD) may affect nodal or extranodal sites, including the gastrointestinal tract, skin, lungs, kidneys, and soft tissues, at an almost equal frequency. However, it is rare for MTX-LPD to manifest as multiple bone tumors with a pathological fracture. The present study reported the case of a 46-year-old Japanese woman with RA who had complications of EBV-positive MTX-LPD during an approximate 5-year course of MTX therapy. The present study indicated a rare case in which the LPD had spread to multiple bones in a patient with a pathologic fracture. Notably, the LPD was subclassified as diffuse large B-cell lymphoma (DLBCL).

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Abbreviations: RA, rheumatoid arthritis; LPD, lymphoproliferative disorder; MTX, methotrexate; MTX-LPD, methotrexate-associated lymphoproliferative disorder; WHO, World Health Organization; CRP, C-reactive protein; LD, lactate dehydrogenase; sIL-2R, soluble interleukin-2 receptor; EBV, Epstein-Barr virus; MRI, magnetic resonance imaging; T1W1, T1-weighted image; ^{18}F-FDG-PET, ^{18}F-fluoro-deoxy-glucose positron emission tomography; DLBCL, diffuse large B-cell lymphoma; non-GCB, non-germinal center B; haplo-PBSCT, haplo-peripheral blood stem cell transplantation

Key words: rheumatoid arthritis, methotrexate-associated lymphoproliferative disorder, diffuse large B-cell lymphoma, multiple bone tumors, pathological fracture

Introduction

Osteolytic lesions of long bones are typical occurring pathological fracture. The most common bone disease pathological fracturse are metastatic tumors. About 10% of patients with primary malignant tumor will develop metastasis of the proximal femur. Common bone metastases are derived from breast, kidney, thyroid, prostate cancer, or myeloma (1,2).

Several studies have documented that patients with rheumatoid arthritis (RA) have an increased risk of developing a lymphoproliferative disorder (LPD). Patients with RA have a high risk of developing LPDs about two to four times compared to the general population (3). Methotrexate (MTX) is currently a widely used disease-modifying anti-rheumatic drug. MTX-associated LPD (MTX-LPD) is a lymphoid proliferation or lymphoma that occurs in patients immunosuppressed with MTX and classified as a part of the 'other iatrogenic immunodeficiency-associated LPDs' category by the World Health Organization (WHO) in 2001 (4). MTX-LPD have characteristics of elderly patients, more females, more Diffuse large B cell lymphoma (DLBCL), more EBV positivity, and poor prognosis (5).

Case report

A 46-year-old woman was admitted to our hospital complaining of right thigh pain and fatigue. She had a medical history of RA for 5 years and 2 months. She had been receiving MTX (8-10 mg/week) for 4 years and 11 months and etanercept (25 mg/week) for 3 years and 5 months. Her RA activity had been well controlled with these drugs. The laboratory data showed the following elevated values: Leukocyte, 8,200/μl (normal range: 4,300-8,000/μl); C-reactive protein (CRP), 10.07 mg/dl (normal range: 0-0.40 mg/dl); calcium, 11.5 mg/dl (normal range: 7.0-10.0 mg/dl); inorganic phosphorus, 6.0 mg/dl (normal range: 2.9-4.3 mg/dl); alkaline phosphatase, 442 U/l (normal range: 115-359 U/l); lactate dehydrogenase (LD), 466 U/l (normal range: 119-229 U/l); and soluble interleukin-2 receptor (sIL-2R), 2,900 U/ml (normal range: 124-466 U/ml). On examination for infection, serological tests revealed that the Epstein-Barr virus (EBV)

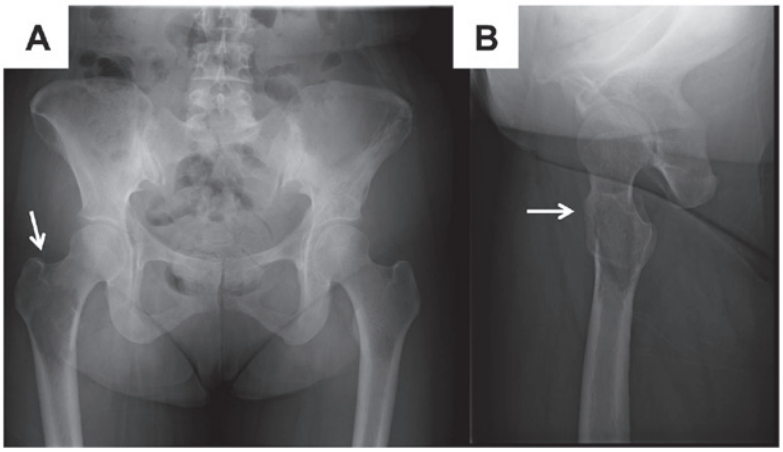

Figure 1. Initial hip X-ray image. Ill-defined osteolytic lesion and pathological fracture of the right femoral trochanter were detected. (A) Anteroposterior view; (B) lateral view. The white arrows indicate pathological fracture of femoral neck.

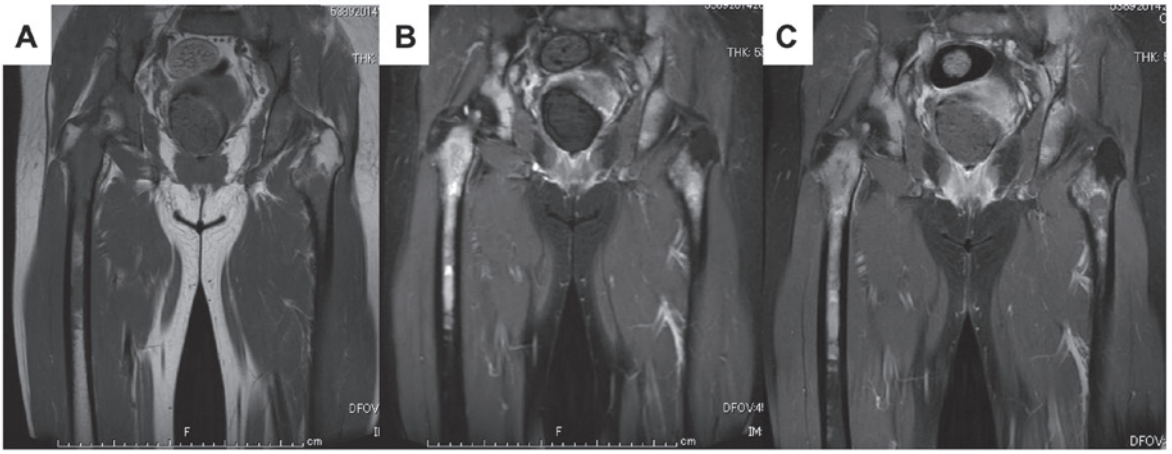

Figure 2. Initial magnetic resonance imaging. The mass was detected diffusely at the bilateral femur and iliac. (A) T1-weighted image; (B) T2-weighted image; (C) contrast-enhanced T1-weighted image.

viral capsid antigen immunoglobulin G titer was high, which indicated a current infection.

Hip X-ray image showed an ill-defined osteolytic lesion and pathological fracture of the right femoral trochanter (Fig. 1A and B, white arrows). Magnetic resonance imaging (MRI) showed that the masses in the bilateral femur and iliac had a low intensity on the T1-weighted image (T1WI) and high intensity on the T2-weighted image and were enhanced on gadolinium enhanced-T1WI (Fig. 2A-C). Whole-body computed tomography demonstrated axillary, mediastinal, and external iliac lymphadenopathies. Further, ^{18}F-fluoro-deoxy-glucose positron emission tomography (^{18}F-FDG-PET) showed some abnormal uptakes in the ribs, pelvis, femur, and lymph nodes (Fig. 3A-D).

We performed open biopsy and palliative surgery using an intramedullary nail, *because we considered that complete resection was impossible*. The specimen showed diffuse infiltration of monotonous lymphoid cells (Fig. 4A). Immunohistochemical studies demonstrated that the infiltrating mononuclear cells were predominantly positive for CD79a, CD20 and MUM-1. CD10 and B-cell lymphoma 6 were not detected (Fig. 4B-D). The histological diagnosis was diffuse large B-cell lymphoma (DLBCL) of non-germinal center B type (non-GCB type).

We referred the patient to a hematologist. Following withdrawal of MTX, her LD and sIL-2R levels decreased gradually at 4 weeks. Furthermore, osteoblastic change in the iliac bone was observed on an X-ray image. Based on the overall clinical data, the multiple bone tumors were diagnosed as MTX-LPD.

However, her LD and sIL-2R levels increased rapidly after 2 months. Further, ^{18}F-FDG-PET revealed progressive disease. She received a total of five cycles of R-CHOP (rituximab, 375 mg/m^2; cyclophosphamide, 750 mg/m^2; doxorubicin, 50 mg/m^2; vincristine, 1.4 mg/m^2; and oral prednisolone, 225 mg) on days 1-5 on a 21-day schedule. After chemotherapy, she experienced nausea and headache. Thus, she underwent MRI of the head, and intracranial dissemination of the DLBCL was observed. Then, she also underwent cranial irradiation, one cycle of mini MEAM (ranimustine, 50 mg/day; etoposide, 100 mg/day; cytarabine, 200 mg/day; and melphalan, 20 mg/day) on days 1-3, and two cycles of IT triple (MTX, 15 mg; cytarabine, 40 mg; and prednisolone, 10 mg). After the three cycles of chemotherapy, she received haplo-peripheral blood stem cell transplantation (haplo-PBSCT). After

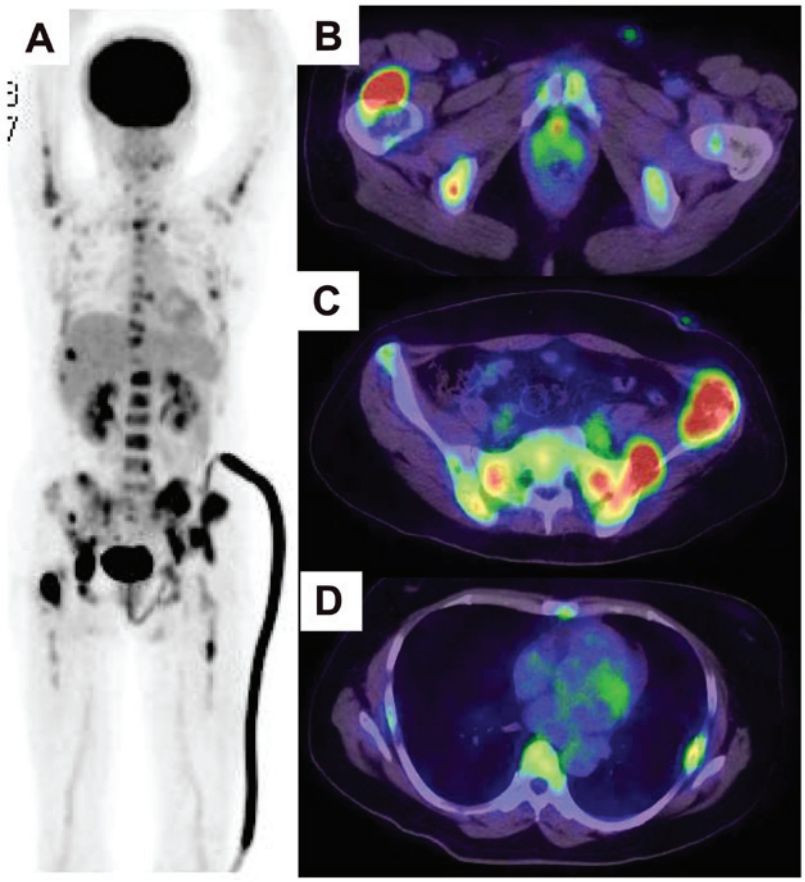

Figure 3. ^{18}F-fluoro-deoxy-glucose positron emission tomography (PET). (A) Whole-body PET showed multiple abnormal uptakes. (B) PET-computed tomography (CT) of the thoracic level. The SUV_{max} was 21.6 at the right axillary lymph node. (C) PET-CT of the iliac bone. The SUV_{max} was 10.2 at the left iliac bone. (D) PET-CT of the ribs showed abnormal uptakes at some ribs. The SUV_{max} was 5.46-7.82.

haplo-PBSCT, her intracranial lesion disappeared, and her symptoms improved.

At the final follow-up, *tumor condition* was no evidence of disease. *She had no pain of her lower legs, and walking alone. X-ray showed sclerotic change of bilateral proximal femurs were observed* (Fig. 5).

Discussion

The prevalence of RA is slightly different among countries worldwide; however, the prevalence is ~0.5%, and the estimated number of affected patients is 800,000 in Japan (6). RA is a systemic inflammatory disease characterized by the destruction of the articular structures and synovitis in multiple joints. MTX is an anti-rheumatic drug that is expected to have an excellent suppressive effect on articular destruction (7). For this reason, MTX is currently a widely used key drug for the treatment of patients with RA. However, patients with RA have a high risk of developing LPDs (3). Furthermore, LPD in patients with RA treated with MTX is defined as MTX-LPD in the 2001 WHO classification of tumors of hematopoietic and lymphoid tissues (4). Although the detailed mechanism of the occurrence of MTX-LPD is unknown, it is considered that MTX is involved as an etiology because there are cases where LPD had a complete regression after withdrawal of MTX alone (8). Furthermore, patients with RA treated with high-dose MTX (over 8 mg/week) are at a high risk of developing LPDs (9).

The clinical findings of MTX-LPD include fever, weight loss, and swelling of superficial lymph nodes. In the blood sampling data, high levels of CRP, LD, and sIL-2R are observed. In MTX-LPD, lymphomas occur in half of the lymph nodes and half of the extranodal lesions, such as the skin, gastrointestinal tract, salivary gland, thyroid, and nasal cavity (4,10). As in this case, multiple bone lesions accompanying a pathological fracture were not detected. The percentage of the pathological diagnosis of lymphomas in patients with RA is 35 to 60% for DLBCL and 12 to 25% for Hodgkin's lymphoma (5). In our case, the pathological diagnosis was DLBCL.

EBV is a known oncogenic virus involved in lymphomagenesis. An immunodeficiency status is considered to provide the basis for the onset of malignant lymphomas through the activation of EBV. The EBV-positive rate in MTX-LPD is 27.6 to 95%, which is significantly higher than that in sporadic LPD (9.9%) (3,11,12). Kamel *et al* (13) reported that MTX-LPD was associated with EBV because some cases of EBV-positive MTX-LPD spontaneously regressed after the withdrawal of MTX. Further, Feng *et al* (14) showed that MTX directly releases infectious virions and induces reactivation of EBV infection. No case of non-MTX-LPD showed spontaneous regression. In our case, the EBV result was positive; thus, she stopped using MTX. However, her condition did not improve, and the LD and sIL-2R levels in her blood sampling data increased rapidly after 2 months. Miyazaki *et al* (8) reported that the complete remission rate of MTX-LPD was ~30% with

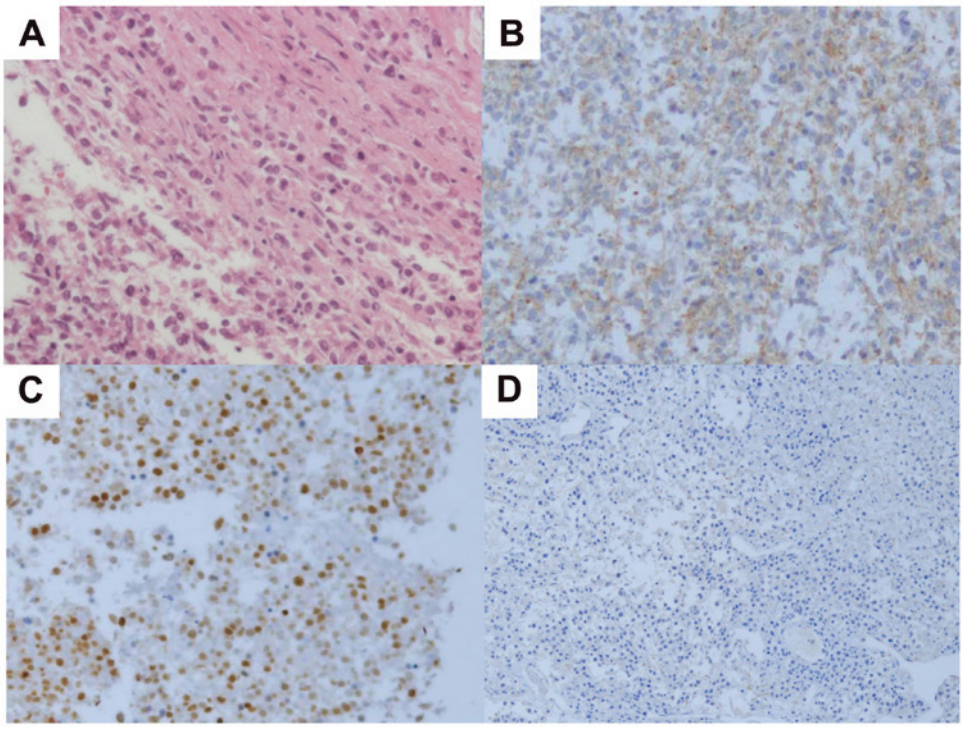

Figure 4. Histological findings. (A) H&E staining showed diffuse infiltration of monotonous lymphoid cells. (B-D) Immunohistological studies. Infiltrating mononuclear cells were predominantly positive for CD20 (B) and MUM-1 (C), but negative for B-cell lymphoma 6 (D).

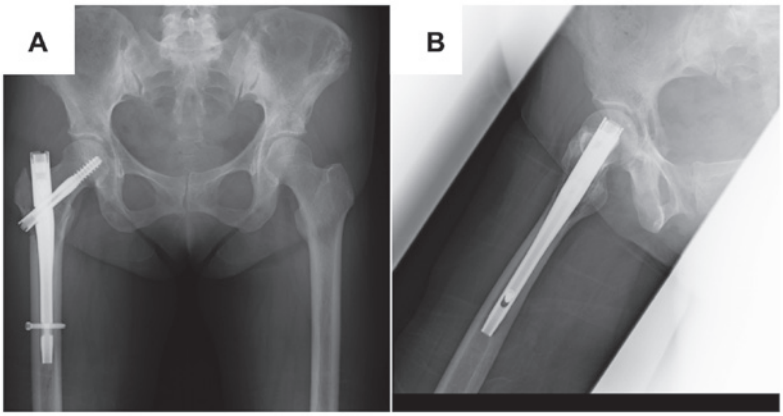

Figure 5. At the final follow-up, X-ray shows sclerotic change of bilateral proximal femurs. (A) Anteroposterior view; (B) Lateral view.

MTX withdrawal; however, the complete remission rate was as high as 60% in their EBV-positive cases. Therefore, many cases resulted in complete remission within 2 weeks. In this case, temporary improvement was obtained after MTX withdrawal; however, complete remission was not achieved within 2 weeks. Therefore, the patient was determined to have progressive disease after 2 months. For cases wherein complete remission cannot be obtained within 2 weeks, we should consult with hematologists and need to introduce chemotherapy.

Since DLBCL of a non-GCB type diagnosed on immunohistochemistry usually has a poor prognosis (15), we need to consider introducing chemotherapy. In summary, we experienced an MTX-LPD case with a pathological fracture. We need to consider MTX-LPD when pathological fractures occur in patients with RA treated with MTX.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Author's contributions

NO designed the study and wrote the initial draft of the manuscript. MH contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. MI, TI, ST, MO and HN contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

Ethics approval and consent to participate

The patient provided consent.

Patient consent for publication

The patient and her family were informed that the data from her case would be submitted for publication and provided consent.

Competing interests

The authors declare that they have no competing interests.

References

1. Hage WD, Aboulafia AJ and Aboulafia DM: Incidence, location, and diagnostic evaluation of metastatic bone disease. Orthop Clin North Am 31: 515-528, vii, 2000.
2. Ricci AI, Wodajo FM and Malawer M: Metastatic carcinoma of the long bones. Am Fam Physician 76: 1489-1494, 2007.
3. Ekström K, Hjalgrim H, Brandt L, Baecklund E, Klareskog L, Ekbom A and Askling J: Risk of malignant lymphomas in patients with rheumatoid arthritis and in their first-degree relatives. Arthritis Rheum 48: 963-970, 2003.
4. Harris NL and Swerdlow SH: Methotrexate-associated lymphoproliferative disorders. In: Jaffe ES, Harris NL, Stein H, Vardiman JW (eds). Pathology and genetics, tumours of haematopoietic and lymphoid tissues, World Health Organization classification of tumours. Lyon: IARC Press: pp270-271, 2001.
5. Hoshida Y, Xu JX, Fujita S, Nakamichi I, Ikeda J, Tomita Y, Nakatsuka S, Tamaru J, Iizuka A, Takeuchi T and Aozasa K: Lymphoproliferative disorders in rheumatoid arthritis: Clinicopathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol 34: 322-331, 2007.
6. Ministry of Health, Labour and Welfare: Rheumatoid arthritis and allergy information 6: 123-154, 2010.
7. Heldmann F and Braun J: Perioperative use of methotrexate. Clin Exp Rheumatol 28(5 Suppl 61): S110-S113, 2010.
8. Miyazaki T, Fujimaki K, Shirasugi Y, Yoshiba F, Ohsaka M, Miyazaki K, Yamazaki E, Sakai R, Tamaru J, Kishi K, *et al*: Remission of lymphoma after withdrawal of methotrexate in rheumatoid arthritis: Relationship with type of latent Epstein-Barr virus infection. Am J Hematol 82: 1106-1109, 2007.
9. Kameda T, Dobashi H, Miyatake N, Inoo M, Onishi I, Kurata N, Mitsunaka H, Kawakami K, Fukumoto T, Susaki K, *et al*: Association of higher methotrexate dose with lymphoproliferative disease onset in rheumatoid arthritis patients. Arthritis Care Res (Hoboken) 66: 1302-1309, 2014.
10. Mariette X, Cazals-Hatem D, Warszawki J, Liote F, Balandraud N and Sibilia J; Investigators of the Club Rhumatismes et Inflammation: Lymphomas in rheumatoid arthritis patients treated with methotrexate: A 3-year prospective study in France. Blood 99: 3909-3915, 2002.
11. Hoshida Y and Aozasa K: Malignancies in organ transplant recipients. Pathol Int 54: 649-658, 2004.
12. Nalesnik MA, Jaffe R, Starzl TE, Demetris AJ, Porter K, Burnham JA, Makowka L, Ho M and Locker J: The pathology of posttransplant lymphoproliferative disorders occurring in the setting of cyclosporine A-prednisone immunosuppression. Am J Pathol 133: 173-192, 1988.
13. Kamel OW, Van de Rijin M, Weiss LM, Del Zoppo GJ, Hench PK, Robbins BA, Montgomery PG, Warnke RA and Dorfman RF: Brief report: Reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. N Engl J Med 328: 1317-1321, 1993.
14. Feng WH, Cohen JI, Fischer S, Li L, Sneller M, Goldbach-Mansky R, Raab-Traub N, Delecluse HJ and Kenney SC: Reactivation of latent Epstein-Barr virus by methotrexate: A potential contributor to methotrexate-associated lymphomas. J Natl Cancer Inst 96: 1691-1702, 2004.
15. Hans CP, Weisenburger OD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Müller-Hermelink HK, Campo E, Braziel RM, Jaffe ES, *et al*: Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 103: 275-282, 2004.