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Methotrexate-Associated Lymphoproliferative Disorder in Two Patients with Rheumatoid Arthritis Whose Treatment Included Kampo Medicines

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Abstract

Methotrexate (MTX) is used to treat Rheumatoid Arthritis (RA). Methotrexate-associated Lymphoproliferative Disorder (MTX-LPD) has been reported. Here we report two cases of MTX-LPD in patients with RA treated with MTX and Kampo medicines. Case 1 was a 70-year-old woman who developed MTX-LPD on MTX 8 mg, tacrolimus, and daibofuto. Case 2 was a 50-year-old woman who had had RA for 9 years and been treated with MTX 8 mg per week for 6 years; she developed MTX-LPD while also taking abatacept, bakumondoto, and unkeito. In case 1, MTX-LPD only resolved after discontinuation of MTX; her RA was subsequently controlled by Minocycline and daibofuto. In case 2, MTX-LPD resolved after treatment with rituximab; her RA was then controlled with prednisolone 3 mg, iguratimod 50 mg, and Negative Nepi or Rio. Some Kampo medicines may have immunoregulatory activity and affect the serum MTX level. These medicines should be used cautiously in patients with RA if they are being treated with MTX.

Keywords: Rheumatoid arthritis; Kampo medicines; Methotrexate; *Glycyrrhizae radix*; Methotrexate-associated lymphoproliferative disorder

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Introduction

Kampo (traditional Japanese) medicines were first introduced from China via the Korean Peninsula 1500 years ago and since then have developed in a way unique to Japan. Kampo medicines are integrated into the Japanese national healthcare system. One hundred and forty-eight formulations containing Kampo extracts and 187 crude Kampo formulations are approved by the Ministry of Health, Labor, and Welfare and used under the national health insurance program [1].

Rheumatoid Arthritis (RA) is an autoimmune disease that causes joint pain and damage throughout the body. RA was described as early as 1500 BC in the Ebers Papyrus and has been treated with Kampo medicines for hundreds of years. Kogure et al. [2] reported that a Kampo decoction known preparations of carnitine (Gui Zhi Er Yue Bi Yit Tang Jia Zhu Fu Tang; KNEIJB) in combination with methotrexate (MTX) is safe and well tolerated and has clinical and economic benefits [2]. A systematic review by Daily et al. [3] highlighted the usefulness of guizhi-shaoyao-zhimu, which is used as Ignorant tenant for RA in Japan [3].

The guidelines describe MTX as Avery effective treatment for RA. However, it has serious adverse effects, including liver disease, interstitial pneumonia, and myelosuppression. Lymphoma was first reported in a patient treated with MTX for RA in 1991 [4]. Lymphoma in such patients is now known as MTX-associated lymphoproliferative disorder (MTX-LPD). Here we report two cases of MTX-LPD in patients with RA who were treated with Kampo medicines in combination with MTX.

Case Presentation

Case 1

She was a 70-year-old woman who had been diagnosed with RA 16 years earlier. She had been taking MTX 8 mg/week for 6 years, a Kampo decoction known as daibofuto (Da Fang Feng Tang; DBFT) for 2 years, and tacrolimus 1 mg/day for 6 months. Although her RA activity was stable,

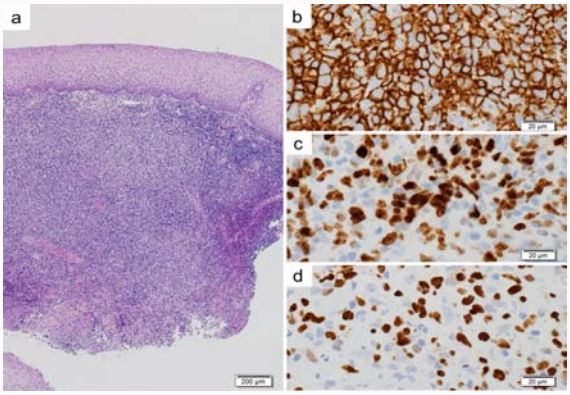

Figure 1: Pathologic findings in the pharyngeal mucosa. a) Heterogenous stratified squamous epithelium is observed. Hematoxylin-eosin staining reveals an infiltration of lymphoid cells with necrosis beneath the epithelium. The lymphoid cells are mainly of the large type. b) The atypical lymphoid cells were positive for CD20 and c) 70% were positive for MIB-1. d) Most of the atypical lymphoid cells were positive on EBER in situ hybridization. Scale bars: (a) 200 μm and (b,c) 20 μm.

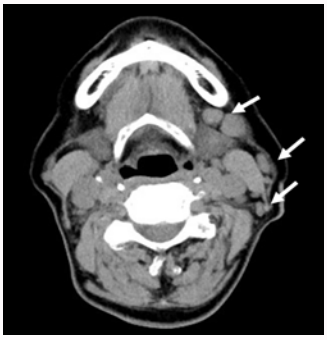

Figure 2: Axial computed tomography images showing swelling of multiple lymph nodes in the neck (white arrow). However, there is no evidence of a tumor in the pharynx.

she developed a low-grade fever. A month later, she complained of a sore throat, which led to detection of a pharyngeal ulcer. MTX was discontinued and garenoxacin was started. One week later, her sore throat had improved but the ulcer had not healed completely. A biopsy of her pharyngeal mucosa revealed an infiltration of lymphoid cells, mainly of the large type, with necrosis beneath normal epithelium (Figure 1a). The atypical lymphoid cells were positive for CD20, had a high Ki-67 (MIB-1) labeling index, and were positive on EBER in situ hybridization (Figure 1b-1d) but were negative for CD3, CD5, and CD10. Her blood test results were as follows: white blood cell count, 4,100/μL; hemoglobin, 11.4 mg/dL; platelet count 14.4 × 10^4/μL; serum lactate dehydrogenase, 234 IU/L (normal, 110-210); aspartate transaminase 22 IU/L (normal, 12-31); alanine transaminase 25 IU/L (normal, 8-40); serum creatinine 0.64 mg/dL (normal, 0.40-0.80); C-reactive protein 4.03 mg/dL (normal <0.14); ferritin 331 ng/mL (normal, 12-60); and solubleinterleukin-2 receptor 2305 U/mL (normal, 122-469). Test results for anti-neutrophil cytoplasmic antigens, hepatitis B virus antigen, and hepatitis C virus antibody as well as an interferon-gamma releasing assay for tuberculosis were all negative. Serum antigen tests and an enzyme immunoassay revealed previous Epstein-Barr virus infection (anti-viral-capsid antigen IgG antibody 160 times; anti-viral-capsid antigen IgM <10 times; anti-Epstein-Barr nuclear antigen IgG 40 times; anti-early antigen IgG <10 times). Computed tomography revealed multiple swollen lymph nodes in the patient's neck (Figure 2). She was diagnosed to have MTX-LPD. Within a few weeks of discontinuing MTX, DBFT, and tacrolimus, her fever resolved, her pharyngeal ulcer healed, her serum C-reactive protein level normalized, and her serum lactate dehydrogenase and soluble interleukin-2 receptor levels returned to their baseline values. In the 3 months following resolution of her pharyngeal ulcer, she was treated with minocycline 100 mg and DBFT. A complete remission of MTX-LPD was achieved. The patient has remained recurrence-free for 1 year, and her RA clinical disease activity has remained in remission.

Case 2

She was a 50-year-old woman who had had RA for 9 years. She was taking various Kampo medicines and had taken MTX 8 mg/week for 6 years. She had also taken abatacept (a fusion protein composed of the Fc region of IgG1 fused to the extracellular domain of CTLA-4) at a dose of 125 mg/week for 1.5 years after 2 years of treatment with etanercept (her treatment was switched because of loss of efficacy) in combination with two Kampo formulations, i.e. bakumondoto (Mai Men Dong Tang; BAK) extract 7.5 g and unkeito (Wen Jing Tang; UKT) extract 7.5 g (both from Tsumura Co., Tokyo, Japan). Although her RA activity was stable, she developed left-sided cervical lymphadenopathy. Therefore, MTX, abatacept, BAK, and UKT were discontinued. After 2 weeks, there was improvement but not complete resolution of her lymphadenopathy. A lymph node biopsy revealed tumor cells with large, irregular, clear nuclei and multiple nucleoli (Figure 3a). The atypical lymphoid cells were positive for CD20 and had a high Ki-67 (MIB-1) labeling index (Figure 3b,3c) but were negative for CD3, CD5, cyclin D1, MUM-1, and EBER in situ hybridization (Figure 3d). Fluoro-deoxy-glucose positron emission tomography/computed tomography showed uptake in the pharynx, right axillary lymph nodes, and the right elbow (Figure 4a). We attributed the uptake in the right elbow to arthritis that predated the onset of lymphadenopathy. Her blood test results were as follows: white blood cell count, 4,990/μL; hemoglobin, 13.1 mg/dL; platelet count, 28.1 × 10^4/μL; serum lactate dehydrogenase 174 IU/L (normal, 115-245); aspartate transaminase 19 IU/L (normal 12-31); alanine transaminase 10 IU/L (normal, 8-40); serum creatinine 0.54 mg/dL (normal 0.40-0.80); C-reactive protein 0.33 mg/dL (normal

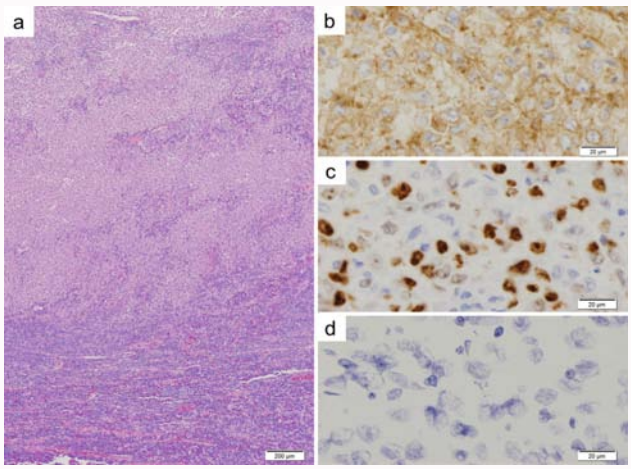

Figure 3: Pathologic findings in the lymph nodes from the neck. a) On hematoxylin-eosin staining, the tumor cells in the lymph nodes have large, irregular clear nuclei and multiple nucleoli. b) Atypical lymphoid cells in the nodes were positive for CD20 and c) 80% were positive for MIB-1. d) Most of the atypical lymphoid cells were negative on EBER in situ hybridization. Scale bars: (a) 200 μm, (b-d) 20 μm.

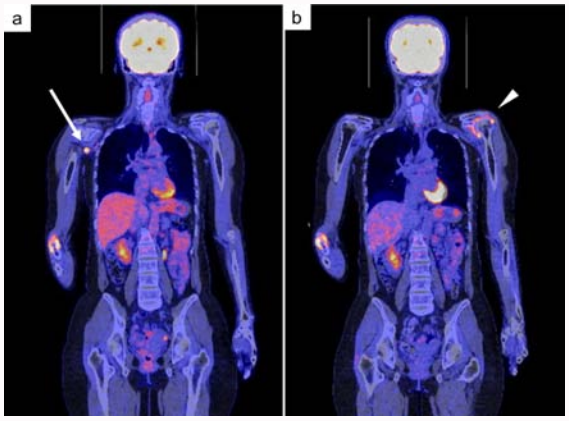

Figure 4: FDG-PET/CT of the whole body and head. a) Whole body FDG-PET/CT showed increased FDG uptake in the right axillary lymph nodes (white arrow). b) Whole body FDG-PET/CT showed no abnormal FDG uptake after rituximab monotherapy except in the swollen right elbow and right axilla (white arrowheads). FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography.

<0.14); ferritin 97 ng/mL (normal 3.6-114); and soluble interleukin-2 receptor 241 U/mL (normal 145-519). Tests for antineutrophil cytoplasmic antigens, hepatitis B virus antigen, and hepatitis C virus antibody were negative, as was an interferon-gamma releasing assay for tuberculosis. Serum antigen tests with an enzyme immunoassay for Epstein-Barr virus showed previous infection (anti-viral-capsid antigen IgG antibody, 80 times; anti-viral-capsid antigen IgM <10 times; anti-Epstein-Barr nuclear antigen IgG 40 times; and anti-early antigen IgG <10 times). She was diagnosed with MTX-LPD. Her right-sided axillary lymph node swelling did not improve in the 8 weeks following cessation of the MTX, abatacept, and Kampo medicines. Therefore, we started rituximab as monotherapy (an injection of 375 mg/m^2 at weekly intervals for 8 weeks). After 8 cycles of treatment, the patient achieved a complete remission and has remained recurrence-free for 1year (Figure 4b). Her RA clinical disease activity has remained low while on prednisolone 3 mg, iguratimod 50 mg, and the KNEIJB decoction.

Discussion

To the best of our knowledge, these are the first reports of MTX-LPD in patients with RA who have been taking Kampo medicines. Kampo medicines have long been used in the treatment of arthritis and in Japan may be used in combination with other agents for various reasons in the treatment of RA. For example, KNEIJB can be used in combination with MTX to increase the therapeutic effect [2].

In case 1, DBFT was administered to alleviate joint pain. DBFT is a herbal medicine that contains 15 compounds (i.e. *Astragali Radix* 6 g, *Paeoniae Radix* 3 g, *Rehmanniae Radix* 3 g, *Angelicae Radix* 3 g, *Atractylodis Rhizoma* 3 g, *Glehniae Radix cum Rhizoma* 3.0 g, *Saposhnikoviae Radix* 3g, *Eucommiae Cortex* 3 g, *Cnidii Rhizoma* 2 g, *Glycyrrhizae Radix* 1.5 g, *Notopterygii Rhizoma* 1.5 g, *Achyranthis Radix* 1.5 g, *Zizyphi Fructus* 1.5 g, *Ginseng Radix* 1.5 g, *Zingiberis Peocessum Rhizoma* 1.0 g, and *Processi Aconiti Radix* 14 g) and is used to treat RA. Inoue et al. [5] investigated the effect of DBFT on collagen-induced arthritis in mice and suggested that its ability to attenuate the symptoms of arthritis might involve immunomodulatory and anti-osteoclastogenic mechanisms [5].

In case 2, BAK and UKT were used to treat dryness of the mucosa and skin. These products have been reported to increase secretion of saliva and improve immune status in patients with dry eye and mouth associated with Sjögren's syndrome [6] of note; both BAK and UKT contain *Glycyrrhizae Radix*.

Kampo medicines are considered to be relatively safe with the exception of some side effects, such as interstitial pneumonia and hepatic impairment caused by *Scutellaria Radix* and pseudoaldosteronism caused by *Glycyrrhizae Radix* [1]. However, it is also known that some herbal medicines affect the blood levels of certain drugs, and it is possible that *Glycyrrhizae Radix* increased the serum MTX level in the two patients described in this report. Although we were not able to monitor the serum MTX level in either of our two patients, Lin et al. [7] reported that *Glycyrrhizin* and *licorice* (the root of *Glycyrrhizae uralensis*) significantly increased the area under the blood concentration-time curve and mean residence time in rats. Therefore, it is possible that concomitant administration of MTX and Kampo herbal medicines containing *Glycyrrhizae Radix* resulted in an increase in the area under the blood concentration-time curve and mean residence time for MTX in our two patients.

Meta-analyses of epidemiologic studies in RA have identified clinically and statistically significant associations between RA and certain types of malignancy, particularly lymphoma [8]. MTX has been used in the treatment of RA since the 1990s; since then, there have been an increasing number of reports of MTX-LPD. In 1997, Georgescu et al. [9] reviewed 25 cases of lymphoma in patients with RA who were treated with MTX and described the following four important features: a predominance of large or polymorphous B-cell non-Hodgkin lymphoma (90%), a high rate of extranodal involvement (69%), a high frequency of Epstein-Barr virus infection (41%), and the possibility of remission only after withdrawal of MTX. Several case series and literature reviews have confirmed their findings. Our first case had all four of the above-mentioned features and the second had polymorphous B-cell non-Hodgkin lymphoma. Hashimoto et al. [10] reported that older age and use of MTX and tacrolimus were associated with lymphoma in the NinJa cohort and we believe that Kampo medicines may have immunomodulatory activity that can increase the risk of MTX-LPD in the same way as tacrolimus. Furthermore, the *Glycyrrhizae Radix* contained in Kampo medicines may increase the serum MTX level, which is also thought to increase the risk of MTX-LPD. MTX-LPD did not recur in either of our patients even when Kampo medicines were restarted after remission. We think it unlikely that Kampo medicines alone cause LPD; however, MTX-LPD may develop when MTX and Kampo medicines are taken at the same time.

We are aware of only these two cases of MTX-LPD so far, and it is not certain if the risk of MTX-LPD is increased when MTX and Kampo medicines are used in combination. However, awareness of MTX-LPD is essential when Kampo medicines are used with MTX. Although research on MTX-LPD is ongoing, there is still no research on the risk of MTX-LTD when MTX is administered concomitantly with traditional Chinese medicines, Kampo medicines, or *Glycyrrhizae Radix*. We believe that concomitant use of agents such as *Glycyrrhizae Radix* may affect the serum MTX level and that this possibility should be investigated in the future.

In conclusion, we have encountered two cases of MTX-LPD in patients with RA treated with a combination of MTX and Kampo medicines. We consider that Kampo medicines should be used with caution in patients with RA who are being treated with MTX because they may have immunoregulatory activity and affect the MTX level.

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Conflicts of Interest

TN and NS have received lecture fees from Tsumura & Co. The Department of Japanese Oriental Medicine, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, and the Department of Kampo Diagnostics, Institute of Natural Medicine, University of Toyama, where the authors are employed, have received a research grant from Tsumura & Co. but not for purposes related to this case report.

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