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

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 as 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 a very 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.

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,
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 of her pharyngeal mucosa. 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).

**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, 14.4 × 10^4/μL; serum lactate dehydrogenase, 234 IU/L; aspartate transaminase 10 IU/L; serum creatinine 0.54 mg/dL; 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.
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 Glycyrrhiza Radix [1]. However, it is also known that some herbal medicines affect the blood levels of certain drugs, and it is possible that Glycyrrhiza 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 Glycyrrhiza 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 Glycyrrhiza 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 Glycyrrhiza 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 Glycyrrhiza Radix. We believe that concomitant use of agents such as Glycyrrhiza 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 immunomodulatory activity and affect the MTX level.
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Conflicts of Interest

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References