Case Report

Spontaneous regression of a renal mass and multiple lung nodules after methotrexate cessation

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Abbreviations & Acronyms
LPD = lymphoproliferative disorder
MRI = magnetic resonance imaging
MTX = methotrexate
MTX-LPD = methotrexate-related lymphoproliferative disorder
WHO = World Health Organization

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Introduction: Methotrexate has been reported to increase the risk of lymphoproliferative disorders. We report a rare case who was clinically diagnosed with methotrexate-associated lymphoproliferative disorders of the kidney.

Case presentation: A 77-year-old patient with rheumatoid arthritis had taken low-dose methotrexate for 13 years. The patient developed left renal mass 3 cm in size and multiple pulmonary nodules. Initially, renal malignant tumor with lung metastases was considered and the renal biopsy was planned. However, under possible diagnosis of methotrexate-related lymphoproliferative disorder, we withdrew methotrexate treatment at first and then observed spontaneous regression of the tumorous lesions of the kidney and lungs.

Conclusion: Although methotrexate-related lymphoproliferative disorder in kidneys is very rare, our case advocates the importance of a relevant differential diagnosis of methotrexate-related lymphoproliferative disorder under the setting of long-term treatment of methotrexate for rheumatoid arthritis.

Key words: kidney, methotrexate, MTX-LPD, multiple tumors, rheumatoid arthritis.

Keynote message
We reported a rare case of MTX-LPD of the kidney, which is an adverse event of MTX treatment in patients with rheumatoid arthritis. In this case, we experienced spontaneous regression of a renal mass and multiple lung nodules after MTX cessation. Because MTX has been widely used as the first-line treatment for rheumatoid arthritis, physicians should keep this disorder in mind.

Introduction
MTX-LPD is a rare adverse event characterized by a lymphoid proliferation or lymphoma found in immunosuppressed patients mainly with rheumatoid arthritis who have been receiving low-dose MTX therapy. We report here a 77-year-old female patient with rheumatoid arthritis who had been treated with MTX for 13 years and presented a renal mass and multiple lung nodules. Given the possibility of extranodal MTX-LPD, we stopped her MTX treatment and observed spontaneous regression of all the tumorous lesions. This case is a rare instance of renal and pulmonary manifestations closely mimicking a renal malignant tumor with lung metastasis.

Case report
A 77-year-old female was referred to our urology department for the differential diagnosis of a left renal mass and multiple bilateral lung nodules. The patient had no family history of renal cancer. Her bilateral lung nodules appeared 1 month ago on a chest X-ray taken in a preoperative examination of her pituitary adenoma, which was diagnosed at another hospital based on the patient’s complaint of restricted visual field. Rheumatoid arthritis had been diagnosed 14 years ago, and the patient had been receiving low-dose MTX (2–12 mg/week) for
13 years. Contrast-enhanced computed tomography revealed a slightly enhanced, 3-cm left renal mass and multiple pulmonary nodules with a maximal diameter of 2.5 cm (Figs 1 left and 2 left).

As a differential diagnosis, renal malignancy with multiple lung metastases was first considered, and a renal biopsy was planned. However, the possibility that all the lesions might be a rare presentation of MTX-LPD was raised because of long-term administration of MTX. After discussion, we decided to cease MTX administration and to monitor the patient closely. Twenty-four days after stopping treatment, shrinkage of the multiple lung lesions was observed on a chest X-ray. Enhanced computed tomography 7 weeks after the cessation of treatment revealed significant regression of the renal and lung masses (Figs 1 middle and 2 right). An enhanced computed tomography 8 months later disclosed complete regression of the lung lesions and considerable reduction in the renal mass (Fig. 1 right). At the 12-month follow-up, no recurrence was observed.

After stopping low-dose MTX, tacrolimus hydrate 0.5 mg was given for the patient’s rheumatoid arthritis with no significant adverse event, and remission has been maintained. A head MRI performed 10 months after stopping MTX showed no change in the pituitary adenoma, and surgery was planned.

**Discussion**

LPD occasionally develop in immunodeficient individuals. The current WHO classification of lymphoid neoplasms (4th edn, 2017) categorizes MTX-LPD as a representative instance of iatrogenic, immunodeficiency-associated LPDs under the subtype of immunodeficiency-associated LPDs. MTX-LPD develops in patients taking MTX, and its presentation includes superficial lymphadenopathy, extranodal mass, and much less frequently, abdominal pain, bone pain, fever, cough, and thrombocytopenia. MTX-LPD is characterized by a wide variation in its primary presentation, which is not limited to enlargement of the lymph nodes; extranodal presentation is as common as nodal presentation. In a report of 76 rheumatoid arthritis patients with MTX-LPD or non-MTX-LPD, the primary sites were mainly distributed among the lymph nodes (44.7%), epipharynx (5.3%), and lungs (5.3%). Genitourinary presentations as in the present case are comparatively rare (2.6% in the urinary tract and 1.3% in the testes). Our patient developed multiple nodular lesions in the bilateral lungs as well as a left renal mass, which had the appearance of renal cell cancer with multiple lung metastasis. To the best of our knowledge, no previous report of an MTX-LPD presentation like the present one has been reported.

While malignant lymphomas require chemotherapy, some lymphomas associated with MTX-LPD regressed spontaneously after cessation of MTX treatment. The pathological findings of MTX-LPD are most frequently diffuse, large B-cell lymphomas (51.9–60.4%). Patients with rheumatoid arthritis reportedly have a 2- to 5.5 times higher risk of developing lymphoma than the
general population. Since Ellman’s first report on frequent lymphomas in a patient with rheumatoid arthritis who was receiving low-dose MTX, the relationship of MTX administration with the development of LPD has been much discussed. MTX-LPD is also characterized by a long period of clinical onset. In the present case, 13 years had passed since the initiation of MTX treatment before symptoms of MTX-LPD were observed. Previous studies have reported that the median duration of MTX administration until the diagnosis of MTX-LPD ranged from 54 to 71.1 months.

As the initial step in treatment, stopping MTX after a biopsy of the lesion is recommended. The lesion usually starts to regress in 1–2 weeks. On the other hand, 41% of cases do not show spontaneous regression and require chemotherapy for malignant lymphoma. We did not perform a renal biopsy based on a careful consideration of the patient’s condition as our tentative diagnosis of MTX-LPD was made on the basis of clinically observed, rapid regression of the lesions following the cessation of MTX.

In general, patients who have experienced MTX-LPD are no longer able to receive MTX treatment for rheumatoid arthritis. In 5 of the 11 previously reported cases, recurrence of a mass associated with MTX-LPD was reported 2–10 months after the cessation of MTX treatment. Fortunately, our patient did not show any recurrence of her renal mass at the 12-month follow-up, and remission of her rheumatoid arthritis was maintained without MTX use.

The present case demonstrated the possibility of LPD as a differential diagnosis in cases of a genitourinary mass in patients with rheumatoid arthritis taking MTX. MTX-LPD is a rare complication of MTX treatment of patients with rheumatoid arthritis and is unfamiliar to urologists; however, because MTX has recently begun to be used widely as a first-line therapy for rheumatoid arthritis and other systemic rheumatic diseases, the number of complications is expected to increase.

Conflict of interest

The authors declare no conflict of interest.

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