Methotrexate-related lymphoproliferative disorder of the lumbar spine origin presenting with severe low-back pain: case report

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The use of methotrexate (MTX) to treat rheumatoid arthritis (RA) is increasing. Recently, MTX-associated lymphoproliferative disorder (MTX-LPD) has been frequently reported as lymphoma occurring during MTX therapy. The authors report their experience with a relatively rare case of MTX-LPD presenting in the lumbar spine. The patient, a 73-year-old woman who experienced low-back pain while receiving MTX therapy for RA, was suspected of having developed MTX-LPD based on her medical history, images of the L1 vertebra, and transpedicular biopsy results. One week after discontinuing MTX, the patient's low-back pain reportedly improved. The woman was diagnosed with MTX-LPD based on histopathological findings. MTX discontinuation alone coincided with spontaneous tumor regression. Because MTX-LPD can occur in tissues other than lymph nodes, such as in bones and joints, it is a disease that should be considered when diagnosing spinal tumors in patients receiving MTX therapy.

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METHOTREXATE (MTX) is a highly effective treatment recommended for rheumatoid arthritis (RA) based on guidelines. In Japan, the estimated prevalence of RA was 1.24 million and MTX was prescribed to 329,000 individuals.¹⁴ However, serious adverse effects are widely known to be associated with MTX therapy, including liver disorders, interstitial pneumonia, and myelosuppression, among others. Of the various adverse effects associated with MTX therapy, lymphoma was the first to be reported in a patient with RA in 1991.¹ Since that time, lymphoma has been attracting attention as an MTX-associated lymphoproliferative disorder (MTX-LPD). Here, we report a case of MTX-LPD in the lumbar spine of a patient with RA who was treated with MTX.

Case Report

History and Examination

A 73-year-old woman presented with low-back pain in the absence of any triggers, such as trauma. The patient visited our department because her low-back pain was severe, resulting in reduced mobility. The patient was diag-

nosed with RA at 69 years of age and was immediately started on a regimen of 6–10 mg/wk MTX after being diagnosed. Her approximate cumulative dose of MTX was 1800 mg. Routine follow-up visits were performed at our hospital's rheumatology department.

On admission, the patient reported severe pain in the upper lumbar spine. No neurological abnormalities of the lower limbs were observed. A laboratory investigation revealed a normal lactate dehydrogenase level (211 IU/L), a slightly elevated C-reactive protein level (2.09 mg/ml), apparent elevation in the soluble interleukin-2 receptor value (3220 U/ml), and an increased Epstein-Barr virus (EBV) immunoglobulin G antibody titer.

MRI revealed low signal intensity in the L1 vertebral body on both T1- and T2-weighted images, as well as a soft-tissue mass compressing the dural sac (Fig. 1). Contrast-enhanced CT showed swollen cervical and mediastinal lymph nodes on the left.

Pathological Findings

We performed a transpedicular biopsy of the L1 vertebral body to rule out a suspected spinal tumor based on

ABBREVIATIONS EBV = Epstein-Barr virus; LPD = lymphoproliferative disorder; MTX = methotrexate; MTX-LPD = MTX-associated LPD; RA = rheumatoid arthritis.

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FIG. 1. Sagittal T1- (a) and T2- (b) weighted MR images and axial T2-weighted MR image (c) obtained at the L1 vertebra at admission, showing an epidural mass with low signal intensity.

the imaging findings. Examination revealed pathological trabecular destruction and diffuse infiltration of lymphoid cells in the inter-trabecular spaces with fibrilization in the background (Fig. 2a). Epstein-Barr encoding region in situ hybridization indicated EBV positivity (Fig. 2b). Immunohistochemical examination showed large atypical CD30-positive cells and a scattered distribution of PAX5-positive cells (Fig. 2c and d), suggesting a diagnosis of Hodgkin's lymphoma-like LPD.

Clinical Outcome

MTX therapy was discontinued based on a working diagnosis of MTX-LPD. The patient regained the ability to walk unassisted 8 days after the discontinuation of MTX. Soluble IL-2 receptor levels decreased to 565 U/ml 1 month after MTX discontinuation, and a contrast-enhanced CT scan revealed regression of the swollen lymph nodes. Follow-up MRI showed attenuation of both the epidural mass compressing the dural sac and the signal changes in the L1 vertebral body. Residual signal changes and the collapse of the superior lumbar endplate were observed, suggesting a vertebral fracture (Fig. 3). Radiography and MRI 6 months after MTX discontinuation showed no signs of MTX-LPD recurrence.

Discussion

MTX-LPD is a lymphoproliferative disorder that can occur in patients receiving MTX therapy for diseases such as RA; it is classified as the "other iatrogenic subgroup of immunodeficiency-associated lymphoproliferative disorders" according to the 2008 *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*.¹² MTX-LPD is a generic term referring to all the LPDs that develop in patients on MTX therapy and can include

common LPD as well as LPD accompanying RA, both of which are difficult to differentiate.

The symptoms of MTX-LPD are B symptoms similar to those in normal lymphoma (high fever, weight loss, and night sweats). MTX-LPD is not characterized by specific histology, and the reported proportions of histology consist of 52% diffuse large B-cell lymphoma and 8.9% Hodgkin's lymphoma.⁴ EBV is said to be associated with MTX-LPD, and 30%–50% of patients affected by this disease have been reported to be EBV positive.^{3,8,11} Compared with EBV-negative cases, EBV-positive MTX-LPD cases often undergo spontaneous regression by only discontinuing MTX,³ suggesting that the tumor cells proliferate due to MTX-induced suppression of cellular immunity.⁹ MTX-LPD commonly develops 40%–50% of the time as extralymphatic lesions mainly in the gastrointestinal tract, skin, liver, and lungs.^{3,11} MTX-LPD can also occur in the musculoskeletal system, and bone marrow infiltration accounts for the pathology in approximately 3% of all MTX-LPD patients.⁶ Cases of MTX-LPD developing in the metacarpal-phalangeal joints⁷ and the elbow joint² have been previously reported. For the first time, we report a rare case of MTX-LPD originating from the lumbar spine. However, the absence of similar previous reports at this time should not preclude MTX-LPD from being considered in the differential diagnosis for spinal tumors in patients receiving MTX therapy. Our finding confirms that MTX-LPD can develop in the spine similar to other lymphoproliferative disorders.

Reportedly, 60% of MTX-LPD cases spontaneously regress when MTX is discontinued, suggesting that tumor cells may proliferate in response to MTX-induced immunosuppression.⁹ Reports have indicated that spontaneous regression can easily be achieved in cases of EBV-positive, nondiffuse large B-cell lymphoma com-

FIG. 2. **a:** Histological findings on the pedicle of the arch of the L1 vertebra showing trabecular destruction and diffuse infiltration of lymphoid cells in the inter-trabecular spaces with fibrilization. H & E. **b–d:** Findings from immunohistochemical analysis showing positive staining for the Epstein-Barr encoding region via in situ hybridization (b), CD30 (c), and PAX5 (d). Bar = 40 μ m. Figure is available in color online only.

pared with other types of LPD.⁴ Therefore, biopsy and EBV testing, as well as MTX discontinuation, are required when MTX-LPD is the working diagnosis. The optimal duration for observation remains unclear at this time in the presence of conflicting reports describing the different durations required for spontaneous regression of MTX-LPD after the discontinuation of MTX therapy. Most previous reports have indicated that the spontaneous regression of MTX-LPD takes approximately 2 weeks from the time of MTX discontinuation, although one report described a case in which spontaneous regression took 8 weeks.⁵ It is imperative that an optimal duration for the observation of spontaneous regression of MTX-LPD after MTX discontinuation be explored and established in order to not delay chemotherapy as the next line of defense.

Even if the spontaneous regression was achieved by MTX discontinuation, a previous study reported that during a mean follow-up of 34 months, among 8 patients who were treated by MTX discontinuation alone, 2 had a relapse 12 to 14 months later.¹⁰ According to the result of this report, follow-up is necessary for at least 2 years, although it is impossible to clearly state the optimal follow-up period at present.

Biopsy is an important tool to determine the precise treatment strategy under appropriate diagnosis in patients with spinal tumors. Operative treatment would be considered on the basis of the indications for neurological impairment and/or local instability. In the spinal tumor cases without neurological compromise and segmental instability, needle biopsy rather than surgical biopsy appears to be more suitable as an initial treatment option because of its fewer complications and lower cost in comparison with those of surgical biopsy.¹³ In the current case, we decided to perform a needle biopsy rather than surgery, because no neurological symptoms and/or local instability were

FIG. 3. Sagittal (a) and axial (b) T2-weighted MR images obtained at L1 on admission, and sagittal (c) and axial (d) T2-weighted MR images obtained at L1 3 months after MTX discontinuation. Note the comparative attenuation of both the epidural mass compressing the dural sac and signal changes in the vertebral body after 3 months.

found, even though a large vertebral tumor with epidural extension was observed.

The patient in the present case was diagnosed with MTX-LPD when she presented with low-back pain. The disease course was typical for a patient with EBV-positive, nondiffuse large B-cell lymphoma that achieved spontaneous regression by MTX discontinuation alone, as reported previously.

The patient should be followed up and rigorously observed, even when there is no sign of recurrence at a follow-up visit as late as 6 months after an apparent spontaneous regression of MTX-LPD.

Conclusions

We report the case of an MTX-LPD originating in the lumbar spine. Although spontaneous regression was achieved by MTX discontinuation alone, the patient requires continuous and rigorous follow-up at 6-month intervals. MTX-LPD should be considered as one of the differential diagnoses of spinal tumors in patients receiving MTX therapy.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Kikuchi. Acquisition of data: Kikuchi. Drafting the article: Kikuchi. Critically revising the article: Kikuchi, Uesugi, Koda. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kikuchi. Study supervision: Kikuchi, Uesugi.

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