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Case Report

The first case of methotrexate-associated lymphoproliferative disorder in the sacrum: a case report

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Abstract

Methotrexate (MTX) is a drug used for treating rheumatoid arthritis. Recently, the reported incidence of methotrexate-associated lymphoproliferative disease (MTX-LPD) has increased, especially in Japan. Extranodal involvement is observed in half of MTX-LPD cases. However, only a few spinal lesions have been reported, with none in the sacrum. Additionally, Epstein-Barr virus (EBV) infection has also been implicated in the pathogenesis of MTX-LPD. Herein, we describe the case of a 74-year-old woman with MTX-LPD in the sacral spine who complained of severe back pain and nocturnal pain. Radiographs revealed a tumour on the right wing of the sacrum and a positive EBV immunoglobulin G antibody titre. MTX-LPD was suspected based on imaging findings and a history of MTX administration. A pathological examination was performed on the CT-guided biopsy specimen. The histopathological diagnosis was MTX-LPD, and MTX was discontinued. Three months after MTX administration ended, the tumour tended to shrink, and 1 year later, significant tumour shrinkage was observed. This experience suggests that MTX-LPD can be treated by discontinuing MTX administration. Therefore, early and accurate diagnosis is required, as is avoiding unnecessary treatment such as surgery. MTX-LPD should be considered, especially in spinal origin tumours in EBV-infected patients on MTX.

Keywords: methotrexate-related lymphoproliferative disease; sacral vertebrae; Epstein-Barr virus; spinal tumour; rheumatoid arthritis.

Introduction

Methotrexate (MTX)-associated lymphoproliferative disorder (LPD) refers to lymphoma that develops in patients immunosuppressed by administration of MTX.[1] MTX has gained acceptance in recent years as a first-line treatment for rheumatoid arthritis (RA) and other systemic rheumatic diseases, and the incidence of MTX-LPD is therefore expected to continue increasing.[2] Although the first reported case of MTX-LPD was reported in 1991 as lymphoma in a patient with RA who had received MTX,[1] it has not been well characterized due to its rarity. Spinal lesions are rare in MTX-LPD, and no cases of sacrum have been reported to date.[3] Here, we present a case of MTX-LPD of the sacral spine in a 74-year-old woman with RA complaining of severe sciatica. In this patient, significant MTX-LPD regression was observed after MTX cessation.

Case presentation

A 74-year-old RA patient complained of severe low back pain and sciatica at night. She was undergoing treatment with MTX (10 mg/week). Sacral magnetic resonance imaging revealed a tumour in the right wing of the sacrum (Figure 1A-C). Considering the possibility of a metastatic tumour, a CT scan of the entire body was performed to detect primary cancer, revealing a mass lesion in the right lobe of the thyroid gland extending to the upper mediastinum. However, the patient had no history of cancer. Laboratory data showed a normal lactate dehydrogenase (169 IU/L), elevated C-reactive protein (CRP; 8.3 mg/mL), serum soluble interleukin 2 receptor levels (1312 U/mL), and a positive result for Epstein-Barr virus (EBV) immunoglobulin G antibody titre.

The patient underwent a CT-guided biopsy of the sacral tumour to confirm the diagnosis. Pathological findings revealed the proliferation of atypical medial to large-sized lymphoid round cells, with mildly nuclear atypia and massive necrosis with inflammation (Figure 2A and B). Immunohistochemically, atypical cells were positive for Cluster Designation (CD) 20 (Figure 2C) and CD10 (focal), but negative for CD79a, CD3, CD5, bcl2, bcl6, MUM1, and c-Myc. A few large, atypical cells were positive for EBV-encoded small RNA (EBER; Figure 2D). These results suggested the possibility of lymphoproliferative disease of the B-cell lineage.

The combination of pathological findings, EBV positivity, and the history of MTX treatment confirmed the diagnosis of MTX-LPD. Therefore, the patient's MTX therapy was discontinued. One week after the discontinuation of MTX, the patient reported a reduction in pain, and the analgesics were tapered. Three months after MTX withdrawal (Figure 3A and C), we observed a decreased CRP and shrinkage of the tumour. Ten months after stopping MTX, a flare of RA was observed. Treatment with prednisolone (5 mg) was subsequently initiated. Since then, the RA disease has tended to improve.

One year after discontinuing MTX (Figure 3B and D), no evidence of local recurrence could be found.

Discussion

The mean age at diagnosis of MTX-LPD is 67 (34-87) years, the male-to-female ratio is 1:2, and the average total dose of

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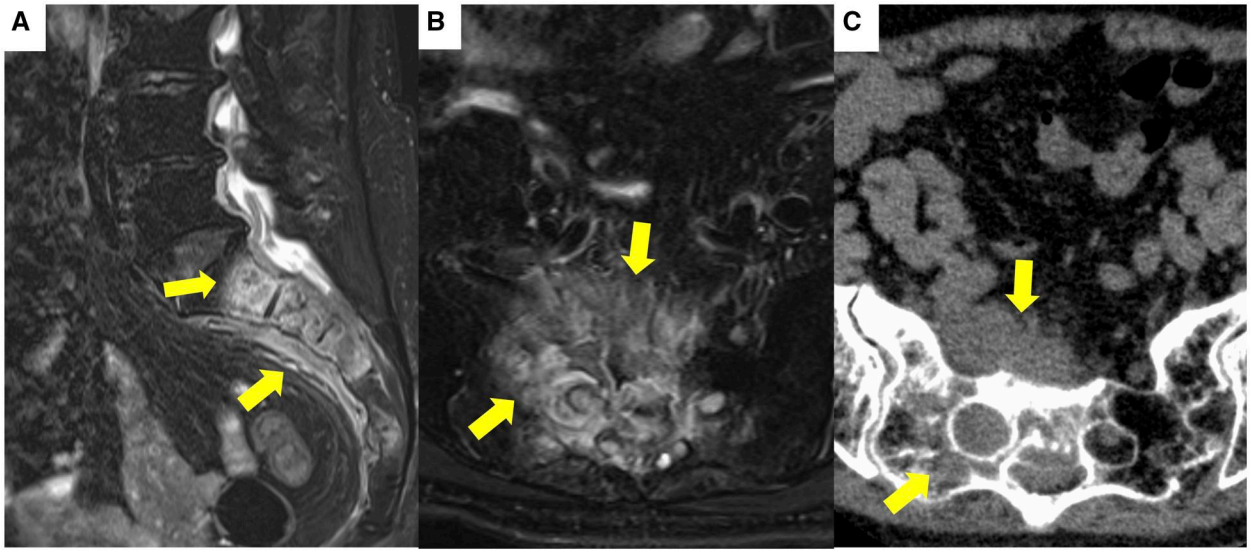

Figure 1. Initial MRI and plane CT examination. T2-weighted Dixon MR sagittal image (A) and T2-weighted axial image (B) showing an intraosseous tumour at the S1-3 level of the right sacrum with an anterior extraosseous extension of the tumour. Planar CT showing an intraosseous tumour in the right sacrum with an anterior extraosseous tumour extension (C).

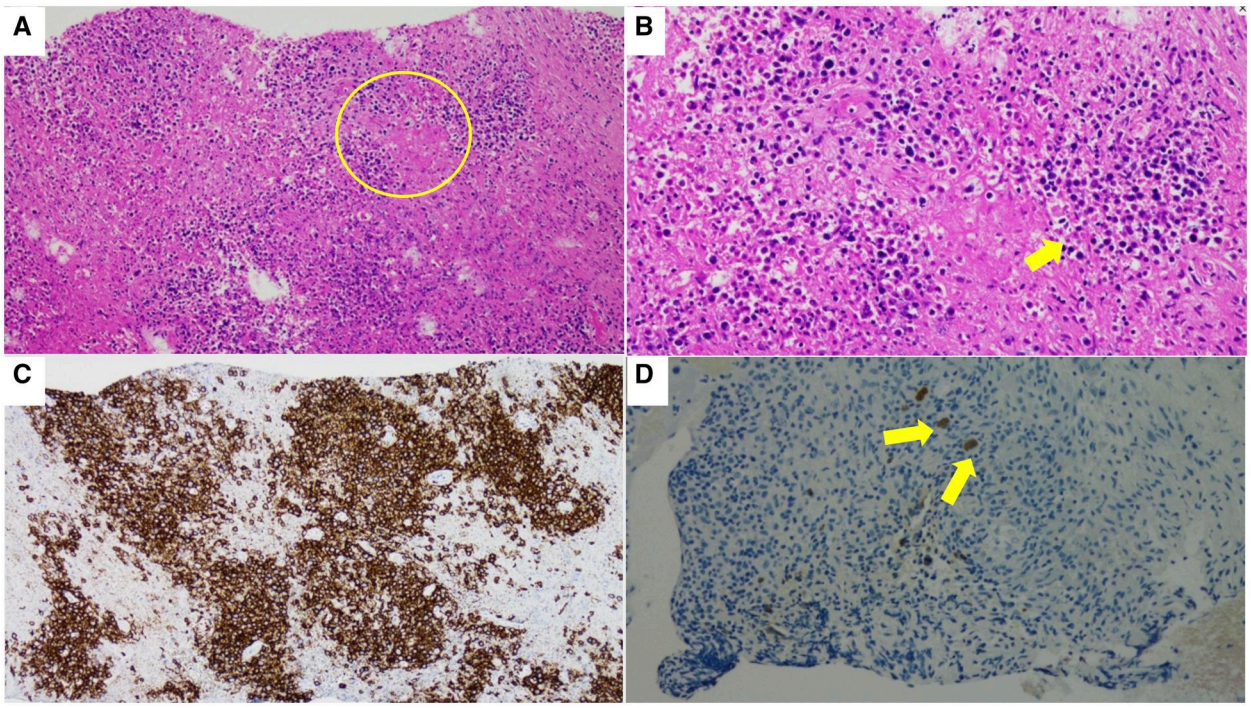

Figure 2. Histologic findings of the tumour in the sacral vertebrae. Haematoxylin-eosin stain demonstrated scattered lymphocyte clusters in the stromal connective tissue with necrosis (A). Medium-to-large clusters of lymphocytes with mild nuclear irregularities are visible in areas of marked necrosis, and round cells having mildly nuclear atypia, accompanied by massive necrosis with inflammation (B). Medium-to-slightly larger lymphocytes showed CD20(+) on immunostaining (C). EBER-positive cells in a small number of large lymphocytes (D).

MTX is 1500 mg (180-3600 mg),[4] although higher amounts of MTX have been reported to promote LPD development.[5] The sites of MTX-LPD include the lymph nodes and extranodal lesions. Extranodal involvement is most common, observed in about 50% of the cases.[4,6,7] However, bone involvement is rare, accounting for only approximately 3% of all MTX-LPDs.[8] MTX-LPD in the spinal region is also rare, with only 5 cases reported to date (Table 1[2,3,7,9,10]). To the best of our knowledge, this is the first reported case in the sacral spine.

Reports suggest that 50%-60% of MTX-LPD cases resolve spontaneously with the discontinuation of MTX.[7,11] In addition, 30%-50% of MTX-LPD patients are EBV positive; these patients are more likely than EBV-negative patients to experience spontaneous resolution with discontinuation of MTX.[12]

EBV is involved in lymphocyte proliferation through its effects on apoptotic and B-cell transformation.[13] MTX affects EBV reactivation at the onset of EBV-associated LPD while activating EBV release from EBV-infected cells by

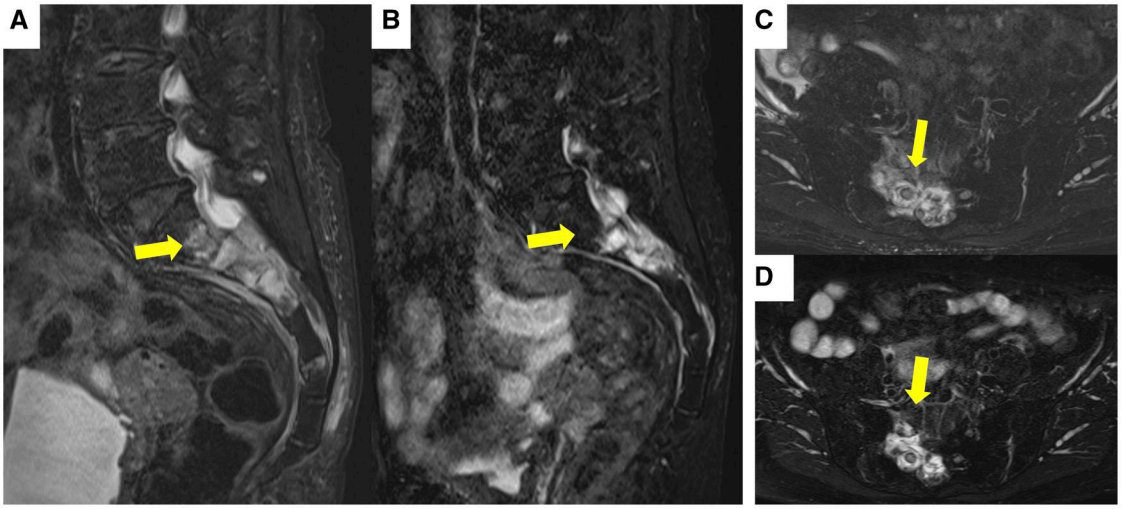

Figure 3. MRI following MTX withdrawal. (A, C) The tumour, which had penetrated intra- and extra-anteriorly up to the S1-3 level of the right sacral bone, reduced in size 3 months after MTX withdrawal. (B, D) MRI after 1 year from MTX withdrawal. The tumour, which was primarily intraosseous at the S1-3 level of the right sacrum and had developed extraosseously in the anterior direction, was even further reduced in size.

Table 1. Spinal lesions in past methotrexate-associated lymphoproliferative diseases (MTX-LPD).

Author	Year	Country	site of lesion	Duration to diagnosis (years)	EBV	Treatment	Recurrence
Kikuchi N[7]	2018	Japan	L2	4	+	MTX withdrawal	+
Tokuhira M[9]	2017	Japan	L1,3	15	–	Chemotherapy	–
Kamio S[10]	2021	Japan	Th10	7	+	MTX withdrawal and procedure	–
Hirata C[2]	2021	Japan	Th6-7	6	–	MTX withdrawal	–
Tsukamoto M[3]	2022	Japan	Th7	10	+	MTX withdrawal and procedure	–

suppressing T cell activity and decreasing the expression of T cell adhesion molecules. This synergistic effect is thought to promote lymphocyte proliferation and contribute to the development of MTX-LPD.[14] As such, it can be inferred that discontinuing MTX has a spontaneous shrinking effect in EBV-positive patients with MTX-LPD.

There have been reports of relapse of RA after discontinuing MTX,[15] although the relapse rate is currently unclear. Tacrolimus and tocilizumab-associated LPD have been reported, raising the issue of treatment choice for RA.[16,17] The 2015 American College of Rheumatology guidelines recommend abatacept and tocilizumab for active RA after remission of LPD. However, there is little evidence, and more research on the use of biologics in patients after remission of LPD is warranted.[18]

In the present case, MTX-LPD was suspected early because the patient had a history of MTX use and was EBV positive. As MTX-LPD can occur in various sites, it is essential to perform various investigations and avoid unnecessary surgery in a patient with a history of MTX use and an EBV-positive spinal tumour, even without previous reports of such cases, as in the present case of sacral onset. This is also a case of RA recurrence after the discontinuation of MTX, so future recurrences of LPD should be carefully monitored.

Conclusion

Herein, we report the first case of an MTX-LPD in the sacrum spine which required differential diagnosis from spinal tumour. Discontinuation of MTX is the first choice for EBV-positive lymphoma patients receiving MTX.

Learning points

- It is necessary to consider MTX-LPD as a differential diagnosis in patients with spinal tumours on MTX.
- Attention should be paid to relapse of the underlying disease after discontinuation of MTX.

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Conflicts of interest

The authors have no conflicts of interest.

Informed consent statement

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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