

## Case Report

# Epstein-Barr virus-related diffuse large B-cell lymphoma type methotrexate-associated lymphoproliferative disorders presenting in the adrenal gland

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### Abbreviations & Acronyms

DLBCL = diffuse large B-cell lymphoma  
EBER = EBV-encoded RNA transcript  
EBV = Epstein-Barr virus  
IVC = inferior vena cava  
LPD = lymphoproliferative disorder  
MRI = magnetic resonance imaging  
MTX = methotrexate  
PET-CT = positron emission tomography and computed tomography  
RA = rheumatoid arthritis  
sIL2-R = soluble interleukin-2 receptor  
VCA = viral capsid antigen

**Introduction:** Methotrexate-associated lymphoproliferative disorders appear during treatment with methotrexate as an immunosuppressive drug. However, the mechanism and frequency are still unknown, and the treatment is undefined.

**Case presentation:** A 76-year-old woman was admitted to the hospital with back pain, and magnetic resonance imaging showed a tumor in the right adrenal region. She had received methotrexate for rheumatoid arthritis. Enhanced computed tomography showed a tumor of 90 mm in diameter on the dorsal side of the liver abutting to the inferior vena cava. The preoperative diagnosis was a hepatic invasion of right adrenocortical carcinoma and right adrenalectomy was performed. The histopathological diagnosis was diffuse large B-cell lymphoma. The final diagnosis was methotrexate-associated lymphoproliferative disorders.

**Conclusion:** It is important to consider methotrexate-associated lymphoproliferative disorders before surgery when neoplastic lesions are found in patients taking methotrexate.

**Key words:** DLBCL, EBV, methotrexate, MTX-LPD, primary adrenal lymphoma.

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## Keynote message

MTX-LPD is a tumor that occurs in patients taking MTX, which rarely involves adrenal glands. We should be aware of MTX-LPD as a differential diagnosis when neoplastic lesions are found in patients taking MTX.

## Introduction

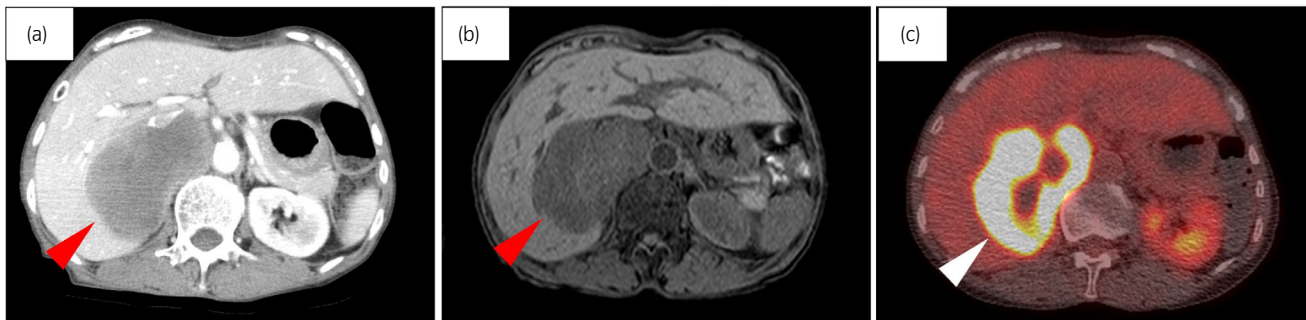
MTX-LPD is a lymphoproliferative disease that appears during treatment with methotrexate as an immunosuppressive drug. It is particularly common in patients with rheumatoid arthritis.<sup>1–4</sup> Kawano *et al.* recently reported 2 out of 23 Japanese patients with primary adrenal DLBCL had the treatment history with MTX for RA.<sup>5</sup> There are a few other cases of primary adrenal MTX-LPD, but reports are very few.<sup>6,7</sup>

MTX-LPD is usually treated by discontinuing or reducing the MTX. However, the mechanism and frequency of MTX-LPD is still unknown, and the treatment of MTX-LPD is undefined. This case report provides important insights into the pathogenesis and treatment of MTX-LPD.

## Case presentation

A 76-year-old woman was admitted to our hospital with back pain. MRI revealed a tumor in the adrenal region. She had been diagnosed with RA in 1992 and had received MTX (14 mg/week) since 2006. Her family history was not remarkable. A physical examination showed no specific abdominal findings.

The results of routine blood tests were normal, and her serum tumor marker levels (CEA, CA19-9, NSE) were within the normal limits. Her serum cortisol level was 13.3 µg/dL (normal range : 3.7–19.4 µg/dL), and her ACTH level was 43.5 pg/mL (normal range : 7.2–63.3 pg/

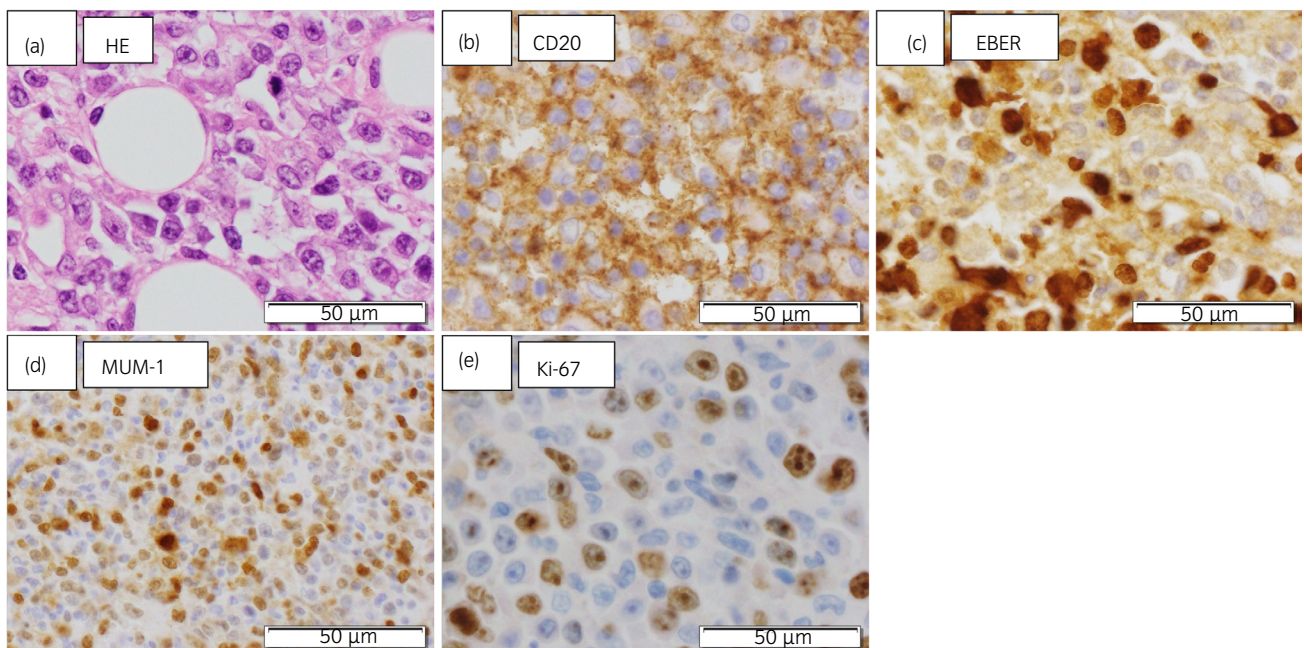


**Fig. 1** (a) Enhanced CT revealed a 90-mm mass at the right adrenal area extending to the S7 region of the right lobe of the liver. The IVC was compressed. (b) The tumor showed low signal on T1-weighted MRI. (c) PET-CT showed accumulation in the tumor area.

mL). Her other serum hormone values were as follows: epinephrine, <0.01 ng/mL (normal range: <0.1 ng/mL); norepinephrine, 0.38 ng/mL (normal range: 0.1–0.50 ng/mL); dopamine, <0.01 ng/mL (normal range: <0.03 ng/mL); testosterone, 17.8 ng/mL (normal range: 10.8–56.9 ng/mL); DHEA-S, 203 ng/mL (normal range: 7–177 ng/mL), and renin activity was 0.9 ng/mL/hr (normal range: 0.2–3.9 ng/mL/hr). The 24-h urinary level of norepinephrine was within the reference ranges. Enhanced computed tomography revealed a 90 mm mass at the right adrenal area extending from the S7 region of the right lobe of liver to the right renal head. The hepatic vein to IVC was compressed and displaced by the tumor (Fig. 1a). MRI revealed the mass showing a low-signal intensity on T1 and a high-signal on T2, with a low-signal region in the center (Fig. 1b). PET-CT showed accumulation in the tumor area (Fig. 1c). The preoperative differential diagnosis included intrahepatic cholangiocarcinoma, adrenal tumor, and hepatic malignant lymphoma, but did not reach a definitive diagnosis. We discussed biopsy to make a definitive diagnosis; however, it was determined that complete

resection of the tumor was possible. Under the preoperative diagnosis of adrenal carcinoma (cT4N0M0), we performed resection of the right adrenal tumor, extended resection of the posterior lobe of liver and blood vessel prosthesis implantation. The tumor was hard and adhered tightly to the IVC. Histologically, there was diffuse growth of medium to large round atypical cells (Fig. 2a). Immunohistochemistry was positive for CD20, EBER, and MUM-1 (Fig. 2b–d) and negative for bcl-6, CD30, CD5, CD10, and Cyclin D1. The Ki-67 labeling index was 50% (Fig. 2e).

Given these findings, we finally diagnose EBV-positive DLBCL-type primary adrenal MTX-LPD. Serum anti-EBV VCA IgG antibody and anti-EBNA antibody were positive, and anti-EBV VCA IgM antibody was negative, and the sIL-2R level was 1320 U/mL (normal range: 122–496 U/mL) in additional blood tests. Postoperatively, PET-CT was performed, but no hot spot was found. We withdraw MTX, and the patient was followed up periodically. The patient has remained free from recurrence for 22 months.



**Fig. 2** (a) Microscopic findings of the tumor. (b–d) Atypical lymphocytes were confirmed by positive immunohistochemical staining of CD20, EBER and MUM-1. (e) The Ki-67 labeling index was 50%.

## Discussion

MTX-LPD is a lymphoproliferative disease that appears during treatment with methotrexate as an immunosuppressive drug. It is particularly common in patients with RA. The mechanism and frequency of the disease are still unknown; however, RA, the use of MTX, and EBV virus infection are thought to be the three main causes. The probability of developing LPD is 2.0–5.5 times higher in patients with RA, than that in the general population.<sup>8–10</sup> Disease activity in RA is associated with a higher risk on the development of lymphoma; exposure to systemic inflammation may result in the developing lymphoma. In addition IL-10 (which is a cytokine known to be increased in RA) may function as autocrine growth factors in B-cell lymphoma.<sup>11</sup> EBV is thought to have a mechanism for causing lymphoma.<sup>12</sup> RA patients treated with MTX have higher EBV loads in their blood than those treated without MTX. Thus, RA and use of MTX promote the activation of EBV, leading to the development of LPD.

There is no comprehensive report on the imaging findings of MTX-LPD. It is known that most EBV-associated LPD is associated with internal necrosis, whereas normal LPD is rarely associated with internal necrosis. In this case, the patient only complained of back pain. Although the imaging findings were consistent with LPDs, this could not be distinguished from adrenal carcinoma. Thus, we should pay attention to MTX-LPD as a differential diagnosis when neoplastic lesions are observed in patients undergoing MTX therapy.

Rashidi and Fisher define primary adrenal lymphoma as a histologically proven lymphoma that involves one or both adrenal glands and has both of the following features at presentation: (i) there is no prior history of lymphoma elsewhere; (ii) if lymph nodes or other organs are involved, adrenal lesions are unequivocally dominant.<sup>13</sup> In this case, PET-CT showed no other lesions, and the adrenal lesions with hepatic invasion were clearly dominant; thus, it can be regarded as primary adrenal malignant lymphoma. Primary adrenal MTX-LPD is rare, with only about a few cases documented in the literature before this.<sup>5–7</sup>

MTX-LPD regresses in 70% of patients who discontinue MTX.<sup>14</sup> The duration from the withdrawal of MTX to relapse is reported 27.2 months<sup>14</sup>; thus, long-term follow-up is necessary, even after the regression of lesions.

## Conclusion

Urologists should pay attention MTX-LPD as a differential diagnosis when neoplastic lesions are observed in patients undergoing MTX therapy. In such cases, discussion with immunologists is encouraged in order to determine the treatment strategy.

## Author Contributions

Kazuki Doi: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Writing – original draft; Writing – review & editing. Mototsugu Muramaki: Formal analysis; Investigation; Project administration; Supervision. Tetsuro Yamamoto: Data curation. Daiki Katsura:

Data curation. Hiroyuki Fukunaga: Data curation. Kosuke Takahashi: Data curation. Minoru Matsumoto: Data curation. Yuji Yamada: Methodology; Project administration; Supervision.

## Conflict of interest

The authors declare no conflict of interest.

## Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

## Informed consent

Not applicable.

## Registry and the Registration No. of the study/trial

Not applicable.

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