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【 CASE REPORT 】

Diffuse Large B-cell Lymphoma with Adrenal Involvement Presenting as Other Iatrogenic Immunodeficiency-associated Lymphoproliferative Disorders: Sustained Remission with Methotrexate Termination Alone in Two Cases

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Abstract:

Methotrexate-associated lymphoproliferative disorders (MTX-LPDs) with diffuse large B-cell lymphoma (DLBCL) pathology present with high rates of spontaneous regression after methotrexate (MTX) termination, especially in Epstein-Barr virus-encoded RNA (EBER)-positive cases. DLBCL with adrenal involvement is known for an extremely dismal prognosis. However, the prognosis of adrenal DLBCL in the context of MTX-LPD is unknown. We herein report two EBER-positive adrenal DLBCL MTX-LPD patients who achieved long-term remissions of 22 and 40 months with MTX termination alone. Both patients are doing well with no relapse at the time of reporting. Unlike adrenal DLBCL in general, adrenal involvement may not be a poor prognostic factor when restricted to DLBCL MTX-LPDs.

Key words: OIIA-LPDs, MTX-LPDs, primary adrenal lymphoma, PAL, EBER

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Introduction

Other iatrogenic immunodeficiency-associated lymphoproliferative disorders (OIIA-LPDs) are defined by the 2017 WHO classification as lymphoid proliferations or lymphomas that arise in patients receiving immunosuppressants for various conditions other than in the post-transplantation setting (1). Methotrexate (MTX) is the most common of these immunosuppressants that cause OIIA-LPDs, and such cases are often referred to as methotrexate-associated lymphoproliferative disorders (MTX-LPDs). MTX is the upfront drug of choice for rheumatoid arthritis patients, and an aging population leading to more patients with rheumatoid arthritis has resulted in an increase in patients with MTX-LPDs (2).

We herein report two MTX-LPD cases presenting as diffuse large B-cell lymphoma (DLBCL) with adrenal involvement that achieved long-term remission with MTX termination alone. In general, the prognosis of DLBCL with adrenal involvement is extremely poor (3), but we report that this may not apply when restricted to adrenal DLBCL of MTX-LPDs.

Case Reports

Case 1

A 77-year-old woman with rheumatoid arthritis treated with oral MTX therapy for more than 20 years developed systemic lymphadenopathy, multiple lung lesions, and bilateral adrenal tumors in November 2018. The patient presented with a fever of 38.5°C and an Eastern Cooperative Oncology Group performance status score of 1. LDH was elevated at 541 U/L. A right cervical lymph node biopsy

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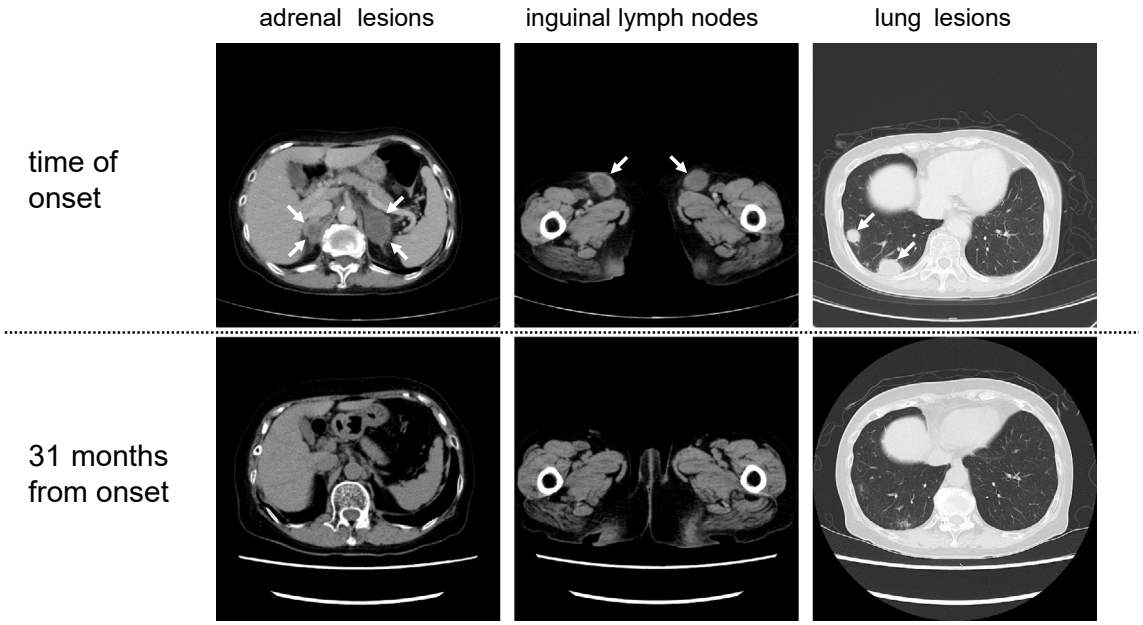

Figure 1. **Case 1: CT scans before and after methotrexate termination.**

and lung lesion biopsy were carried out, and DLBCL was diagnosed from both sites (stage IV, IPI: high). Clinical findings suggestive of central nervous system (CNS) invasion were absent. Immunohistochemistry showed that the DLBCL was positive for CD20, Epstein-Barr virus-encoded RNA (EBER), and LMP1 and negative for CD3, CD5, CD10, and Epstein-Barr virus nuclear protein 2 (EBNA2). A fluorescence *in situ* hybridization (FISH) analysis showed no MYC split signal and no IgH/BCL2 fusion signal.

MTX administration was terminated from November 2018, and computed tomography (CT) performed 1 month later showed an approximately 50% size reduction of the DLBCL lesions. The DLBCL lesions continued to regress, and CT performed 12 and 31 months later showed complete remission (Fig. 1). The patient remains well at present with no recurrence 40 months from MTX termination.

Case 2

A 68-year-old woman who had been on oral MTX therapy for 8 years was found to have bilateral adrenal tumors and lung lesions on CT. LDH was elevated at 1,301 U/L. An adrenal tumor biopsy was carried out in the beginning of June 2020, and DLBCL was diagnosed (stage IV, IPI: high). Clinical findings suggestive of CNS invasion were absent. Immunohistochemistry showed that the DLBCL was positive for CD20, EBER, LMP1, and EBNA2 and negative for CD3, CD5, and CD10. A FISH analysis showed no MYC split signal.

MTX was terminated, and CT performed 3 weeks later showed regression of the tumors, while follow-up CT performed 4 and 20 months later showed complete remission (Fig. 2). The patient remains well with no DLBCL recurrence at 22 months from MTX termination.

Discussion

We describe two adrenal MTX-LPD patients with DLBCL pathology who achieved long-term remissions of 22 and 40 months with MTX termination alone.

Adrenal DLBCL in general has been reported to present with an extremely poor prognosis. In a systematic review by Rashidi et al. including 187 adrenal lymphoma patients (of whom information on the outcome was available in 149), the 3-, 6-, and 12-month survival rates were reported to be low at 67%, 46%, and 20%, respectively (3). However, prognosis of adrenal DLBCL in the context of MTX-LPD is unknown. There are only two case reports of MTX-LPDs involving the adrenal glands, of which one had pathology of Hodgkin-like lesions and one DLBCL (Table) (4, 5). The DLBCL case achieved complete remission with MTX termination alone, but information on the long-term follow up was not provided. We herein report for the first time the long-term follow-up and sustained remission of two adrenal DLBCL MTX-LPD patients requiring no chemotherapy, suggesting that adrenal DLBCL may not have a dismal prognosis when restricted to MTX-LPDs.

MTX-LPDs are most commonly DLBCL or classic Hodgkin's lymphoma (cHL), accounting for 35-60% and 12-25% of cases, respectively (1). In a large, retrospective, single-center study by Kurita et al., regression of MTX-LPDs was seen with MTX termination alone in 31 of 70 DLBCL patients (44%) and 2 of 19 cHL patients (11%). In line with this, the median progression-free survival was 20 months for DLBCL and 5 months for cHL (6). EBER is positive in approximately 40% of MTX-LPDs (1). Kurita et al. reported that EBER positivity significantly correlated with a better progression-free survival (PFS) in DLBCL

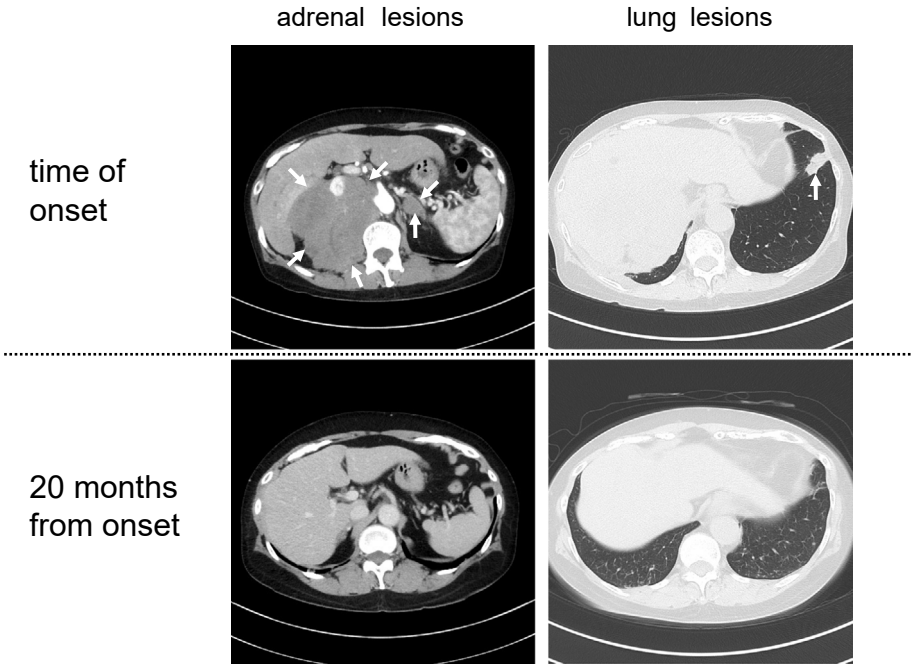

Figure 2. **Case 2: CT scans before and after methotrexate termination.**

Table. **Characteristics of Patients with MTX-associated Lymphoproliferative Disorders with Adrenal Involvement Described in the Literature.**

Reference	sex	age	lymphoma type	stage	EBER status	duration of MTX administration	sites of lymphoma at onset	response after MTX termination	outcome
(4)	M	70	Hodgkin-like lesions	IE	Positive	8 years	Right adrenal lesion	Adrenal lymphoma completely resected before MTX termination	No relapse at 1 year after tumor resection and MTX termination
(5)	F	72	DLBCL	IV	Positive	12 years	Bilateral adrenal lesions	CR	Maintains CR at 6 months from biopsy
Case 1	F	77	DLBCL	IV	Positive	>20 years	Systemic lymphadenopathy, lung lesions, bilateral adrenal lesions	CR	Maintains CR at 40 months from MTX termination
Case 2	F	68	DLBCL	IV	Positive	8 years	Lung lesions, bilateral adrenal lesions	CR	Maintains CR at 22 months from MTX termination

CR: complete remission, DLBCL: diffuse large B-cell lymphoma, F: female, M: male, MTX: methotrexate

MTX-LPD patients (6). Other investigators have demonstrated that EBER positivity correlates with an increased incidence of spontaneous regression of MTX-LPDs after MTX cessation (4, 5, 7). The two cases in the current report were both EBER-positive DLBCLs, so spontaneous regression and sustained remission were well-foreseeable events, due to the fact that they were MTX-LPDs. However, since adrenal DLBCL is known to generally have an extremely poor and aggressive disease course, whether or not the two cases would both have an optimal outcome was very questionable.

EBV-positive DLBCL MTX-LPDs typically correspond to EBV latency type II (LMP1-positive, EBNA2-negative, EBER-positive) or else EBV latency type III (LMP1-positive, EBNA2-positive, EBER-positive) (6, 8). Regarding the present patients, Case 1 corresponded to EBV latency type II, and Case 2 corresponded to latency type III.

Adrenal lymphoma is very rare, and Singh et al. reported that among 241 cases of non-Hodgkin's lymphoma, only 4 patients (1.6%) had adrenal involvement, all of whom had DLBCL pathology (9). Many adrenal lymphoma cases in the literature are described as "primary adrenal lymphoma (PAL)," but whether or not the two cases presented here would be classified as PAL is a matter of debate, as different investigators have used different arbitrary definitions of PAL. Rashidi et al. used a relaxed definition of PAL as a histologically proven lymphoma with unilateral or bilateral

adrenal involvement, no history of lymphoma elsewhere, and adrenal lesions being unequivocally dominant when other sites were involved (3). Conversely, investigators like Zhou et al. used much stricter criteria for PAL, requiring histologically proven unilateral or bilateral adrenal lymphoma without nodal involvement, the absence of leukemic blood picture, and a lack of involvement of other organs for at least six months after the diagnosis (10). The two cases presented here may meet the criteria for PAL established by Rashidi et al. but would not meet those established by Zhou et al. We therefore refrained from using the term PAL and merely described these cases as "adrenal DLBCL" or "adrenal involvement."

In conclusion, adrenal DLBCL in general has an exceptionally poor prognosis, but this may not be true in the context of DLBCL MTX-LPD. Providing patients with information on disease-specific life-expectancies is an important part of informed consent, but from our observations, DLBCL MTX-LPD with or without adrenal involvement may have similar outcomes. The accumulation of more cases is needed to confirm our findings.

The authors state that they have no Conflict of Interest (COI).

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