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Case Report

Successful treatment of acute uric acid nephropathy with rasburicase in a primary central nervous system lymphoma patient showing dramatic response to methotrexate – case report

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Abstract: Background: Primary central nervous system lymphomas (PCNSLs) are sensitive to chemotherapy. Standard treatment is high-dose methotrexate (MTX)-based chemotherapy. There are no reports of successful treatment of acute uric acid nephropathy with rasburicase after MTX administration in PCNSL. **Case presentation:** A 54-year-old man with a history of gout presented with character change and memory loss. MRI showed a large, enhancing mass spanning the bilateral frontal lobes and right temporal lobe. After endoscopic biopsy, MTX, procarbazine and vincristine (MPV) regimen was initiated for treatment of PCNSL. After initiation of chemotherapy, the patient suffered from a gout attack and blood examination revealed acute renal failure (ARF) and hyperuricemia. The considered causes of ARF included MTX toxicity and acute urid acid nephropathy. Since a good response to chemotherapy was observed, the latter was assumed. After improvement of renal function, MTX was resumed, initiating rasburicase for control of hyperuricemia. A complete response was obtained after induction chemotherapy. Hyperuricemia was controlled with rasburicase and renal function was preserved. **Conclusions:** Acute uric acid nephropathy should be considered when ARF occurs after initiation of MTX in PCNSL. For newly diagnosed PCNSL patients with large tumors or hyperuricemia, upfront usage of rasburicase should be considered to prevent it.

Keywords: PCNSL; high-dose methotrexate; acute uric acid nephropathy, rasburicase

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1. Introduction

Primary central nervous system lymphomas (PCNSLs) account for approximately 4% of all primary brain tumors [1]. Sensitivity to high dose methotrexate (HD-MTX) has been observed in multiple prospective and retrospective studies, so HD-MTX-based regimens are standard for induction chemotherapy [2,3]. Since PCNSL is sensitive to chemotherapy, acute uric acid nephropathy due to tumor lysis can occur.

Rasburicase is a recombinant version of uric acid oxidase, an enzyme that metabolizes uric acid to allantoin, and is a highly effective treatment for hyperuricemia during chemotherapy. In the present case, we report for the first time, successful control of hyperuricemia by rasburicase after MTX-induced acute uric acid nephropathy.

2. Case Presentation

A 54-year-old Japanese man presented with a change in character and memory loss from 1 month before. The patient had a history of gout and hyperuricemia, which was untreated. Magnetic resonance (MR) imaging showed large lesion spanning both frontal lobes, the right temporal lobe and corpus callosum. The lesion showed hypointensity on T1-weighted imaging (T1WI) (Figure 1A), hyperintensity on T2WI (Figure 1B), fluid-attenuated inversion recovery (FLAIR) (Figure 1C) and diffusion-weighted imaging (DWI) (Figure 1D) and was homogeneously enhanced on post-contrast MR images (Figure 1E). Pronounced perifocal edema was observed. The lesion was slightly high dense on pre-contrast computed tomography (CT) with accompanying perifocal low density and homogeneous enhancement was observed on post-contrast CT (Figure 1F). No systemic lesions were detected on pre- and post-contrast body CT scans.

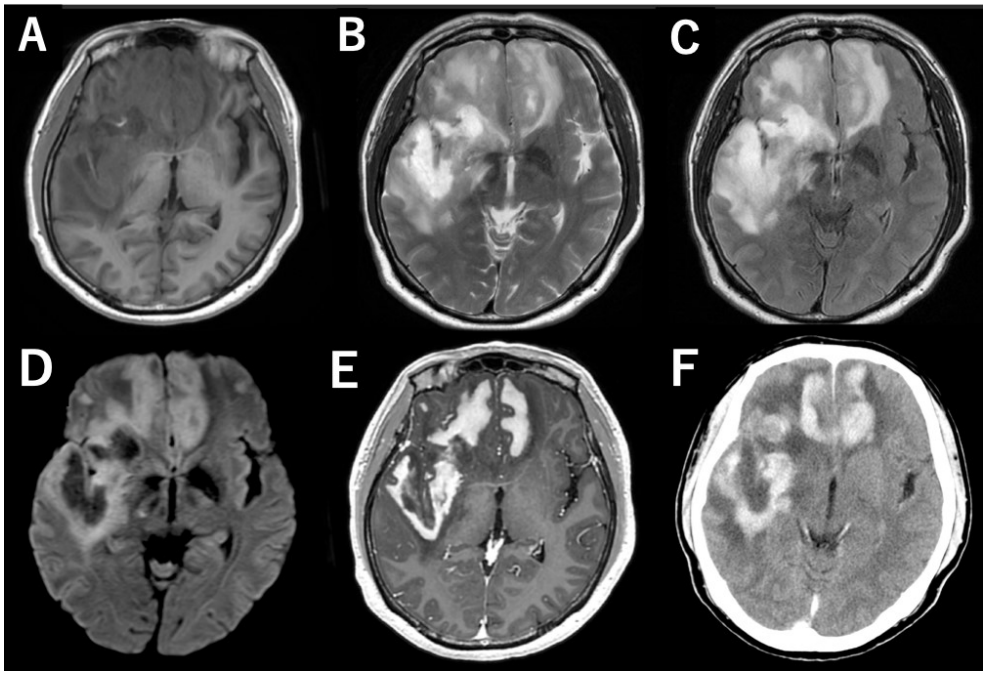

Figure 1. MR and CT images show a large, homogenously enhancing lesion spanning the bilateral frontal lobes and right temporal lobe. (A) T1-weighted image (T1WI), (B) T2WI, (C) FLAIR, (D) DWI, (E) post-contrast MRI, (F) post-contrast CT

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The lesion at the right frontal lobe was endoscopically biopsied. Histological examination revealed perivascular and diffuse distribution of relatively large lymphoma cells (Figure 2A,B), positive for CD20 (Figure 2C), and smaller lymphocytes, thought to be reactive. Tumor cells were highly positive for SLFN11, a marker for sensitivity to DNA damaging agents (Figure 2D).

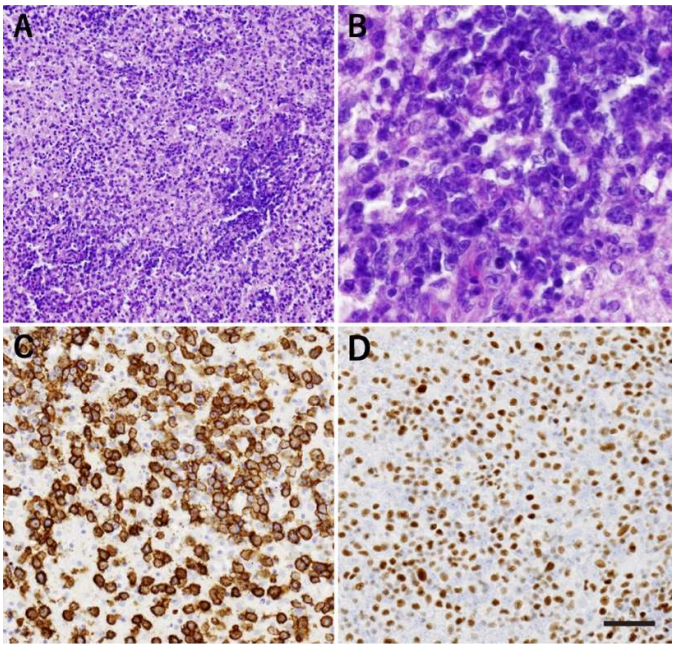

Figure 2. (A, B) Histopathological examination revealed perivascular and diffuse distribution of relatively large lymphoma cells and smaller, reactive lymphocytes. (Hematoxylin-eosin stain). (C) The large cells were positive for CD20. (D) The tumor cells were highly positive for SLFN11, suggesting sensitivity to chemotherapy. Scale bar = 80 μm (A), 20μm (B), 40 μm (C, D).

Intravenous dexamethasone was started at 16 mg per day and tapered, and subsequently, tumor size considerably decreased, and symptoms improved before commencement of chemotherapy (Figure 3A, B).

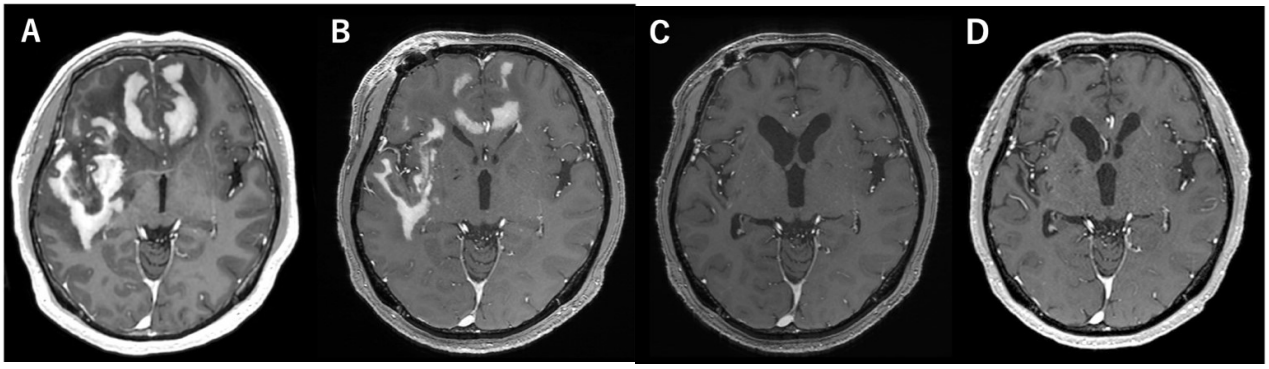

Figure 3. Post-contrast MR images showing dramatic response to steroids and chemotherapy. (A) At presentation. (B) After steroid treatment. (C) After 3 cycles of methotrexate (MTX). (E) After 5 cycles of MTX.

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For induction therapy, MTX (3.5 g/m²), procarbazine (100 mg/m²/d for 7 days) and vincristine (1.4 mg/m²) (MPV regimen) were simultaneously started (Day 0) in accordance with our protocol, which has previously been published [4]. After administration, the patient suffered from nausea, appetite loss, diarrhea and acute swelling, discoloration and severe pain of the left ankle. Before initiation of induction chemotherapy, no abnormal data was observed on complete blood count and biochemical testing. Blood examination revealed acute renal failure (serum Cr 4.87 mg/dL, BUN 31 mg/dL, eGFR 10.93 ml/min/1.73m²) at Day 2 and hyperuricemia (serum UA 10.5 mg/dL) at Day 6. Urine volume was maintained at 2520 to 2880 ml/d and electrolytes including serum potassium, phosphorus and calcium were in the normal range. Therefore, ARF was treated by increasing the volume of intravenous fluids and the dosage of leucovorin, and MTX was eliminated from plasma after 10 days [5] and renal function was normalized over a period of 3 weeks (Figure 4).

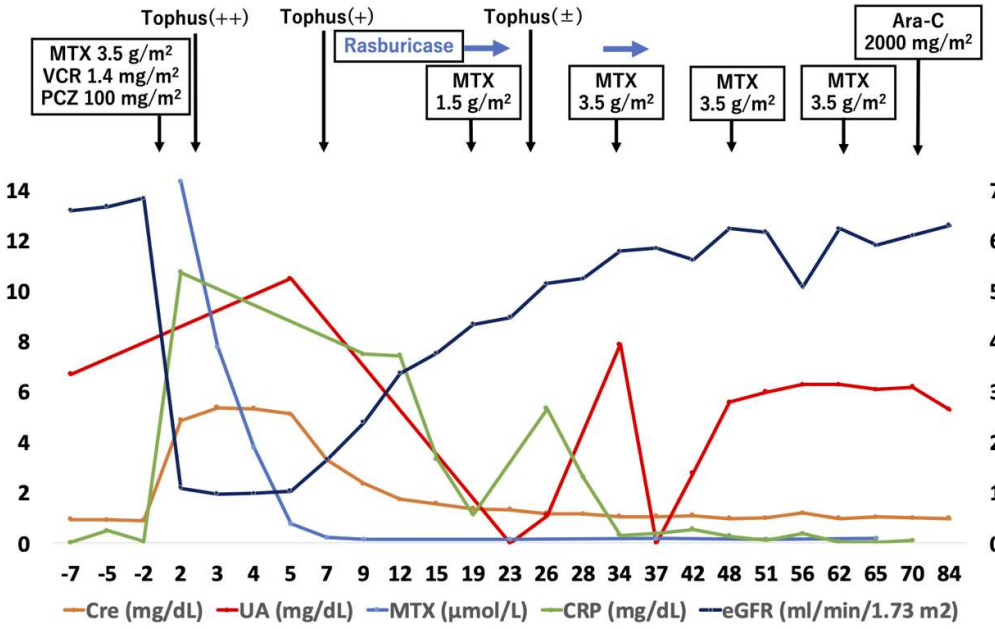

Figure 4. Timeline of treatment, symptoms and blood test results.

Diuretics or blood dialysis was not used. ARF was thought to be due to either acute MTX toxicity or hyperuricemia. Because clinical and radiographical response to treatment was observed, we decided to continue MTX treatment by decreasing the dose of second MTX course to 1.5mg/m² and treating hyperuricemia with rasburicase. 0.2 mg/kg rasburicase was administered from Day 28 to Day 31, and 1.5 mg/m² of MTX on Day 29. Serum uric acid levels did not elevate after the second course of MTX, although swelling of the right ankle was observed; renal function was preserved. Likewise, rasburicase was administered from Day 42 to Day 45, and the third course of MTX at the maximal dose of 3.5 mg/m² on Day 42 without complication. The fourth and fifth courses of MTX (3.5 mg/m²) were administered on Day 57 and Day 71, respectively, without complications. Hyperuricemia was treated by febuxostat. At Day 80, Ara-C (2000 mg/m²/d for 2 days) was

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successfully administered and the patient was discharged. Post-contrast MR images showed dramatic response (CRu) after 3 courses (Figure 3C) of MTX and complete response (CR) after 5 courses (Figure 3D).

Informed written consent was obtained from the patient for publication of this case report and inclusion of clinical and imaging details in the manuscript.

4. Discussion

Tumor lysis syndrome (TLS) is an oncologic emergency, when metabolic abnormalities such as hyperkalemia, hyperphosphatemia, hypocalcemia and hyperuricemia occur as the result of large amounts of tumor cells being killed off by treatment. Hyperuricemia occurs as the result of rapid metabolism of nucleic acids. TLS consists of laboratory TLS (LTLS) and clinical TLS (CTLS). LTLS is defined by the presence of two or more of the following criteria: hyperuricemia, hyperkalemia, hyperphosphatemia and/or hypocalcemia between 3 days before treatment and 7 days after treatment. CTLS is defined by one of renal dysfunction of more than 1.5 times of upper limit of normal (ULN), arrhythmia/sudden death, or convulsions, in addition to LTLS [6]. Suggested risk factors for TLS include large tumor volume, rapid growth rate, and high sensitivity to chemotherapy. Likewise, the presence of hyperuricemia or hyperphosphatemia before chemotherapy, history of nephropathy or prior exposure to nephrotoxic agents, oliguria, aciduria and dehydration are also risk factors [6].

The present case does not fit the definition of LTLS because of lack of hyperkalemia, hyperphosphatemia and/or hypocalcemia, but after initiation of induction therapy, hyperuricemia and ARF were observed. MR images taken before treatment show large tumor volume, which was dramatically reduced after steroid and MTX treatment. Also, this patient had a history of hyperuricemia, and loss of appetite, nausea and diarrhea, probably adverse effects of induction chemotherapy, probably led to relative dehydration despite ample hydration. Therefore, this patient should have been regarded as high risk for TLS. We hypothesized that ARF was caused by acute uric acid nephropathy due to a TLS-like pathophysiology. Renal toxicity due to MTX was also considered. However, since renal function was preserved after repeated MTX administration, we believe the former was more likely.

Acute uric acid nephropathy is due to deposition of uric acid at distal convoluted tubules and collecting duct. Allopurinol, febuxostat and rasburicase are known to lower serum uric acid levels [7,8]. Allopurinol is a hypoxanthine analog, known to inhibit xanthine oxidase, which oxidates xanthine and hypoxanthine, leading to production of uric acid. Febuxostat is a selective xanthine oxidase inhibitor. Lastly, rasburicase is a recombinant version of uric acid oxidase, an enzyme that metabolizes uric acid to allantoin, and is not found in humans [6]. Rasburicase is known to be superior to allopurinol in lowering serum uric acid levels during MTX treatment in acute lymphoblastic leukemia [7]. Febuxostat has biliary elimination and needs no dose adjustment in patients with renal impairment [9]. In the present case, we administered rasburicase before and during the second and third courses of MTX treatment, in addition to febuxostat administration. Uric

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acid levels did not elevate, and renal function was preserved during induction and consolidation treatment. MR images taken after the third course of MTX showed that tumor volume had dramatically decreased, and because of the risk of producing anti-rasburicase autoimmune antibodies and anaphylaxis due to repeated exposure, rasburicase was not used during the fourth and fifth courses of MTX.

Schlafen11 (SLFN11) is a DNA/RNA helicase, whose expression is known to correlate well with sensitivity to DNA damaging agents [10]. The present case had a relatively high expression of SLFN11 by immunohistochemistry, suggesting sensitivity to chemotherapy (Figure 2C). Interestingly, a recent report suggests that non-germinal center B (non-GCB)-type lymphomas, the predominant type in PCNSL, have higher SLFN11 compared to GCB-type [11], although SLFN11 expression in PCNSL has not been studied to date. We analyzed the CellMinerCDB database and found that there was a weak, positive correlation between SLFN11 expression and sensitivity to methotrexate in lymphoma cell lines ($r = 0.44$, Supplemental figure 1) [12]. Thus, SLFN11 is a candidate to predict sensitivity to chemotherapy, thus anticipate the risk of TLS and acute uric acid nephropathy.

In the present case, acute uric acid nephropathy was observed after the first course of MTX. Fortunately, renal function normalized, induction chemotherapy was successfully completed, and post-contrast MR images taken after induction therapy showed CR. We believed that in the present case, acute uric acid was a signal for good response to chemotherapy and thus continuation of chemotherapy was actively pursued.

5. Conclusions

PCNSLs are chemosensitive tumors, and routine screening of serum uric acid and metabolites should be done during induction chemotherapy, especially when initial tumor volume is large. When serum uric acid levels are high, treatment with rasburicase, febuxostat and/or allopurinol treatment should be considered to prevent acute uric acid nephropathy.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Figure S1: CellMinerCDB database analysis showing a weak, positive correlation between SLFN11 expression and sensitivity to methotrexate in lymphoma cell lines.

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