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# Short-term corticosteroid therapy consecutive to hemodialysis and charcoal hemoperfusion for methotrexate-induced acute kidney injury in an elderly lymphoma patient

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ABSTRACT

Acute kidney injury (AKI) due to delayed methotrexate (MTX) elimination is a severe potential adverse event of high-dose (HD)-MTX treatment. However, no treatment for HD-MTX-induced AKI has been established. In addition, there are no reports of corticosteroids being administered for HD-MTX-induced AKI. Here, we report the case of a 77-year-old male with central nervous system lymphoma, who developed an AKI after the second course of HD-MTX. He underwent charcoal hemoperfusion and hemodialysis immediately after the development of the AKI. He also received short-term corticosteroid therapy due to inflammatory findings and a positive drug-induced lymphocyte stimulation test for MTX. Our case suggests that short-term corticosteroid therapy consecutive to hemodialysis and charcoal hemoperfusion may be useful for AKI induced by delayed MTX elimination even in the elderly.

## 1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is a clinically diverse hematological malignancy, which sometimes involves central nervous system (CNS) (Chin and Cheah, 2017). DLBCL with CNS involvement remains therapeutically challenging because both the standard therapy for DLBCL and CNS-targeted therapy based on the treatment for primary central nervous system lymphoma (PCNSL) are required (Perry et al., 2019; Schaff and Grommes, 2022). High-dose methotrexate (HD-MTX)-based chemotherapy is the standard induction therapy for PCNSL and CNS involvement in DLBCL (Schaff and Grommes, 2022). MTX doses of $> 1.5$ g/m$^2$ are needed for CNS lesions because the standard doses of chemotherapeutic agents lack efficacy due to their poor penetration of the blood-brain barrier. HD-MTX therapy can cause acute kidney injury (AKI) in approximately 10 % of malignant lymphoma patients, which requires supportive care, comprising hydration, urine alkalinization, and leucovorin administration (Howard et al., 2016). Renal function declines with age, which alters the pharmacokinetics of chemotherapeutic drugs and increases the risk of toxicities associated with chemotherapy. Therefore, even with appropriate supportive care, MTX elimination may be delayed in elderly patients due to renal dysfunction. We managed a case of an elderly DLBCL patient with CNS involvement who experienced successful treatment for HD-MTX-induced AKI.

There is no established management strategy for HD-MTX-induced nephrotoxicity, especially in areas where glucarpidase is not available (Howard et al., 2016; Rosales et al., 2021). Extracorporeal techniques have sometimes been used. However, the usefulness of charcoal hemoperfusion (CHP) combined with hemodialysis (HD) in elderly patients with CNS lymphoma remains unclear. In addition, there are no reports of corticosteroids being administered for acute renal failure during HD-MTX therapy. Here, we report successful combination treatment including HD, CHP, and corticosteroid therapy for AKI after HD-MTX in an elderly DLBCL patient and discuss therapeutic options for HD-MTX-induced AKI.

## 2. Case report

A 77-year-old male with hypertension presented with systemic DLBCL and was admitted to our hospital to undergo treatment for CNS

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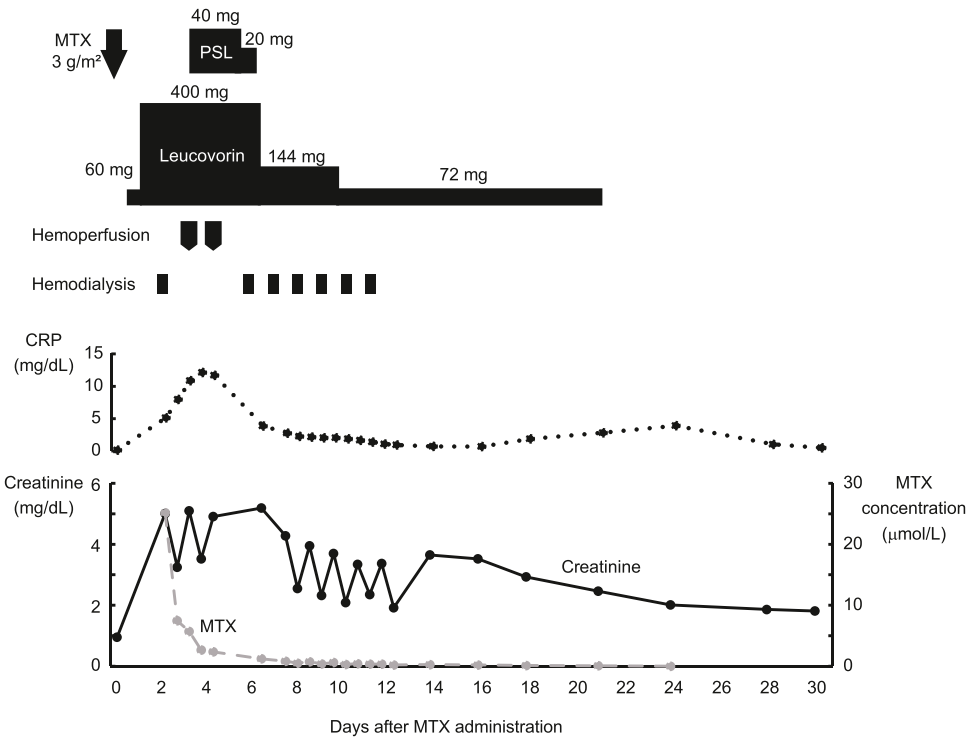


**Fig. 1.** The patient's clinical course after the second course of high-dose methotrexate therapy. PSL: prednisolone; MTX: methotrexate; CRP: C-reactive protein.

involvement. Six months before admission, he developed weakness in the left lower extremity and unsteadiness when walking. Magnetic resonance imaging (MRI) showed a gadolinium-enhanced lesion in his right thalamus. However, a biopsy of the lesion did not show malignancy. Two months before admission, an MRI examination revealed a new lesion in his right frontal lobe. A biopsy of the lesion resulted in a diagnosis of DLBCL. Positron emission tomography-computed tomography (PET-CT) showed the abnormal accumulation of $^{18}$F-fluorodeoxyglucose in the right frontal lobe, right pericardial and left perirenal soft tissue, and right adrenal gland. Thus, he was diagnosed with DLBCL with concurrent CNS involvement. A combination of rituximab (375 mg/m$^2$) and HD-MTX (3 g/m$^2$) was administered. MTX was infused over 3 h, and leucovorin (15 mg) was administered every 4 h, starting 24 h after the initiation of MTX therapy. During the first course of HD-MTX therapy, he did not develop renal insufficiency or any other organ dysfunction. His-serum MTX level at 72 h after the initiation of MTX therapy was 0.07 mmol/L (reference value: 0–0.1 mmol/L). Thus, MTX excretion was not delayed during the first course of HD-MTX therapy. MRI performed after the first course of HD-MTX revealed that the contrast-enhanced brain tumors had vanished.

Three weeks after the first course, the second course of HD-MTX was administered. Before this course of treatment, the patient showed normal renal (serum creatinine level: 0.95 mg/dL) and liver function. The supportive care provided during this course, including hydration (2.5 L/day), urine alkalinization, and leucovorin, was the same as that provided during the first course. The patient's urinary pH was monitored, and additional intravenous sodium bicarbonate was administered to keep his urinary pH above 7.0 as previous reported (Hosoi et al., 2023). Twenty-four hours after the initiation of MTX therapy, his urine output began to decrease. Laboratory tests performed 48 h after the initiation of MTX therapy revealed that his creatinine level had increased to 5.01 mg/dL. At that time, his serum MTX level was 25.2 mmol/L. In addition, he developed a fever and an elevated C-reactive protein (CRP) level (5.1 mg/dL). He underwent HD for acute renal failure on the day that the elevated creatinine and MTX levels were detected. One session of HD reduced his serum MTX level to 7.44 mmol/L. On the following two days, CHP was performed using a Hemosorba® CHS-350 column (Asahi Kasei Medical Co. Ltd., Tokyo, Japan), according to the manufacturer's protocol (Fig. 1). His-MTX level decreased from 5.70 mmol/L to 1.21 mmol/L after two sessions of CHP.

His-CRP level had increased to 12.1 mg/dL at 72 h after the administration of HD-MTX (Fig. 1). We considered that this inflammatory finding was due to MTX because of a lack of infectious signs. Prednisolone (0.5 mg/kg) was administered for excessive inflammation concomitant with MTX-induced nephrotoxicity. A drug-induced lymphocyte stimulation test (DLST) confirmed that the patient had a high stimulation index score of 5.6 for MTX (the cut-off value for DLST positivity is 1.8). The administration of prednisolone was continued for four days. The patient's fever was ameliorated, and his CRP level decreased to 2.75 mg/dL. After two sessions of CHP, HD was conducted for six consecutive days, which led to a reduction in his MTX level to 0.25 mmol/L. Grade 3 neutropenia, according to the Common Terminology Criteria For Adverse Events (CTCAE) developed. Elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels (CTCAE grade 2) were also seen. However, no MTX-induced oral mucositis was observed. The patient's serum MTX concentration had decreased to the target level (< 0.1 mmol/L) by 20 days after the administration of HD-MTX. His-renal function gradually recovered.

PET-CT performed after two courses of HD-MTX therapy showed a complete metabolic response. The patient's serum creatinine level had decreased to the reference range by two months after the second course of HD-MTX therapy. Therefore, R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, and prednisolone) therapy for nodal DLBCL was started. He received five courses of R-CHOP therapy without any recurrence of the renal insufficiency.

## 3. Discussion

AKI is a serious potential adverse event of HD-MTX therapy, which may lead to treatment delays and increased morbidity. Previous studies showed no significant differences in the incidence or severity of MTX-related toxicity or the delayed elimination of MTX by age. However,

**Table 1**
Hemoperfusion in MTX-related acute kidney injury in patients older than 70 years old.

| Case | Age | Sex | Primary disease | Number of courses | MTX dose ($g/m^2$) | Extracorporeal method | Corticosteroid therapy | Outcome | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 71 | N.A. | N.A. | N.A. | 1.5 | HD, CHP, PE | N.A. | N.A. | Bouffet et al. (1986) |
| 2 | 70 | Male | DLBCL | 1 | 0.65 | PD, CHP, PE | No | Died 1 month later | Wakita et al. (1995) |
| 3 | 72 | Female | Osteosarcoma | N.A. | 8.6 | HD, HP | No | Renal function recovered 8 months later | Fujikawa et al. (2017) |
| Present case | 77 | Male | DLBCL | 2 | 3 | HD, CHP | Yes | Renal function recovered 2 months later | |

MTX: methotrexate, N.A.: not applicable, DLBCL: diffuse large B-cell lymphoma.
HD: hemodialysis, CHP: charcoal hemoperfusion, PE: plasma exchange, PD: peritoneal dialysis, HP: hemoperfusion.

in older patients, it is important that such complications, including renal impairment, are dealt with immediately because of the frailty of elderly patients (Ranchon et al., 2018; O'Donoghue et al., 2022). Delayed MTX elimination causes nephrotoxicity. In our elderly patient, who developed AKI due to delayed MTX elimination, a combination of HD and CHP decreased the serum MTX concentration rapidly. In addition, the administration of corticosteroids may support recovery and prevent inflammatory damage to the kidneys in such cases, as has been found for acute interstitial nephritis (Sanchez-Alamo et al., 2022).

AKI is a critical potential adverse event of HD-MTX therapy and develops in approximately 10 % of malignant lymphoma patients who receive HD-MTX (Ranchon et al., 2018). Blood purification therapies, including HD and CHP, were reported to be effective against MTX-induced AKI. CHP involves the use of an activated carbon absorption membrane, which enables the elimination of protein-bound substances (King et al., 2019). However, CHP is often performed for HD-MTX nephrotoxicity in younger patients, and there are few reports of the effectiveness of CHP combined with HD in elderly (over 70 years of age) lymphoma patients (Rosales et al., 2021). Previously reported cases in which blood purification therapies, including CHP, were used for MTX-induced AKI in patients older than 70 years are summarized in Table 1. In our patient, blood purification therapies; i.e., HD and CHP, were conducted promptly on the day that the patient's serum creatinine level increased. As MTX has a protein-binding rate of approximately 50 % and a high intracellular distribution, performing HD alone was reported to lead to MTX levels rebounding after the HD (Rosales et al., 2021; King et al., 2019). CHP involves the adsorption of toxins to charcoal particles, which enables the elimination of protein-bound MTX. The combined use of HD and CHP may result in rapid reductions in MTX levels without a significant rebound. Renal function is often poor in the elderly. Thus, prompt combination therapy consisting of HD and CHP may be useful in cases of delayed MTX elimination.

The pathogenesis of AKI induced by HD-MTX therapy has not been fully elucidated. The main cause of nephrotoxicity was reported to be crystal nephropathy (Howard et al., 2016). To prevent crystal formation, urine alkalinization is required. Drug crystals do not form in urine with an alkaline pH (Howard et al., 2016). Our patient underwent successful urine alkalinization and urinary pH monitoring. However, his renal function rapidly worsened after the administration of HD-MTX. On the other hand, other mechanisms, such as a direct toxic effect of MTX, have also been proposed to cause HD-MTX-induced AKI (Widemann and Adamson, 2006). Acute interstitial nephritis is a cause of AKI, and most cases of acute interstitial nephritis are induced by drug exposure (Sanchez-Alamo et al., 2022). Interestingly, a DLST for MTX was positive in this patient. The positive result of DLST indicated the activation of lymphocytes by MTX. Although we did not examine the renal histology, the activated lymphocytes might infiltrate the kidney and result in AKI via an allergic mechanism similar to acute intestinal nephritis triggered by allergic reactions in our patient (Sanchez-Alamo et al., 2022). Fever and elevated CRP levels, which can occur in drug-induced interstitial nephritis, were also observed (Sanchez-Alamo et al., 2022; Zheng et al., 2020). In the treatment of acute interstitial nephritis, corticosteroids help to reduce the infiltration of inflammatory cells into the kidney interstitium and prevent subsequent fibrosis (Sanchez-Alamo et al., 2022). There are no reports of prednisolone being administered for acute renal insufficiency following HD-MTX therapy. In our patient, the corticosteroid therapy may have helped to improve the patient's renal function, although it was used in combination with blood purification therapies. Further studies are warranted to elucidate whether the short-term administration of corticosteroids is useful in cases in which positive DLST test results for MTX are obtained in patients that exhibit delayed MTX elimination.

Glucarpidase is a recombinant enzyme, which cleaves MTX and reduces serum MTX levels (Howard et al., 2016). Although glucarpidase was approved in the U.S. 10 years ago, it is not available in some countries and regions, including Japan. In addition, some hospitals do not have the drug on hand, and it may not be readily available in rural areas, even in the U.S. A previous report demonstrated that hemoperfusion was useful in young patients who were treated in areas where glucarpidase was not immediately available (Rosales et al., 2021). Our case also suggests that combination treatment including hemodialysis, CHP, and short-term corticosteroid therapy is effective against MTX-induced AKI when glucarpidase is not available. Large cohort studies are warranted to determine which patients with MTX-induced AKI would benefit from combination therapy, including short-term corticosteroid administration. Additionally, long-term follow-up is needed to assess whether corticosteroid administration can improve renal function in MTX-induced AKI with a possible allergic mechanism.

## 4. Conclusion

Short-term corticosteroid therapy consecutive to hemodialysis and CHP may be a useful treatment for AKI induced by delayed MTX elimination, especially in elderly patients. The number of elderly patients with DLBCL requiring HD-MTX therapy is increasing. Since the renal functional reserves of the elderly are reduced, it is important to establish an appropriate management strategy for AKI that arises after HD-MTX therapy.

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## Ethical approval and informed consent

All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the relevant institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from the patient for publication of this case report.

## Patient consent statement

The authors declare that they have obtained consent from the patient.

## CRediT authorship contribution statement

**Misato Tane:** Conceptualization, Investigation, Visualization, Writing – original draft. **Hiroki Hosoi:** Conceptualization, Investigation, Data curation, Visualization, Writing – original draft, Writing – review & editing. **Hideki Kosako:** Investigation, Data curation, Writing – review & editing. **Yukiko Yamano:** Investigation, Data curation. **Takayuki Hiroi:** Investigation, Data curation. **Shogo Murata:** Investigation, Writing – review & editing. **Toshiki Mushino:** Data curation, Writing – review & editing. **Shin-Ichi Araki:** Writing – review & editing, Supervision. **Takashi Sonoki:** Writing – review & editing, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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