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Case Report

Radiation Myelopathy Caused by Palliative Radiotherapy and Intrathecal Methotrexate

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Acute myeloid leukemia · Radiotherapy · Palliative radiation · Intrathecal methotrexate · Radiation myelopathy

Abstract
Radiation myelopathy is a rare, late-stage adverse event that develops following irradiation at or above 50 Gy. Here, we report a case of irreversible paraplegia caused by palliative radiation (20 Gy in 5 fractions) to the spinal cord combined with intrathecal methotrexate (IT-MTX). A 69-year-old man presented with back pain, prompting a diagnosis of acute myeloid leukemia. At the first visit, he complained of muscle weakness and hypoesthesia in both legs; spinal magnetic resonance imaging (MRI) revealed an epidural mass compressing the spinal cord at the fifth to seventh level of the thoracic vertebrae. This was considered to be an extramedullary lesion of leukemia, and he received remission induction therapy including IT-MTX; palliative radiation (20 Gy in 5 fractions) of the epidural mass was initiated the following day. Then, during the course of consolidation therapy, a second IT-MTX was performed after 1 month and a third after 3 months. While the consolidation therapy was complete, yielding remission, he developed sudden paraplegia, as well as bladder and bowel dysfunction (BBD), 10 months later. Spinal MRI showed extensive intramedullary high signal intensity on T2-weighted image, including the irradiation field. It was thought myelopathy was due to irradiation of the spinal cord combined with IT-MTX. He immediately received steroid pulse therapy; however, the paraplegia and BBD did not improve. It is extremely rare for irreversible radiation myelopathy to occur with IT-MTX and palliative radiation to the spinal cord. We believe that even with low-dose palliative radiation, caution is required for combined use with IT-MTX.

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Introduction

Acute myeloid leukemia (AML) is a hematological tumor characterized by myeloproliferation of bone marrow cells and cessation of normal cell division. The treatment for AML is aggressive chemotherapy based on a combination of multiple drugs [1]. At a prevalence of just 1%, it is extremely rare to find lesions of the central nervous system (CNS) at the time of diagnosis in patients with AML [2]. CNS leukemia is treated with intrathecal (IT) chemotherapy, systemic chemotherapy, and radiotherapy [3, 4]. Intrathecally administered drugs include methotrexate (MTX) and cytarabine (Ara-C). The National Comprehensive Cancer Network (NCCN) guidelines recommend adding radiotherapy to systemic chemotherapy if the initial CT/magnetic resonance imaging (MRI) identifies a mass effect or increased intracranial pressure due to a parenchymal lesion in the brain [5]. However, it has been stated that IT chemotherapy or high-dose (HD) Ara-C should not be administered concurrently with cranial radiation because of the increased risks of neurotoxicity [5]. There has been no description of a combination of radiation to the spinal cord and chemotherapy, and its safety is not well understood. In this case, the spinal cord was compressed by an epidural mass at the time of initial examination, resulting in muscle weakness and hypoesthesia in both legs. Therefore, in addition to systemic chemotherapy (including IT-MTX), palliative radiation to the spinal cord was administered. As a result, the patient developed irreversible radiation myelopathy. We report this case because irreversible radiation myelopathy due to combined use of IT-MTX and palliative irradiation to the spinal cord is extremely rare.

Case Presentation

A 69-year-old man sought consultation with chief complaints of epigastric and back pain. Examination by abdominal ultrasonography, thoracoabdominal CT, and upper endoscopy did not show any abnormalities. However, a blood test showed blasts in the peripheral blood, and bone marrow aspiration was performed, resulting in a diagnosis of AML. At the first visit, the patient complained of difficulty moving both legs, and neurological examination revealed muscle weakness and hypoesthesia in both legs; thus, spinal MRI was performed. An epidural mass was revealed inside the spinal canal, compressing the spinal cord at the level of the fifth to seventh thoracic vertebrae (shown in Fig. 1a). T2-weighted image and contrast-enhanced T1-weighted image showed no abnormal signals in the spinal cord suggesting edema or infiltration (shown in online suppl. Fig. 2a; for all online suppl. material, see www.karger.com/doi/10.1159/000524825). As the mass was thought to be an extramedullary lesion of leukemia, induction therapy (daunorubicin 40 mg/m^2 × 3 days and Ara-C 80 mg/m^2 × 7 days) and IT chemotherapy (MTX 15 mg + Ara-C 40 mg) were performed immediately. Palliative radiation of the epidural mass in the spinal cord was initiated the following day.

The patient underwent palliative radiotherapy (20 Gy in 5 fractions for 1 week) using a 6-MV photon beam in the posterior field for the fifth to seventh thoracic vertebrae (Fig. 2). While this prevented progression to paralysis of the legs, leg numbness persisted even after irradiation. This was followed by consolidation therapy (including Ara-C) performed over four and a half months. During the course of consolidation therapy, a second IT chemotherapy (MTX 15 mg + Ara-C 40 mg) was administered after 1 month and a third after 3 months (shown in online suppl. Fig. 1). Follow-up spinal MRI performed 1 month after irradiation showed a marked reduction of the epidural mass (shown in Fig. 1b); at this point, no abnormal signals were observed in the spinal cord (shown in online suppl. Fig. 2b). Once consolidation

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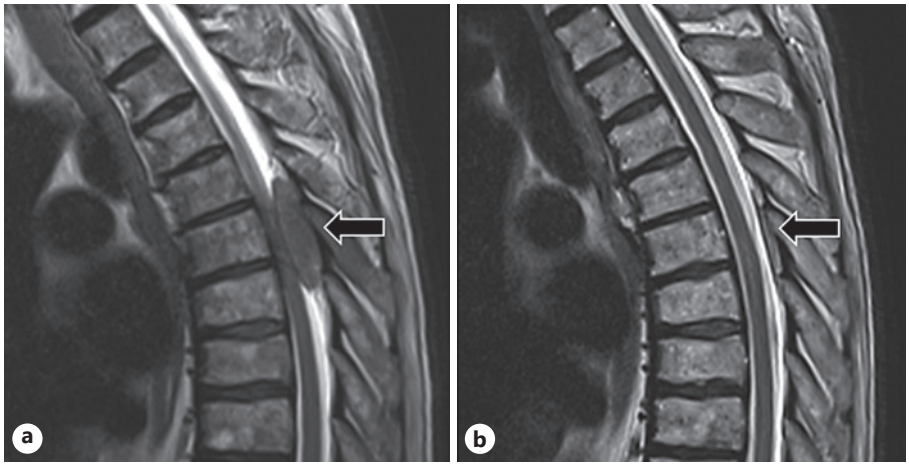

Fig. 1. Spinal MRI. **a** T2-weighted image sagittal section image at first visit showing an extramedullary mass compressing the spinal cord at the fifth to seventh level of the thoracic vertebrae. **b** T2-weighted image sagittal section image at 1 month after palliative radiation; the extramedullary mass had disappeared.

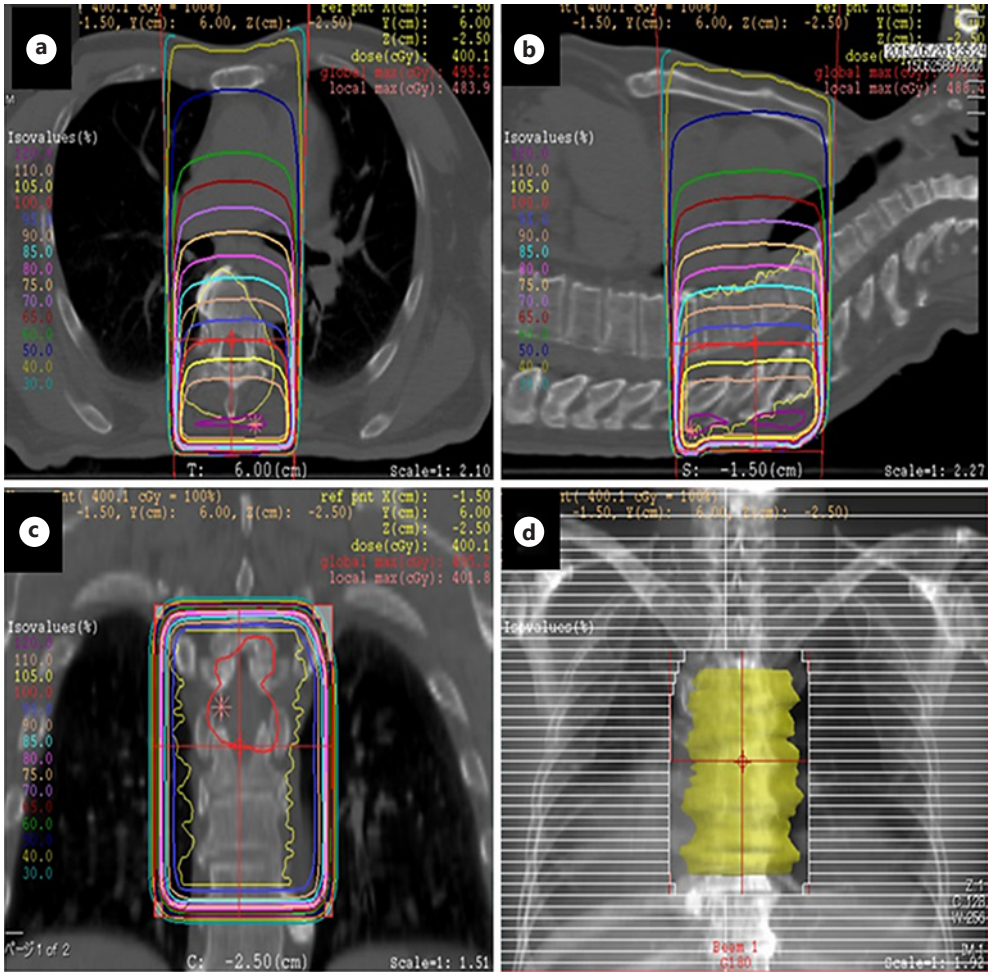

Fig. 2. Dose distribution for palliative radiation. Palliative radiation (20 Gy in 5 fractions) was directed at the mass at the fifth to seventh level of the thoracic vertebrae. **a** Axial image. **b** Sagittal image. **c** Coronal image. **d** Digital reconstructed radiography.

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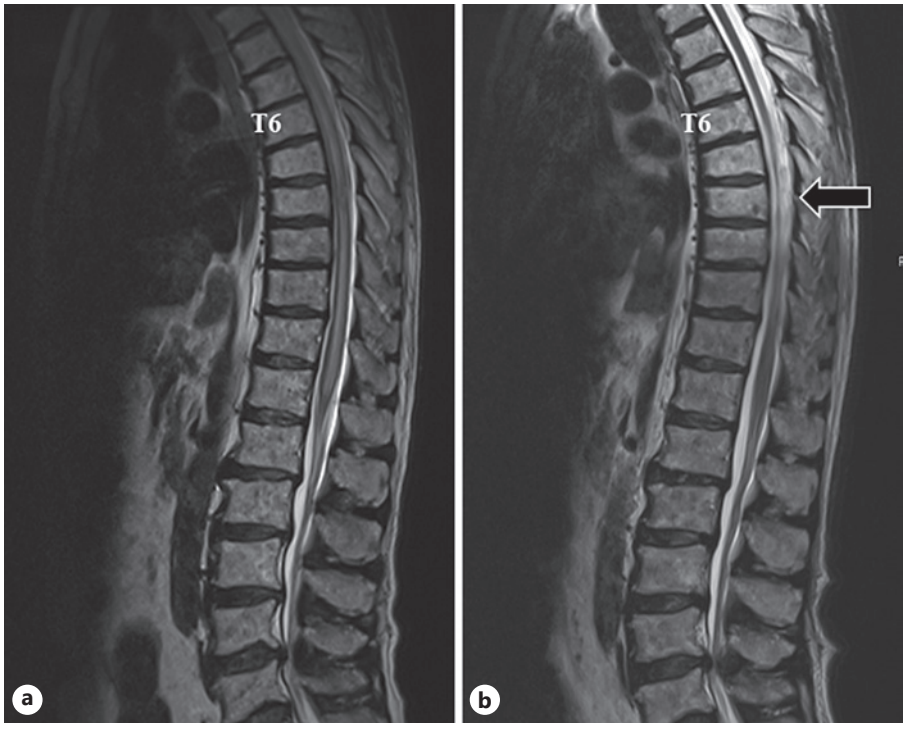

Fig. 3. Spinal MRI. **a** T2-weighted image sagittal section image at 10 months after palliative radiation, showing a hyperintense region over a wide range from the first thoracic vertebra to the conus medullaris. **b** T2-weighted image sagittal section image at 23 months after palliative radiation, showing spinal cord atrophy at the third to tenth level of the thoracic vertebrae. **c** Contrast-enhanced T1-weighted image axial section at 10 months after palliative radiation, showing enhanced effects in the spinal gray matter.

therapy was completed, the patient was discharged and allowed to return home after remission was confirmed by bone marrow aspiration.

However, 10 months later, he developed sudden paraplegia, as well as bladder and bowel dysfunction (BBD), requiring ambulance transport. Spinal MRI showed extensive high signal intensity on T2-weighted image and diffuse swelling of the thoracolumbar spinal cord (first thoracic vertebrae to the conus medullaris) (shown in Fig. 3a). Contrast-enhanced T1-weighted image showed contrast-enhancing effects in the spinal gray matter (shown in online suppl. Fig. 2c). Subsequently, lumbar puncture was performed, but no leukemic cells were observed. Additionally, the spinal fluid was negative for oligoclonal band and myelin basic protein. Furthermore, no anti-aquaporin 4 antibody was detected in blood tests, and no elevation of WT1-mRNA was observed. Thus, demyelinating disease, autoimmune disease, and AML recurrence were ruled out.

Considering the patient's history of radiotherapy and clinical symptoms, drug- or radiation-induced myelitis was suspected. Although he was immediately placed on steroid pulse therapy (methylprednisolone 1,000 mg × 3 days) for myelitis, there was no improvement in his paraplegia and BBD. Spinal MRI performed 23 months later showed that the extensive high signal intensity on T2-weighted image of the spinal cord had disappeared, revealing atrophy in the spinal cord at the level of the third to tenth thoracic vertebrae (shown in Fig. 3b). There was prominent atrophy in the spinal cord at a level that included the irradiation field. The patient was followed up for about 2 years, but his paraplegia and BBD persisted without improvement.

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Discussion

The present case report demonstrates that the combined use of palliative radiation to the spinal cord with IT-MTX has the potential to cause irreversible radiation myelopathy. The patient in this case underwent palliative radiation as an epidural mass was found compressing the spinal cord at the time of the first visit. Since the myelopathy developed at a lower dose than that tolerable for the spinal cord (20 Gy in 5 fractions), and there was an extensive abnormal signal in the spinal cord that extended beyond the irradiation field, the IT-MTX was believed to have been involved in its onset. On the contrary, the prominent atrophy observed in the spinal cord within the irradiation field after approximately 2 years suggests that the radiation had caused necrosis of the spinal cord. This implies that the complex factors of radiation combined with IT-MTX had contributed to the onset of myelopathy in this patient.

In general, the tolerable dose for the spinal cord is believed to be 50 Gy in 2-Gy fractions [6]. The evidence is now that 50 Gy in 25 fractions yields an incidence of radiation myelopathy less than 0.2% [6]. Myelopathy is unlikely to occur with dose fractionation in palliative irradiation such as in the present case. However, there is a risk of myelopathy occurring with a large, single dose – as with stereotactic irradiation – even at or below the tolerable dose [7].

Pathologically, HD irradiation yields glial cell necrosis, causing relatively early paralysis [8]. In contrast, low-dose irradiation causes vascular damage, with a later onset than with HD irradiation [8]. Radiation myelopathy is caused by these two different mechanisms, with a bimodal distribution in the latent period [8].

Although it is rare for IT chemotherapy to cause myelopathy, there are case reports of leg paralysis, as well as bladder and rectal disturbances, occurring after IT-MTX [3, 4, 9]. The time to onset of neurological symptoms is variable, ranging from 2 days to 7 months from the initiation of IT chemotherapy [4]. The occurrence of neurotoxicity due to IT chemotherapy is thought to correlate with a high cerebrospinal fluid level of MTX [3]. A previous report described that acute neurotoxicity from IT-MTX developed without MTX overdose or repeated administration [10]. Although there is no consensus on the treatment of acute neurotoxicity, early therapeutic interventions are required to prevent the occurrence of permanent neurologic events [10]. Additionally, it has been noted that the combined use of chemotherapy and radiotherapy has the potential to lower the tolerable dose to the spinal cord.

Archie et al. [11] reported on cases with paraplegia and BBD occurring 5–9 months after the combined use of IT chemotherapy (Ara-C and MTX) and radiation to the spinal cord (46–50 Gy). Given that all of the patients had clinical signs of myelopathy emanating from the irradiated segment of the cord, they recommend that the total radiation dose or dose rate to the spinal cord should be reduced [11]. The report indicated the possibility that simultaneous administration of chemotherapy and radiotherapy may reduce spinal cord radiation tolerance, but the combined effects for sequential therapy are impossible to predict because of confounding factors – such as timing, drug dose, and uptake [11].

Jan et al. [3] also stated that among patients who developed ascending myelitis or paraplegia after combination including spinal cord irradiation (30–52 Gy), irradiation may have made it easier for subsequent chemotherapy to result in neurotoxicity [3]. They warned that multiple, frequently spaced courses of CNS-directed therapies must be avoided, especially in patients who have received prior CNS radiation [3].

Pinnix et al. [9] reported that autopsies of patients who received both irradiation to the spinal cord and IT-MTX exhibited necrosis and bleeding in the irradiated spinal cord, as well as degeneration of the unirradiated spinal cord. This demonstrates that radiation and IT-MTX are complexly involved in the onset of myelopathy. The possibility of further damage to the spinal cord has also been noted in instances where radiation is administered to patients with existing neurotoxicity due to IT chemotherapy. This concern about neurological damage due

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to the combination of moderate to high doses of radiation therapy and IT chemotherapy is scattered throughout the literature [3, 9, 11, 12]. However, reports on combined low-dose (20 Gy) palliative radiation to the spinal cord and IT-MTX, followed by the development of myelopathy (such as in the present case), are extremely rare.

The effects of combination therapy on the CNS include a high risk of developing leukoencephalopathy when the treatment for primary CNS malignant lymphoma includes whole-brain irradiation followed by HD MTX [13]. As a result, the NCCN recommends that MTX is administered prior to whole-brain radiation. However, the RTOG 93–10 study reported that neurotoxicity occurred in 15% of patients treated with HD MTX and IT-MTX prior to whole-brain irradiation; therefore, careful attention is needed with the combined use of radiotherapy and MTX-based chemotherapy [14].

On the other hand, the NCCN guidelines for CNS leukemia state that because the risk of neurotoxicity increases with the combined use of cranial radiotherapy and HD Ara-C or IT-MTX, combined use should be avoided [5]. In addition, it is recommended that IT chemotherapy following cranial radiotherapy be continued until the spinal fluid is clear; however, the interval is not specified [5].

Pinnix et al. [15] stated that since the combined use of cranial radiotherapy and chemotherapy could potentially trigger unexpected, severe neurotoxicity – even at doses of 18–24 Gy – simultaneous combined use of IT/intravenous chemotherapy and cranial radiotherapy is not recommended. They proposed an interval of at least 2 weeks (preferably 3–5 weeks) between the final administration of MTX/Ara-C (intravenous or IT) and the start of cranial radiotherapy. Similar to how administering MTX after cranial radiotherapy leads to leukoencephalopathy, combined use of irradiation of the spinal cord with IT-MTX is inferred to cause severe nervous system symptoms, such as myelopathy. While the safe timing for the combined use of irradiation of the spinal cord with IT-MTX remains unknown, simultaneous combined use should be avoided except in emergency cases, and the interval between the two treatments should be carefully considered.

The limitations of the present case include the following: regarding the cause of spinal cord atrophy, no abnormal signals were observed in the spinal cord when an epidural mass was found; still, there may have been some spinal cord fragility. Alternatively, it is possible that spinal compression caused by the mass resulted in an abnormal flow of the cerebrospinal fluid, with MTX being retained in the medullary cavity; this would also have had an impact. The patient in the present case underwent both IT-MTX and Ara-C; therefore, a different drug – such as Ara-C – may have been involved in the onset of myelopathy in addition to MTX. Since no pathological examinations were performed in this case, the effects of radiotherapy and MTX on the spinal cord could not be ascertained.

Conclusion

We reported the case of a patient who developed radiation myelopathy caused by the combined use of IT-MTX with irradiation of the spinal cord despite receiving a dose for palliative irradiation thought to be safe by the radiation oncologist. With the recent increase in opportunities for palliative radiation, the combined use of irradiation of the spinal cord with IT-MTX appears to require special care.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. The Jichi Medical University Central Clinical Research Ethics Committee has determined that our project does not meet "Common Rule" definition of human subjects' research and does not require CRB review. The Certified Review Board number is 3200006.

Conflict of Interest Statement

The authors have no conflicts of interest.

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Author Contributions

Yukiko Fukuda was responsible for writing the Introduction, the Case Report, and the Discussion/Conclusion sections. Satoru Takahashi, Michiko Nakamura, and Shoko Ito were responsible for treatment. Masashi Endo, Kazunari Ogawa, Masahiro Kawahara, and Keiko Akahane contributed to the critical revision of the content. Katsuyuki Shirai, Harushi Mori, and Yoshinobu Kanda contributed to the analysis of the content, critical revision of the content, and the final approval of the version to be published.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

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