Nelarabine-induced myelopathy in patients who underwent allogeneic hematopoietic cell transplantation: report of three cases

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Case Report

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Abstract

Background: Nelarabine is an effective treatment for T-cell acute lymphoblastic leukemia/lymphoma. Myelopathy is a problematic adverse event associated with nelarabine. The mechanism leading to myelopathy is unclear. Diagnostic methods and therapy for nelarabine-induced myelopathy have not been established.

Case presentation: Three patients who received allogeneic hematopoietic cell transplantation (allo-HCT) after nelarabine administration at the National Cancer Center Hospital from December 2014 to March 2021 developed myelopathy. They developed myelopathy 20 days before allo-HCT, 12 days after allo-HCT, and 29 days after allo-HCT, respectively. The intervals from last nelarabine administration to onset of myelopathy were 41 days, 121 days, and 47 days, respectively. The initial symptom was paresthesia in the lower legs in all patients. In two of three patients, magnetic resonance imaging showed lesions in the dorsal column or medulla oblongata, a characteristic finding of nelarabine-induced myelopathy that was similar to findings in mitochondrial diseases. We treated all three patients with intravenous immunoglobulin and methylprednisolone, but all became unable to walk. One patient died on day 101 due to the progression of neurotoxicity. In the other two patients, neurological symptoms spontaneously improved. One patient is alive and became able to walk with a cane despite some muscle weakness in his lower extremities by 8 months after allo-HCT. The other patient was able to move around in a wheelchair but died of mucormycosis on day 476 after allo-HCT. Postmortem autopsy of two patients showed spongiosis of the posterior funiculus. One patient also had the same finding in the medulla oblongata.

Conclusions: Nelarabine is a valid treatment option. However, these cases suggest that allo-HCT can worsen nelarabine-induced myelopathy, a potentially fatal condition for which there is no effective treatment. Elucidation of the mechanism and establishment of diagnostic methods and therapies for nelarabine-induced myelopathy are needed.

Background

Nelarabine, a prodrug of 9-beta-D-arabinosylguanine (ara-G), is used to treat T-cell acute lymphoblastic leukemia/lymphoma (T-ALL/LBL). Nelarabine has a demonstrated complete remission (CR) rate of 15–36% as a single agent in relapsed or refractory T-ALL/LBL [1–4]. In addition, front-line therapy incorporating nelarabine has been investigated in recent years [5, 6]. On the other hand, a problematic adverse event is neurotoxicity, which can develop in the peripheral or central nervous system. The incidence of grade 3 or higher neurotoxicity has been reported to be 7–57% [7]. In severe cases, nelarabine causes myelopathy. The mechanism leading to nelarabine-induced myelopathy is not entirely understood. There are no established diagnostic criteria or treatments. A dorsal column lesion on magnetic resonance imaging (MRI) was reported as a characteristic finding in previous studies. However, the characteristic pathological finding is unclear. There has been only one report of postmortem autopsy by Hartz et al [8]. They reported autopsy findings in a boy who developed fatal neurological complications after one cycle of nelarabine.

In patients with T-ALL/LBL, allogeneic hematopoietic cell transplantation (allo-HCT) is often performed after nelarabine therapy. Neurological complications can occur via various mechanisms after allo-HCT [9]. As a result, pre-transplant neurotoxicity associated with nelarabine therapy might increase the risk of severe neurological complications after allo-HCT. In one report, three of six patients with a history of nelarabine therapy for T-ALL/LBL developed irreversible paresthesia and muscle weakness in both lower extremities after allo-HCT [10]. The safety of allo-HCT following nelarabine therapy has not been established yet.

Four patients with T-ALL/LBL who had a history of nelarabine therapy underwent allo-HCT at the National Cancer Center Hospital from December 2014 to March 2021. Three of them developed myelopathy after allo-HCT. We report the detailed clinical course of these three patients, considerations of the mechanism underlying nelarabine-induced myelopathy, and the effect of allo-HCT after nelarabine-induced myelopathy based on the findings from imaging studies and postmortem autopsies.

Case Presentation

Case 1

A 17-year-old male was diagnosed with T-ALL. He achieved CR after induction chemotherapy with L-asparaginase, daunorubicin, cytarabine, and intrathecal methotrexate. Flow cytometry showed no residual disease. He did not tolerate high-dose methotrexate consolidation therapy due to delayed methotrexate elimination and renal impairment. Thus, consolidative allo-HCT was planned. He received three cycles of consolidation chemotherapy with nelarabine (650 mg/m^2 on days 1–5) as a bridging therapy to allo-HCT. He received five cycles of intrathecal chemotherapy as prophylaxis before allo-HCT. At 20 days before allo-HCT (41 days after the last administration of nelarabine), grade 3 tactile disturbances in both feet and grade 3 deep sensory deficits in the lower legs occurred. Vitamin B12 deficiency and copper deficiency were ruled out. At this point, no treatment was given for the neurotoxicity, which remained stable. Although we were concerned about worsening neurotoxicity due to allo-HCT, we were more concerned about the risk of T-ALL relapse without consolidative allo-HCT. Therefore, we decided to conduct allogeneic peripheral blood stem cell transplantation (allo-PBSCT) from an HLA-haploidentical related donor as previously scheduled. During conditioning therapy consisted of fludarabine plus total body irradiation (TBI) of 12 Gy, tactile disturbance in the lower legs worsened and ascended to the thigh. Brain MRI showed no abnormal findings, including in the optic nerve. However, whole spine MRI showed a well-defined area with high signal intensity on T2-weighted imaging (T2WI) in the dorsal column below Th8 (Figure 1). TBI was interrupted at 8 Gy due to concerns about neurotoxicity exacerbation. We started intravenous immunoglobulin (IVIG) and pulse steroid therapy with methylprednisolone, but the neurological symptoms did not improve. On day 3 after allo-PBSCT, the symptoms worsened, and he was unable to kneel on either side in the supine position. Whole spine MRI on day 19 showed expansion of the dorsal column lesion to the C7 level. His neurological symptoms gradually improved without additional treatment around day 30. MRI findings on day 32 were similar to those on day 19. Thus, we started tapering steroids. While tapering steroids, he developed grade 2 acute

graft-versus-host disease (GVHD) of the gut and skin. Although his neurological symptoms did not worsen in association with GVHD, MRI on day 80 showed the dorsal column lesion ascended to the C1 level. Further, positron emission tomography/computed tomography (PET/CT) showed abnormal accumulation of [^{18}F] fluorodeoxyglucose (FDG) in the cervical spinal cord, suggesting continued inflammation (Figure 2) at 84 days after transplantation (132 days after the last administration of nelarabine). Due to concerns about an alloimmune response as the cause of the inflammation, we stopped tapering steroids. FDG accumulation remained present on the PET/MRI performed on day 104, but resolved by day 138. At the last follow-up (8 months after allo-HCT), T-ALL was in CR. Tactile disturbance up to the thigh improved, while deep sensory deficits in the lower legs remained. He was able to walk with a cane, with some muscle weakness in his lower extremities, especially in the extensor muscles.

Case 2

A 40-year-old female was diagnosed with T-LBL. After five cycles of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) alternating with high-dose methotrexate and cytarabine (MA) therapy, she underwent allogeneic bone marrow transplantation from an HLA-matched unrelated donor, resulting in the first CR. Conditioning therapy consisted of cyclophosphamide plus TBI (12 Gy). However, T-LBL relapsed 17 months after transplantation. Although she received two cycles of nelarabine (1,500 mg/m^2 on days 1, 3, and 5, repeated every 21 days) as salvage therapy, her disease progressed. She received other salvage therapies and one intrathecal chemotherapy as prophylaxis, but these resulted in partial remission. She underwent a second allo-PBSCT from an HLA-matched unrelated donor. Neutrophil engraftment was achieved on day 10. On day 12 after allo-HCT (121 days after the last administration of nelarabine), grade 2 tactile disturbances appeared in the lower legs. This symptom gradually ascended and reached the Th8 level by day 29. Loss of pain and temperature, vibration, and positional sensation; loss of tendon reflexes below the Th8 level; and bladder and rectal disturbance were also observed. She had difficulty walking. Given the possibility of Guillain-Barré syndrome, she received IVIG and pulse steroid therapy with methylprednisolone starting on day 36, but the symptoms did not improve. MRI on day 56 showed a markedly high-signal area on diffusion-weighted imaging in the posterior region of the medulla oblongata (Figure 3). The lesion showed an area with high signal intensity on T2WI and fluid attenuated inversion recovery. Apparent diffusion coefficient values were low. No contrast effect of gadolinium was observed. Dyspnea, weakness of the upper limbs, and abnormal sensation below the neck began on day 65. She became unconscious on day 76 and died on day 101 because of the progression of neurotoxicity. She did not develop acute or chronic GVHD throughout the course of transplantation.

Consistent with MRI findings, autopsy revealed posterior funiculus-predominant myelopathy extending from the medulla oblongata to the lower end of the spinal cord (Figure 4). Severe demyelination and spongy vacuolation associated with macrophage infiltration were present in the white matter. The axons were generally preserved, but degeneration and enlargement were seen in the area of severe demyelination. Some reactive astrocytes were observed. These alterations were nearly symmetrical. They

were prominent in the posterior funiculus. The lateral and anterior columns were less affected. In the cerebrum, similar lesions were found in the corpus callosum, tractus opticus, and calcarine sulcus of the occipital lobe. Tumor cell invasion, atherosclerotic changes, hemorrhage, and infarction were not evident.

Case 3

A 47-year-old male was diagnosed with T-LBL. He had a mass localized to the mediastinum. He received four cycles of hyper-CVAD/MA and 30 Gy of radiation to the mediastinum, but the disease progressed. One cycle of nelarabine (1,500 mg/m^2 on days 1, 3, and 5) was administered as a bridging therapy to allo-HCT. He achieved partial remission. He underwent bone marrow transplantation from an HLA-matched unrelated donor. Neutrophil engraftment was achieved on day 17. Although he did not develop acute GVHD, grade 2 sensory disturbances occurred in the fingers and toes on day 29 (47 days after the last administration of nelarabine). He had difficulty walking on day 35 due to deep sensory deficits in the lower legs. Head and whole spine MRI showed no abnormalities. A nerve conduction study showed demyelinating neuropathy (motor > sensory). Given the possibility of Guillain-Barré syndrome, IVIG and pulse steroid therapy with methylprednisolone were started, with no improvement. His muscle weakness became evident. Although we could not make a definite diagnosis, the neurological symptoms spontaneously improved starting around day 130. He became able to move around in a wheelchair. After a transfer to a rehabilitation hospital, he died of systemic mucormycosis on day 476. We were informed that the autopsy revealed spongiosis of the posterior and lateral funiculus from the cervical to lumbar spinal cord. We diagnosed his neurological complication as nelarabine-induced myelopathy.

Discussion

According to past reports [11–15], nelarabine-induced myelopathy develops within approximately 2 months of the last administration of nelarabine. The median cycle to onset duration was 1.5 cycles [16]. Risk factors for the development of myelopathy are unknown. The most common symptoms at onset are paresthesia and muscle weakness in the lower limbs. After onset, patients often experience an ascending progression of symptoms, and many patients present with gait disturbance. These symptoms also occur in various diseases such as vitamin or copper deficiency, infection, neuromyelitis optica spectrum disorders, paraneoplastic syndrome, hemodynamics disturbance, and tumor invasion. Immune-mediated neurotoxicity also occurs after allo-HCT [17–19]. Due to the lack of specific findings on laboratory testing, distinguishing nelarabine-induced myelopathy from these diseases is often difficult. However, a fan-shaped area with high signal intensity on T2WI in the dorsal column is characteristic and helpful for making the diagnosis of nelarabine-induced myelopathy [12–14, 20]. Neuromyelitis optica spectrum disorders have similar MRI findings and need to be ruled out by anti–aquaporin-4 antibody negativity and the absence of dissemination in space [21]. In our three patients (Table 1), we diagnosed nelarabine-induced myelopathy based on the characteristic clinical course and MRI findings.

Table 1
Summary of three patients T-ALL/LBL with onset or worsening of myelopathy after allo-HCT

Patient	**1**	**2**	**3**
Age (years), sex	17, male	40, female	47, male
CNS involvement	No	No	No
Cycle(s) of nelarabine	3	2	1
Allo-HCT			
Source, HLA mismatch	Related PBSC, 3 antigens	Unrelated PBSC, 0 antigens	Unrelated BM, 0 antigens
Conditioning	Flu 180 mg/m^2 + TBI 8 Gy	Flu 180 mg/m^2 + Mel 140 mg/m^2	Flu 180 mg/m^2 + Mel 140 mg/m^2 + TBI 2 Gy
GVHD prophylaxis	TAC + MMF + PTCy	TAC + MTX + ATG 1.25 mg/kg	TAC + MTX
Acute GVHD	Gut stage 1, Skin stage 1	None	None
Neurological symptoms			
Symptoms before allo-HCT	Yes	No	No
Onset after allo-HCT (day 0), days	-20	12	29
Days from last nelarabine	41	121	47

†Pathogens include bacterial, fungal, and viral pathogens, including human herpesvirus 6. ‡Normal value: less than 102 pg/mL.

Abbreviations: ALL, acute lymphoblastic leukemia; LBL, acute lymphoblastic lymphoma; allo-HCT, allogeneic hematopoietic cell transplantation; CNS, central nervous system; HLA, human leukocyte antigen; PBSC, peripheral blood stem cell; BM, bone marrow; Flu, fludarabine; TBI, total body irradiation; Mel, melphalan; GVHD, graft-versus-host disease; TAC, tacrolimus; MMF, mycophenolate mofetil; PTCy, post-transplant cyclophosphamide; MTX, methotrexate; ATG, antithyroglobulin antibody; NA, not available; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; IVIG, intravenous immunoglobulin.

Patient	1	2	3
Symptoms at onset	Tactile disturbance in the feet. Deep sensory deficits in the lower legs.	Tactile disturbances in the lower legs.	Sensory disturbances in fingers and toes.
Ascending symptoms	Yes	Yes	Yes
Most severe symptoms	Unable to kneel on either side in the supine position.	Dyspnea, weakness of the upper limbs, and abnormal sensation below the neck.	Difficulty walking due to deep sensory deficits in the lower legs.
Serum antibodies			
Anti–aquaporin-4 antibody	Negative	Negative	Negative
Paraneoplastic syndrome	Negative	NA	NA
CSF			
Cell count	Not increased	Not increased	Not increased
Protein	Not increased	Increased to 69 mg/dL	Increased to 41 mg/dL
Pathogens†	Not detected	Not detected	Not detected
Myelin basic protein‡	Increased to 1,494 pg/mL	NA	Increased to 1,919 pg/mL
Oligoclonal bands	Negative	NA	Negative
Nerve conduction study	NA	NA	demyelinating neuropathy (motor > sensory)
MRI			

†Pathogens include bacterial, fungal, and viral pathogens, including human herpesvirus 6. ‡Normal value: less than 102 pg/mL.

Abbreviations: ALL, acute lymphoblastic leukemia; LBL, acute lymphoblastic lymphoma; allo-HCT, allogeneic hematopoietic cell transplantation; CNS, central nervous system; HLA, human leukocyte antigen; PBSC, peripheral blood stem cell; BM, bone marrow; Flu, fludarabine; TBI, total body irradiation; Mel, melphalan; GVHD, graft-versus-host disease; TAC, tacrolimus; MMF, mycophenolate mofetil; PTCy, post-transplant cyclophosphamide; MTX, methotrexate; ATG, antithyroglobulin antibody; NA, not available; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; IVIG, intravenous immunoglobulin.

Patient	1	2	3
Conducted prior to allo-HCT	No	No	No
Location of myelopathy	Dorsal column below Th8 (Ascended to C1)	Medulla oblongata	No abnormalities
Treatment	IVIG, pulse steroids	IVIG, pulse steroids	IVIG, pulse steroids
Neurological outcome	Improved	Worsened	Improved
Vital status	Alive	Dead on day 101 (autopsied)	Dead on day 476 (autopsied)
†Pathogens include bacterial, fungal, and viral pathogens, including human herpesvirus 6. ‡Normal value: less than 102 pg/mL.			
Abbreviations: ALL, acute lymphoblastic leukemia; LBL, acute lymphoblastic lymphoma; allo-HCT, allogeneic hematopoietic cell transplantation; CNS, central nervous system; HLA, human leukocyte antigen; PBSC, peripheral blood stem cell; BM, bone marrow; Flu, fludarabine; TBI, total body irradiation; Mel, melphalan; GVHD, graft-versus-host disease; TAC, tacrolimus; MMF, mycophenolate mofetil; PTCy, post-transplant cyclophosphamide; MTX, methotrexate; ATG, antithyroglobulin antibody; NA, not available; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; IVIG, intravenous immunoglobulin.			

The characteristic pathological findings of nelarabine-induced myelopathy are not clear because the condition is rare. Autopsy of Patient 2 showed demyelination and spongiosis centered on the posterior funiculus. This finding resembles the findings in a case report by Hartz et al [8] in that there was a relatively well-demarcated change in the spinal cord, which might be a characteristic histological feature of nelarabine-induced myelopathy. However, there was a difference in localization of the lesion within the medulla oblongata. Changes were most prominent in the posterior funiculus in the present case and in the anterior funiculus in the case described by Hartz et al. This difference might be partly due to the effects of neurotoxic treatments other than nelarabine received in the past, but these two cases alone do not provide a clear answer about this brainstem lesion. If the myelopathy is mild, symptoms might be reversible, as in past reports. However, severe myelopathy, as in our patient, seems to be irreversible.

The mechanism underlying nelarabine-induced myelopathy is not entirely understood. Gollard et al [14] pointed out the possibility of mitochondrial damage. To elucidate the mechanism, we focused on the similarities with mitochondrial diseases. The involvement of the posterior funiculus in nelarabine-induced myelopathy is similar to leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), a mitochondrial disease caused by impaired translation of mitochondrial DNA. Nelarabine is converted to ara-G in vivo, which is then converted to ara-G triphosphate (ara-GTP) by cytosolic deoxycytidine kinase and mitochondrial deoxyguanosine kinase. Ara-GTP stops DNA synthesis in proliferating cells. In brain and nerve tissues, deoxyguanosine kinase activity is high, and cytotoxic ara-

GTP might be present in high concentrations [22]. It is interesting that the spine MRI findings of LBSL [23, 24] and nelarabine-induced myelopathy [12–14] are remarkably similar. Further, the pathological findings of LBSL are described as demyelination and axonal degeneration in the white matter with vacuolar degeneration [25], which is consistent with the findings in our autopsy case. These similarities suggest that mitochondrial damage is deeply involved in the development of nelarabine-induced myelopathy. The treatment of mitochondrial diseases could be applied to nelarabine-induced myelopathy.

Our institution treated four patients who have a history of nelarabine therapy before allo-HCT, including the three patients presented above. Neurological symptoms occurred or worsened early after transplantation in three patients and during conditioning therapy in one patient. Kawakami et al reported that three patients developed nelarabine-induced myelopathy 24 days, 24 days, and 18 days after allo-HCT, and 0.5 months, 2.5 months, and 1 month after nelarabine administration, respectively [10]. Despite variations in the interval between the last administration of nelarabine and onset of symptoms, most patients developed nelarabine-induced myelopathy approximately 3 weeks after allo-HCT. This timing suggests that conditioning treatment might be involved in worsening myelopathy. It is not clear whether the alloimmune response also leads to worsening myelopathy. In Patient 1, PET/CT revealed the presence of inflammation in the spinal cord at 132 days after the last administration of nelarabine (84 days after transplantation). The amount of time that had passed since these treatments indicates that the inflammation was caused by an alloimmune response rather than by nelarabine or conditioning treatment.

Based on the findings in our small case series, we speculate that with the background of nerve inflammation caused by nelarabine, additional damage from conditioning therapy and alloimmune responses can cause further damage. However, our autopsy findings did not include inflammatory cell infiltration at the site of neurotoxicity, except for macrophages. This finding suggests the presence of some inflammatory changes but it does not support our speculation. Despite this limitation, the cases we presented indicate that transplantation adversely affects myelopathy.

Conclusions

Nelarabine is a valid option for T-ALL/LBL, not only for relapsed or refractory disease but also as front-line therapy. However, our findings suggest that conditioning therapy and alloimmune responses worsen nelarabine-induced myelopathy, which can be fatal. No effective treatments exist. Clinicians should be aware of the potential risks of using this drug before allo-HCT. We recommend that clinicians perform a thorough neurological examination and consider head and spine MRI before allo-HCT in patients who have a history of nelarabine therapy. Elucidation of the mechanism and establishment of diagnostic methods and therapies for nelarabine-induced myelopathy are urgently needed.

Abbreviations

ara-G: 9-beta-D-arabinosylguanine; T-ALL/LBL: T-cell acute lymphoblastic leukemia/lymphoma; CR: complete remission; MRI: magnetic resonance imaging; allo-HCT: allogeneic hematopoietic cell transplantation; allo-PBSCT: allogeneic peripheral blood stem cell transplantation; TBI: total body irradiation; T2WI: T2-weighted imaging; IVIG: intravenous immunoglobulin; GVHD: graft-versus-host disease; PET/CT: positron emission tomography/computed tomography; FDG: fluorodeoxyglucose; hyper-CVAD: hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MA: methotrexate and cytarabine; LBSL: leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation; ara-GTP: ara-G triphosphate.

Declarations

Ethics approval and consent to participate

This study was approved by an institutional review board of National Cancer Center Hospital, Japan. Consent to participate has been obtained from case 1-3.

Consent for publication

Consent for publication has been obtained from case 1-3.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TF and TT wrote the first draft of the manuscript. All authors were involved in management of the patient and preparation of this manuscript. All authors provided approval of the manuscript for submission.

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Figures

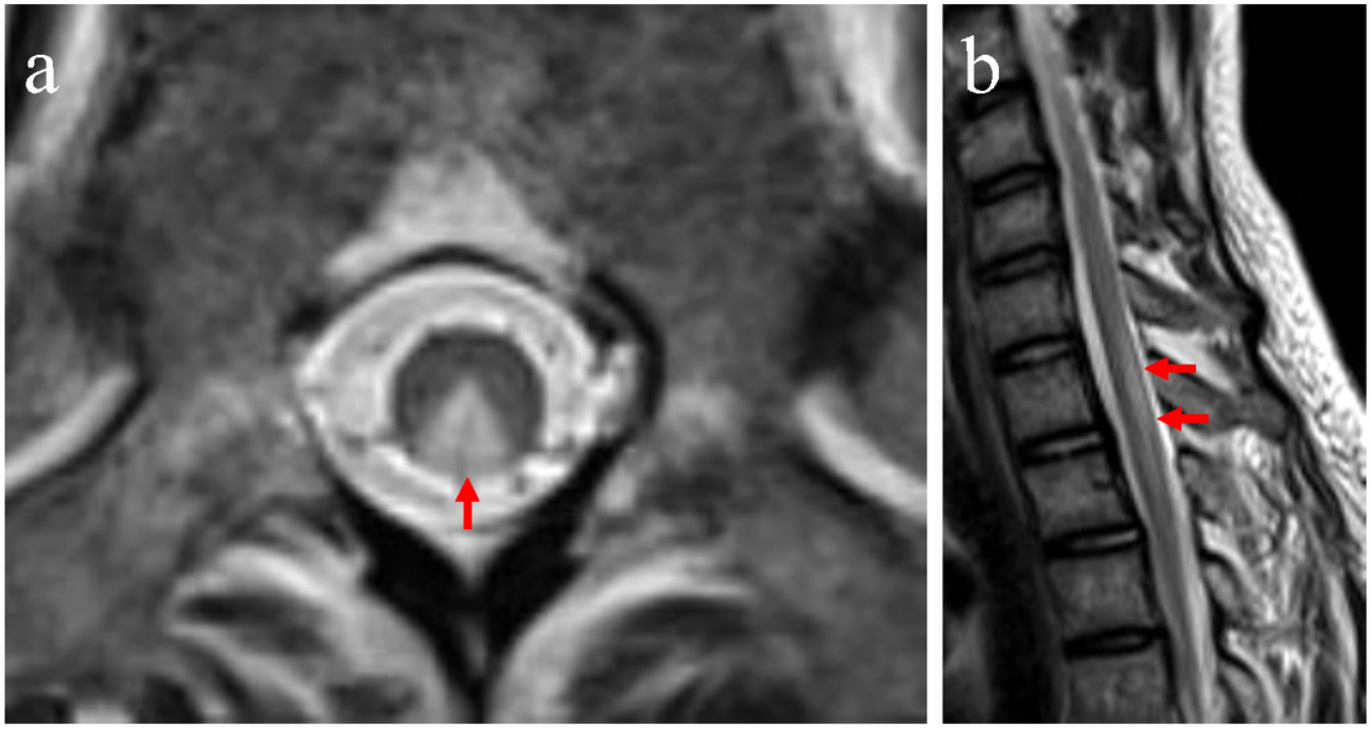

Figure 1

Magnetic resonance imaging findings on T2-weighted imaging in Patient 1. (a) Axial section showed a characteristic fan-shaped area with high signal intensity in the dorsal column below Th8. (b) Sagittal section showed an area with high signal intensity in the dorsal column in the longitudinal direction. Red arrows point out the lesion.

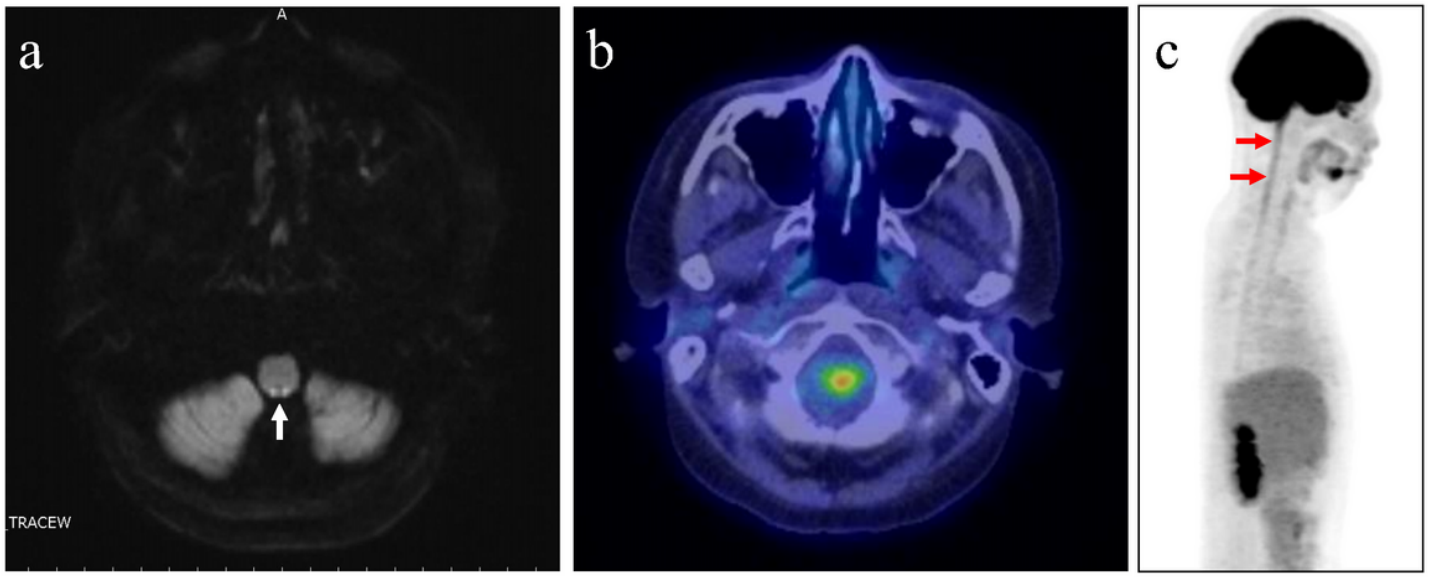

Figure 2

Magnetic resonance imaging and [18F] fluorodeoxyglucose positron emission tomography/computed tomography findings in Patient 1. (a) The dorsal column lesion ascended to the C1 level and had high signal intensity on diffusion-weighted imaging on day 80 after transplantation (white arrow on the lesion). (b) Positron emission tomography scan at the same level had SUVmax/ave.=4.20/3.32 on day 84 after transplantation. (c) The maximum intensity projection image also showed diffuse [18F] fluorodeoxyglucose accumulation in the spinal cord (red arrows on the accumulation).

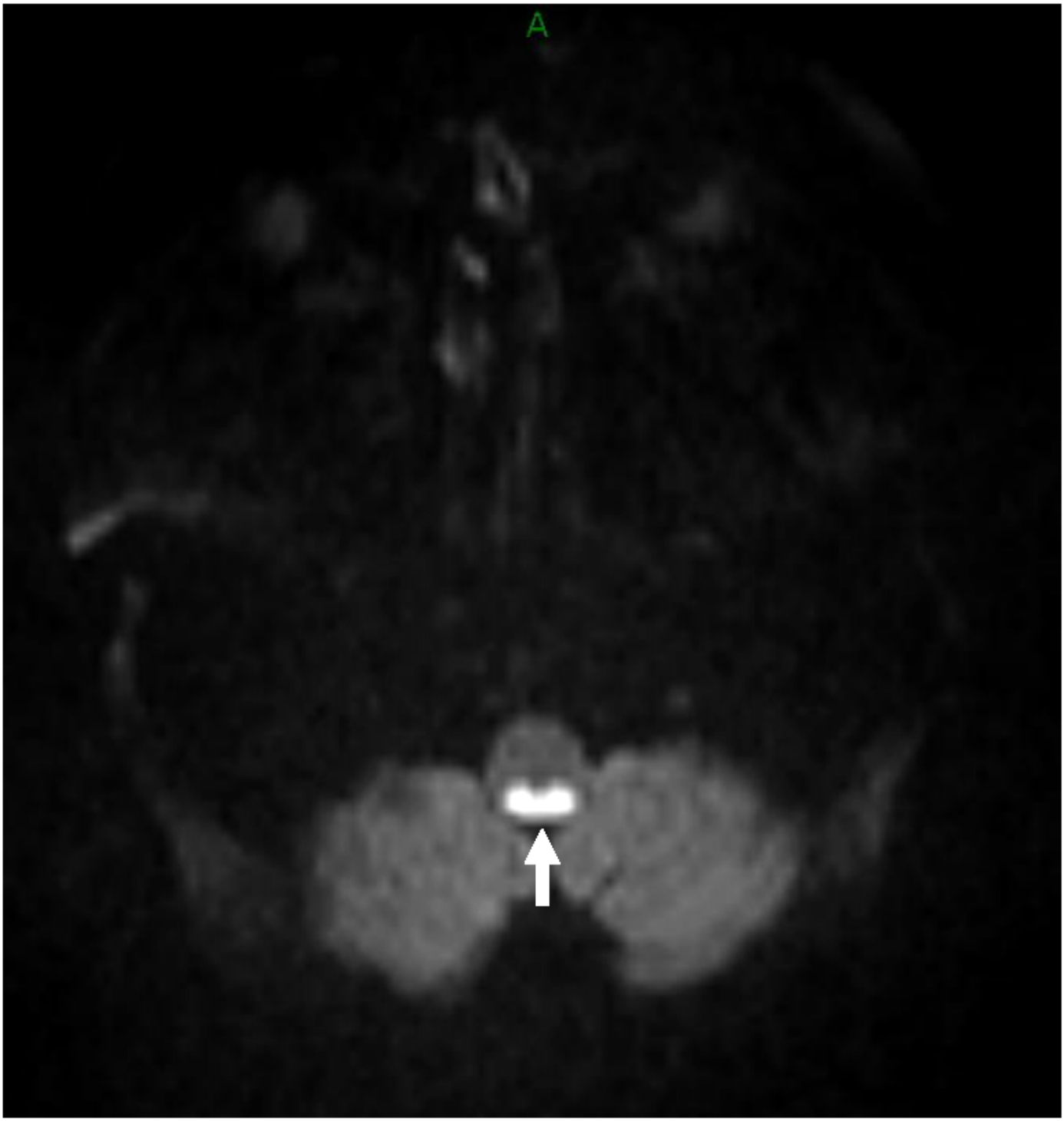

Figure 3

Magnetic resonance imaging findings in Patient 2. The dorsal lesion in the medulla oblongata had high signal intensity on diffusion-weighted imaging (white arrow on the lesion).

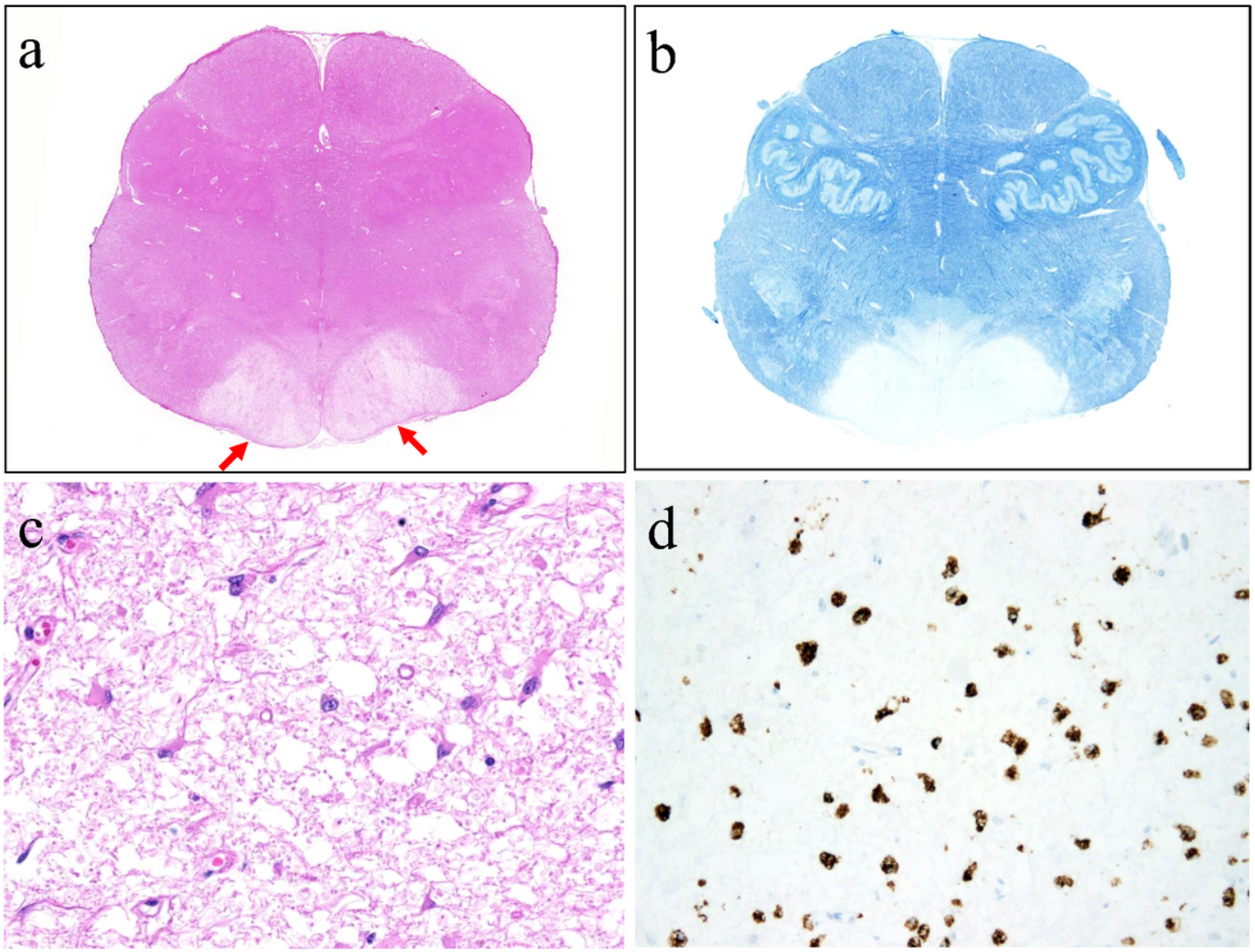

Figure 4

Autopsy findings of the medulla oblongata in Patient 2. (a, Hematoxylin-eosin stain; b, Klüver-Barrera stain) Severe symmetrical demyelination was observed in the posterior funiculus. Red arrows point out the demyelinating lesion. (c) Marked spongiosis and presence of reactive astrocytes. (d) Infiltration of macrophages (anti-CD68 antibody immunohistochemistry).