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Case Report

Radiation-induced spinal cord glioblastoma with cerebrospinal fluid dissemination subsequent to treatment of lymphoblastic lymphoma

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Abstract

Background: Radiation-induced glioma arising in the spinal cord is extremely rare. We report a case of radiation-induced spinal cord glioblastoma with cerebrospinal fluid (CSF) dissemination 10 years after radiotherapy for T-cell lymphoblastic lymphoma.

Case Description: A 32-year-old male with a history of T-cell lymphoblastic lymphoma presented with progressive gait disturbance and sensory disturbance below the T4 dermatome 10 years after mediastinal irradiation. Gadolinium-enhanced magnetic resonance (MR) imaging revealed an intramedullary tumor extending from the C6 to the T6 level, corresponding to the previous radiation site, and periventricular enhanced lesions. In this case, the spinal lesion was not directly diagnosed because the patient refused any kind of spinal surgery to avoid worsening of neurological deficits. However, based on a biopsy of an intracranial disseminated lesion and repeated immmunocytochemical examination of CSF cytology, we diagnosed the spinal tumor as a radiation-induced glioblastoma. The patient was treated with radiotherapy plus concomitant and adjuvant temozolomide. Then, the spinal tumor was markedly reduced in size, and the dissemination disappeared.

Conclusion: We describe our detailed diagnostic process and emphasize the diagnostic importance of immunocytochemical analysis of CSF cytology.

Key Words: Glioblastoma multiforme, nonHodgkin's lymphoma, radiotherapy, spinal cord

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INTRODUCTION

Radiation-induced glioma arising in the spinal cord is extremely rare, with only seven cases previously reported.[3,6,9,14,15,20,25] We report here a patient who developed a radiation-induced spinal glioblastoma with cerebrospinal fluid (CSF) dissemination. We describe our diagnostic process, including the diagnostic importance of immunocytochemical analysis of CSF cytology.

CASE REPORT

History and examination

In May 2001, a 21-year-old male diagnosed with Stage IVB T-cell lymphoblastic lymphoma, and underwent half-CHOP chemotherapy. In November 2001, he underwent focal irradiation for a residual anterior mediastinal lymphadenopathy, consisting of a total of 30 Gy in 20 fractions, with a maximum dose of 37.8 Gy and mean dose of 9.2 Gy to the spinal cord [Figure 1]. In February 2002, he underwent a peripheral blood stem cell transplantation using cells donated by his identical twin, resulting in complete remission. He had not visited a hospital for 9 years.

In January 2012, he was referred to us with a 2-month history of progressive weakness in his right lower extremity. Motor examination revealed mild weakness in the right lower extremity (manual muscle testing, 4/5), and he required a crutch to walk. Sensory examination revealed no sensations for pain or temperature below the T4 dermatome on the left side, 30-50% reduction in touch sensation at the T4-T11 dermatome on the right side, complete loss of all sensation at the T5-T6 dermatome bilaterally, mild reduction of position sense in his right lower extremity, and loss of vibration sense in the bilateral lower extremities. Deep tendon reflexes were hyperactive in the right lower extremity. No bladder or rectal functional disruptions were observed, and there was no evidence of lymphadenopathy.

Gadolinium-enhanced magnetic resonance (MR) imaging of the spine revealed an intramedullary tumor with irregular enhancement extending from the C6 to the T6 level, corresponding to the previous radiation portal [Figures 1 and 2a]. Moreover, the surface of the spinal cord and the dura mater were diffusely enhanced, suggesting dissemination of the CSF. Although we planned to perform a biopsy of the spinal lesion to establish a definitive diagnosis, the patient refused any kind of spinal surgery to avoid worsening of neurological deficits. Cytological examination of the CSF obtained by lumbar puncture revealed large atypical cells with nuclear grooves or clefts [Figure 3a], suggesting the recurrence of lymphoblastic lymphoma. Thus, we planned to start chemotherapy for recurrent lymphoblastic lymphoma. However, gadolinium-enhanced brain MR imaging revealed periventricular enhanced lesions

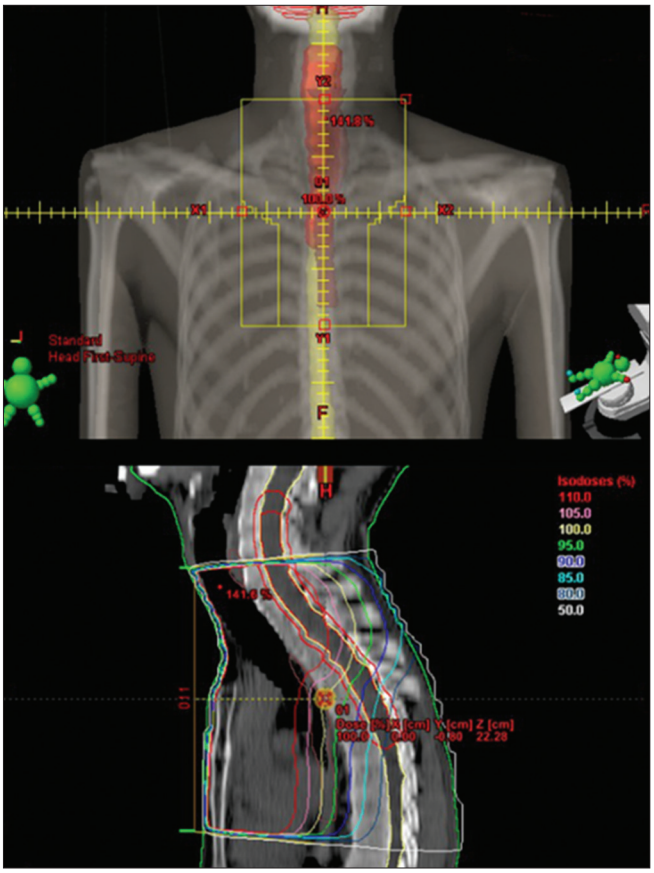

Figure 1: Isodose curve showing the radiation coverage for the anterior mediastinal lymphadenopathy

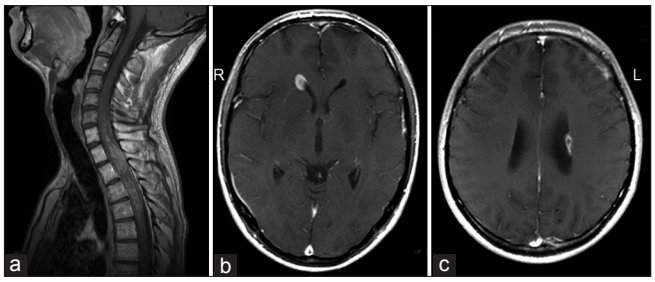

Figure 2: (a-c) Gadolinium-enhanced T1-weighted MR images showing an irregularly enhanced intramedullary lesion at the C6-T6 spinal level with enhancement along the dorsal surface of the spinal cord (a) and intracranial enhanced lesions located along the ventricular surface (b, c)

[Figures 1b and c] and diffuse enhancement of the ventral surface of the pons and the medulla oblongata.

Operation and pathological findings

For more accurate diagnosis, we obtained a sample of the periventricular lesion along the right anterior horn with a stereotactic biopsy through the right frontal lobe without ventricular puncture. Histopathological examination of this sample showed diffuse proliferation of anaplastic glioma cells with hyperchromatic nuclei on a fibrillary background, along with a tendency for perivascular accumulation [Figure 3d]. Microvascular proliferation was

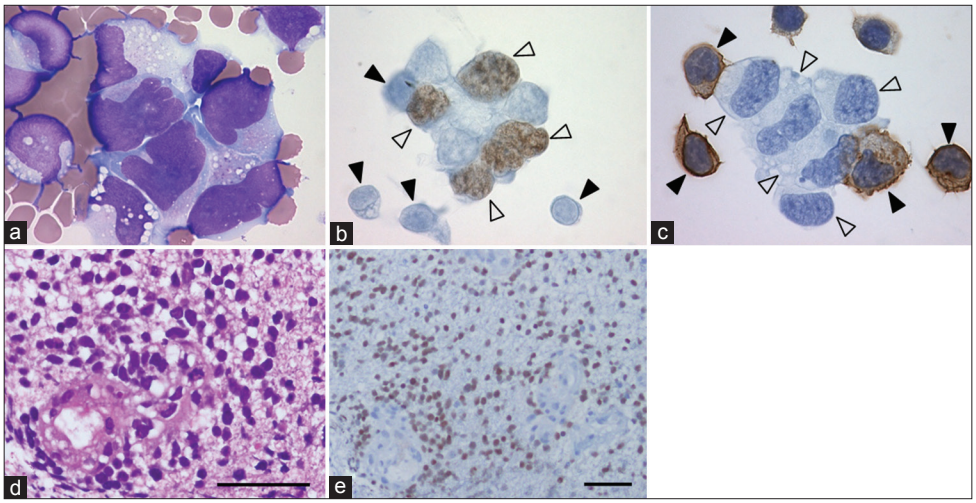

Figure 3: (a) May-Giemsa staining of the CSF sediment showing atypical cells, (b, c) Immunocytochemistry of the CSF sediment showing atypical cells (white arrowheads) with enlarged hyperchromatic delicate irregular nuclei that are positive for Olig2, (b) and negative for LCA (c), The surrounding lymphocytes (black arrowheads) are positive for LCA, (c) and negative for Olig2 (b) (100 × objective), (d, e) Paraffin sections of the biopsy of the intracranial lesion. H and E staining, (d) and Olig2 immunostaining, (e) Scale bars = 50 μm

also noted. Immunohistochemistry revealed that the tumor cells were positive for S-100 protein and Olig2 [Figure 3e] and negative for leukocyte common antigen (LCA), T-cell markers (CD45R0 and CD3), and B-cell markers (CD20 and CD79a) [Table 1]. The MIB-1 staining index was 25.1%. The histopathological diagnosis was glioblastoma. Because there was a discrepancy between the CSF cytology and the histopathology of the intracranial disseminated lesion, CSF cytology and immunocytochemistry were again performed after biopsy. These assays revealed that the atypical cells with enlarged hyperchromatic delicate irregular nuclei in the CSF were positive for Olig2 [Figure 3b] but negative for LCA [Figure 3c]. In contrast, the LCA+/Olig2− lymphocytes showed relatively uniform, smaller roundish nuclei [Figures 3b and c], suggesting that the LCA+ cells in the CSF were nonneoplastic lymphocytes such as reactive lymphocytes rather than lymphoma cells. Finally, we diagnosed the spinal tumor as a radiation-induced glioblastoma with CSF dissemination.

Postoperative course

The patient was treated with radiotherapy plus concomitant and adjuvant temozolomide. He received 30 Gy whole-brain radiation and then boost 30 Gy radiation to the periventricular lesion in 40 fractions, as well as 30 Gy whole-spine radiation and boost 22.5 Gy local radiation to the cervicothoracic spinal cord in 35 fractions. Concomitant temozolomide therapy was administered at a dose of 75 mg/m^2/day, 7 days/week from the first day of radiotherapy until the last day of radiotherapy. After radiotherapy, the spinal tumor was markedly reduced in size, and the dissemination disappeared [Figure 4]. However, reduction in touch sensation at the T4-T11 dermatome on the right side worsened and extended to the entire leg, and sensations for pain and temperature at the T4-T11 dermatome on the right side decreased by 20-30%. In contrast, sensations

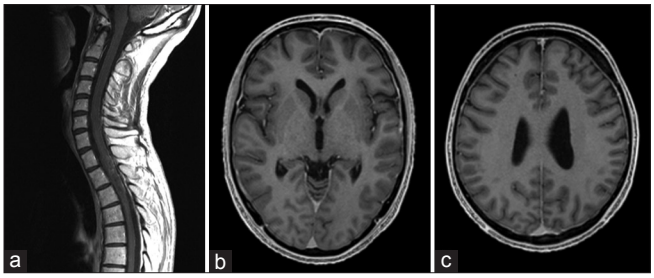

Figure 4: (a-c) Gadolinium-enhanced T1-weighted MR images showing marked reduction in the size of the enhanced lesion of the spinal cord (a) and the disappearance of the periventricular dissemination (b, c)

Table 1: Immunohistochemical markers of tumor differentiation between glioblastoma multiforme and lymphomas

Immunohistochemical marker	Glioblastoma multiforme	B-cell lymphoma	T-cell lymphoma
S-100	+	-	-
Olig-2	+	-	-
LCA	-	+	+
CD45R0	-	-	+
CD3	-	-	+
CD20	-	+	-
CD79a	-	+	-

LCA: Leukocyte common antigen

for pain and temperature at the T5-T12 dermatome on the left side increased by 20-50%. The mild weakness in the right lower extremity remained unchanged. CSF cytology showed an absence of Olig2-immunopositive cells, although lymphocytes were still present in the CSF. Then, the patient was discharged from the hospital. He continued to receive oral temozolomide therapy and underwent follow-up MRI

Table 2: Reported cases of spinal cord glioma with intracranial dissemination

Authors (year)	Age/sex	Primary site of tumor	Pathological findings	Surgery	Interval from surgery to dissemination	Interval from onset to death
Mallory *et al*. (1908)	Child/NR	Lumbosacral	Glioma (grade 3-4)	NR	NR	NR
O'Connell *et al*. (1946)	16/M	Thoracolumbosacral	GBM	+	NR	16 mos
Perese *et al*. (1959)	39/M	Conus medullaris	Astrocytoma (grade 2)	+	11 mos	28 mos
Eade and Urich (1971)	21/F	Thoracolumbosacral	Mixed glioma (grade 2)	+	4 mos	8 mos
	21/F	Thoracic	Mixed glioma (grade 2)	+	3 mos	11 mos
	19/F	Thoracolumbosacral	Mixed glioma (grade 2)	+	NR	6 mos
Salazar and Rubin (1976)	NR	NR	GBM	NR	NR	NR
	NR	NR	GBM	NR	NR	NR
Tashiro *et al*. (1976)	12/F	Thoracolumbosacral	GBM	+	3 weeks	11 mos
Andrews *et al*. (1978)	45/M	Thoracolumbosacral	GBM	+	11 mos	13 mos
Simonati *et al*. (1981)	19/F	Thoracic	Malignant glioma	+	NR	60 mos
Hely *et al*. (1985)	38/F	Thoracic	Malignant astrocytoma	+	NR	9 mos
	19/F	Conus medullaris	Astrocytoma (grade 2)	+	9 mos	28 mos
Sarabia *et al*. (1986)	54/M	Thoracolumbar	Astrocytoma (grade 3)	+	6 mos	13 mos
Johnson and Schwarz. (1987)	9/F	Thoracolumbosacral	Astrocytoma (grade 3)	+	4 mos	17 mos
Kendrick *et al*. (1987)	41/F	Thoracic	GBM	+	NA	NR
Bell *et al*. (1988)	13/M	Thoracic	Anaplastic astrocytoma	+	6 mos	12 mos
	2/M	Cervical	Fibrillary astrocytoma	+	12 mos	17 mos
	3/M	Cervical	Ganglioglioma	+	14 mos	NA
Cohen *et al*. (1989)	17/F	Thoracic	Astrocytoma (grade 4)	+	NR	11 mos
	16/F	Conus medullaris	Astrocytoma (grade 4)	+	NR	16 mos
	27/F	Cervical	Astrocytoma (grade 3)	+	NR	9 mos
	14/M	Conus medullaris	Astrocytoma (grade 4)	+	NR	13 mos
	14/F	Conus medullaris	Astrocytoma (grade 3)	+	NR	29 mos
	15/M	Conus medullaris	Astrocytoma (grade 4)	+	NR	19 mos
	20/F	Cervical	Astrocytoma (grade 3)	+	NR	20 mos
	10/F	Cervical	Astrocytoma (grade 4)	+	NR	6 mos
	9/M	Cervical	Astrocytoma (grade 4)	+	NR	1.5 mos
Yamagami *et al*. (1990)	44/M	Conus medullaris	Astrocytoma (grade 2)	+	54 mos	92 mos
Umezu *et al*. (1992)	40/M	Cervical	Astrocytoma (grade 3)	+	6 mos	14 mos
Tijssen *et al*. (1994)	21/M	Conus medullaris	Astrocytoma (grade 2)	+	36 mos	44 mos
Claus *et al*. (1995)	43/M	Conus medullaris	Pilocytic astrocytoma (grade1)	+	26 mos	46 mos
Ng *et al*. (2001)	9/F	Cervical	Pilocytic astrocytoma	+	30 mos	NA
Yamashita *et al*. (2001)	43/F	Thoracic	Anaplastic astrocytoma	+	2 mos	24 mos
Peraud *et al*. (2004)	14/F	Thoracic	Atypical pilocytic astrocytoma	+	53 mos	NA
Abel *et al*. (2006)	2/M	Cervicothoracic	Pilocytic astrocytoma	+	30 mos	NA

NR: Not reported, NA: Not applicable, mos: Months

every 3 months. Temozolomide was administrated orally at 150 mg/m^2/day on days 1-5 for the first cycle. The dose was increased to 200 mg/m^2/day beginning with the second cycle. Treatment cycles were repeated every 28 days. The patient has been followed for 9 months after the radiotherapy and received total nine cycles of temozolomide therapy. A 9-months follow-up MRI showed no regrowth of the spinal tumor and no disseminated lesions. The patient showed no marked changes in his neurological status. He is now undergoing outpatient temozolomide therapy.

DISCUSSION

The criteria proposed for determining whether a tumor is a radiation-induced neoplasm is as follows: (1) the second tumor must arise in the irradiated field; (2) a latency period of several years must have elapsed between the exposure to radiation and the development of a second neoplasm; (3) the tumor diagnosis must be confirmed histopathologically; and (4) the second tumor must be histopathologically distinct from the original tumor.[15,23] According to these criteria, the present case

does not strictly meet the criteria of radiation-induced glioblastoma because the histopathological diagnosis of the spinal lesion could not be confirmed. Because this patient had already presented with a severe transverse myelopathy and did not want spinal surgery including a biopsy to avoid worsening of the neurological deficits, we could not obtain a biopsy sample from his spinal cord.

In the diagnostic process of this patient, it is noteworthy that the cerebral biopsy specimen consisted of a diffuse proliferation of Olig2-immunopositive glioma cells, and that the CSF cytology also revealed atypical Olig2-immunopositive cells, which disappeared after treatment with radiotherapy plus temozolomide. In contrast, LCA-immunopositive lymphoid cells, which were presumed to be reactive lymphocytes, remained in the CSF after treatment, despite the marked effects of treatment on both the intracranial and spinal lesions. Thus, repeated immunocytochemistry for Olig2 and LCA before and after treatment provided definitive evidence of CSF dissemination of glioblastoma and ruled out the possibility of recurrence of the lymphoblastic lymphoma. Because the spinal lesion was not directly diagnosed, we could not strictly confirm that the primary lesion was a glioblastoma. However, we believe that it is reasonable to regard the spinal tumor as the primary lesion, due to its size and extensive pattern, especially when compared with the other lesions. The intracranial lesions were too small to characterize it as the primary lesion, and the extensions were limited to the ventricular surface. These findings are consistent with the commonly accepted features of CSF dissemination. Intracranial dissemination of a spinal cord glioma is uncommon, but several cases have been reported [Table 2].[1,2,4,5,7,8,10-13,16-19,21,22,24,26-30] Taken together, these findings resulted in a diagnosis of the spinal tumor as a radiation-induced glioblastoma with CSF dissemination.

CONCLUSION

It is important to consider that a tumor arising within an irradiated field several years after radiotherapy may be a radiation-induced glioma. If CSF dissemination is suspected, immunocytochemical assessment of the cells in the CSF is recommended to obtain a more accurate diagnosis.

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