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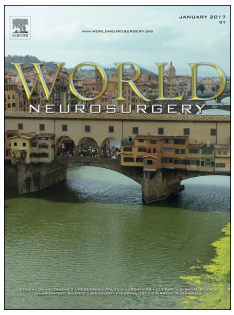

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Radiation-induced spinal cord cavernous malformations associated with medulloblastoma: a case report and literature review

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Abstract

Background: Radiation-induced spinal cord cavernous malformations (CMs) are rare pathologies compared to radiation-induced cerebral CMs. We present a case of a radiation-induced spinal cord CM developed 31 years after radiation therapy for medulloblastoma.

Case Description: A 37-year-old man developed a symptomatic spinal hemorrhagic lesion 31 years after radiation therapy for medulloblastoma. Magnetic resonance imaging revealed an intramedullary cystic lesion with a fluid-fluid level in the C7 area. Surgery was performed leading to an unclear diagnosis. Two years later, the patient had a relapse and underwent a second operation, allowing a definitive diagnosis of radiation-induced spinal cord CM. This is believed to be the second case of *de novo* intramedullary CM formation following spinal radiation therapy for medulloblastoma.

Conclusions: Radiation-induced spinal cord CMs should be recognized as a possible late adverse effect in patients treated with radiation therapy for medulloblastoma.

Introduction

Spinal cord cavernous malformations (CMs) are rare intramedullary vascular lesions, which comprise 5% of all CMs in the central nervous system and account for 5–12% of all spinal cord vascular lesions.[1-5] Although CMs are thought to be congenital, acquired CMs may occur after radiotherapy. The *de novo* presentation of spinal cord CMs after radiation therapy is extremely rare. We present a case of radiation-induced spinal cord CM that developed 31 years after radiation therapy for medulloblastoma.

Case description

A 37-year-old man initially presented at 6 years old with a headache, vomiting, and gait disturbance. Imaging studies in Kanazawa University Hospital had revealed a cerebellar-vermis lesion and obstructive hydrocephalus. The patient underwent a suboccipital craniectomy for posterior fossa lesion excision. A subsequent pathological examination confirmed the desmoplastic-type medulloblastoma diagnosis (Figure 1). Postoperative magnetic resonance imaging (MRI) had revealed a subtotal tumor resection while spinal MRI had identified no lesions nor dissemination. Three weeks after surgery, the patient underwent conventional radiotherapy for 71 days with total radiation doses of 30 Gy (20 fractions), 49.8 Gy (31 fractions), and 14 Gy (10 fractions), respectively to the whole brain, the tumor boost, and the entire spine. Following radiation therapy, chemotherapy, along with interferon-beta

administration, 18 times, in a total dose of 42.5 million units, was performed for 40 days. After treatment, no focal neurological deficits and no clinical nor radiological evidence of recurrence or metastasis were found.

At the age of 37 years, the patient presented with a bilateral back pain in the T1–T2 dermatomes, bilateral lower limb weakness, and gait disturbance, which worsened progressively. On admission, neurological examination and upper-extremity motor status were normal. Conversely, his lower-extremity strength was low (Manual Muscle Testing 4+/5) and diffuse hyperreflexia was present. Functional status was measured with the Aminoff-Logue scale (ALS) of disability.[6] He had reduced tolerance to exercise (grade 2 of gait disturbance), disturbance of micturition (grade 1 of micturition disturbance), and normal defecation (grade 0 of defecation). Although brain MRI showed no evidence of tumor recurrence, spinal MRI identified a 9×10×12-mm intramedullary lesion at C7 (Figures 2A-F) that highlighted a hyper-/hypo-intense fluid-fluid level, with a hypo-intensity rim on T2-weighted images. No enhancement was observed after contrast agent administration. These findings suggested a spinal cord intramedullary CM.

The patient underwent a right C6–T1 hemilaminectomy for the resection of the CM. After opening the dura mater, a yellowish hematoma was identified slightly caudally to the dorsal root entry zone (DREZ) of T1 and was evacuated through a DREZotomy. The lesion was carefully dissected from the surrounding tissue; its histopathological examination only

revealed gliosis but no vascular malformations nor tumoral lesions. MRI on the 11th postoperative day showed a shrinkage of the hematoma cavity (Figure 2G,H). The postoperative course was uneventful, and after rehabilitation, the patient was discharged in stable conditions on the 24th postoperative day. The ALS at discharge was grade 2 for the gait, grade 0 for micturition, and grade 0 for defecation.

His gait had improved further over the 2 years (grade 1 of the gait disturbance of the ALS), but a similar back pain and gait disturbance (grade 2 of the gait disturbance of the ALS) reoccurred. Remarkably, MRI showed the same lesion as 2 years prior (Figures 3A-F). Hence, surgery was performed to improve the symptoms and confirm the diagnosis. After the hematoma aspiration, the discovered dilated blood vessels in the remaining cavity were removed. A subsequent pathological examination revealed blood-filled dilated vessels with a single layer of endothelial cells without neural element, confirming the histological features of CM (Figure 4). Postoperatively, the patient's symptoms improved; however, he developed new sensory disturbances in his left elbow and waist. Postoperative MRI highlighted a much smaller residual cystic cavity compared to that noted preoperatively (Figure 3G,H). No recurrence has been observed six months after the second spinal surgery, and his gait has improved to grade 1 of the gait disturbance of the ALS.

This report was approved by our department's ethics committee, and written informed consent was obtained from the patient.

Discussion

It appears that so far only seven cases of radiation-induced spinal cord CMs have been reported including unconfirmed cases[7-13] (Table 1). A radiation-induced tumor must fulfill all of Cahan's criteria for radiation induced tumors[14]: 1) development in the irradiated area; 2) absence prior to irradiation; 3) latent period history, and 4) histological verification. Although CM is not a tumor, when the Cahan's criteria are applied for proving radiation-induced CMs, there are only five cases, including the present case, in which a definitive diagnosis was reached.

Brain CM is one of the possible complications of high-dose radiation therapy, with several cases reported in the existing scientific literature.[15-17] The most common primitive neoplasms associated with radiation-induced brain CMs include medulloblastoma (34%), malignant hematopoietic neoplasms (30%), and lower-grade gliomas (10%)[15]. Although radiation dose was variable, most patients received a high radiation dose of 40–60 Gy[15]; the time interval between the irradiation and the diagnosis of brain CMs also varied, with most cases occurring within 10 years after irradiation. Regarding radiation-induced spinal cord CMs, the spinal irradiation dose was ≥27 Gy in 3 patients and 12–14 Gy in 3 other patients. Even low-dose radiotherapy may lead to the development of radiation-induced spinal cord CMs. The time interval between the irradiation and the diagnosis of spinal cord CMs was

more than 10 years in half of the cases. Briefly, even if a lower dose of radiation hits the spinal cord, CMs may appear in the long term.

The reason why radiation-induced spinal cord CMs are less frequent than brain CMs is unclear; however, one reason might be that the volume of the spinal cord is considerably smaller than the brain (i.e., approximately one 50^{th}).[13] To the best of our knowledge, our case study is the second reported case of *de novo* spinal cord CMs following treatment for medulloblastoma. This low frequency may be associated with a poor medulloblastoma prognosis, in addition to the aforementioned reasons.

Advances in molecular pathology have revealed significant heterogeneity within medulloblastoma, leading to the identification of four distinct subgroups (i.e., wingless [WNT], sonic hedgehog [SHH], Group 3 [G3], and Group 4 [G4]) in the 2016 WHO classification of the central nervous system.[18] For most patients, optimal management of medulloblastoma includes maximum-safety resection along with adjuvant craniospinal radiation therapy and chemotherapy. Furthermore, long-term survival is expected in low-risk groups (e.g. WNT subtype). Nevertheless, radiation-induced spinal cord CMs may increase in these patients; therefore, a close follow-up is recommended.

Conclusion

Radiation-induced spinal cord CMs are very rare complications following

medulloblastoma treatment that may still occur a long time after low-dose radiation therapy. Long-term follow-up of both the brain and spine is thus necessary, even in cases of low-risk medulloblastoma.

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Declaration of interest

None.

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Figure legends

Figure 1. Histopathological examination revealed that the tumor cells had small-sized, round-to-oval-shaped, hyperchromatic nuclei and minimal cytoplasm with desmoplasia.

Figure 2. (A–F) Spinal MRI showed an intramedullary cystic lesion (arrowhead) at C7. The lesion featured a fluid-fluid level as hyper-/hypo-intense with a hypo-intensity rim on T2-weighted images. Contrast-enhanced MRI showed no contrast effect. (G,H) MRI on 11th postoperative day showed a residual hematoma cavity and return of the thickness of spinal cord.

Figure 3. (A–F) Spinal MRI showed a recurrent multi-cystic intramedullary lesion(arrowhead) at the same level as at the time of initial onset. Cystic lesions revealed hyperintensity and hypointensity on T2 -weighted image, which were suspicious of repeated bleeding at different times. Contrast-enhanced MRI showed no contrast effect. (G,H) MRI on 13th postoperative day showed a shrinkage of the cavity on T2-weighted image.

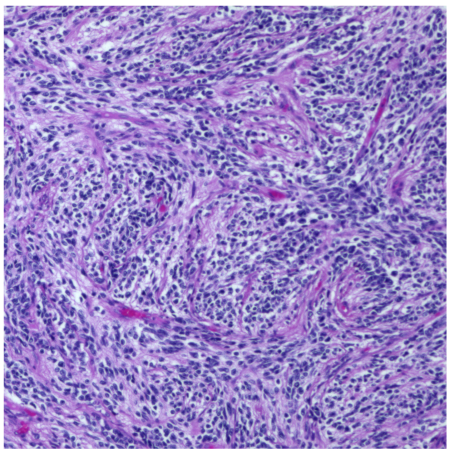
Figure 4. The pathological findings demonstrated abnormally dilated vessels with surrounding hemosiderin.

Tables

Table 1. Summary of patients with radiation-induced spinal cord cavernous malformations.

Table 1. Summary of patients with radiation-induced spinal cord cavernous malformations

No.	Author, year	Age (yrs), sex	Primary tumor	Radiation therapy	Latency period (yrs)	Treatment	Cahan's criteria
1	Mararie JN et al., 1999[7]	22, M	Germinoma	27 Gy, craniospinal 14.4 Gy tumor boost	5	Surgery	Confirmed
2	Narayan P et al., 2003[8]	17, M	Medulloblastoma	30.6 Gy to the whole brain 54 Gy tumor boost 27 Gy to the spine	13	Surgery	Confirmed
3	Jabbour P et al., 2004[9]	33, M	Wilms' tumor	Dose N/A, radiation to the abdomen and pelvis.	N/A	Surgery	Confirmed
4	Yoshino M et al., 2005[10]	16, F	Astrocytoma	40 Gy to the whole spine 20 Gy tumor boost	8	Surgery	Confirmed
5	Mathews MS et al., 2008[11]	27, M	Acute lymphocytic leukemia	Dose N/A, craniospinal	19	Conservative	Suspected
6	Won Y et al., 2015[12]	63, M	Lung cancer	N/A	10	Conservative	Suspected
7	Mikami T et al., 2018[13]	13, M	Acute lymphocytic leukemia	12 Gy, total body irradiation	8	Conservative	Suspected
8	Present case	37, M	Medulloblastoma	30 Gy to the whole brain 49.8 Gy tumor boost 14 Gy to the spine	31	Surgery	Confirmed



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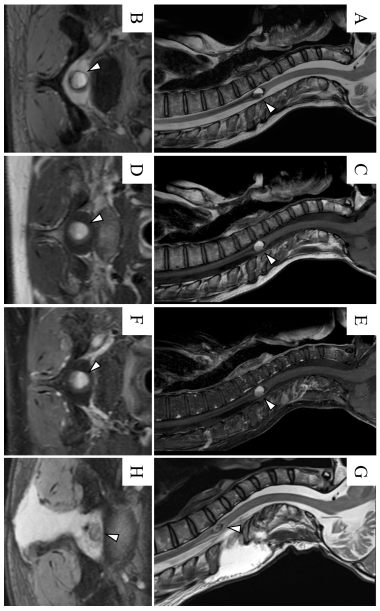

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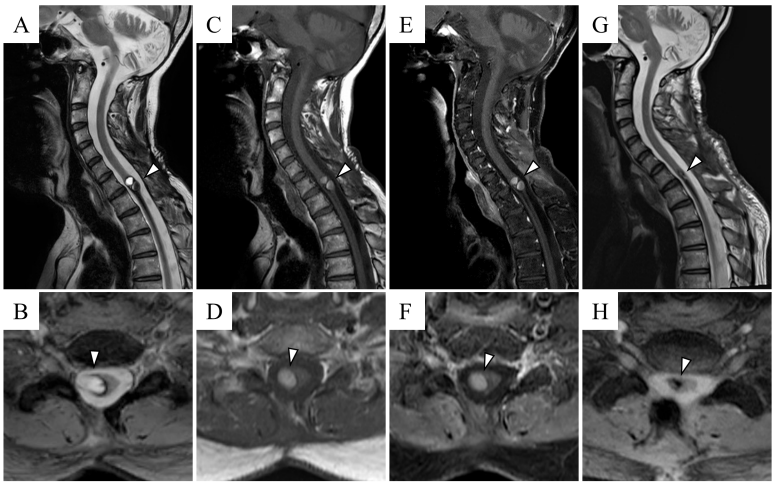

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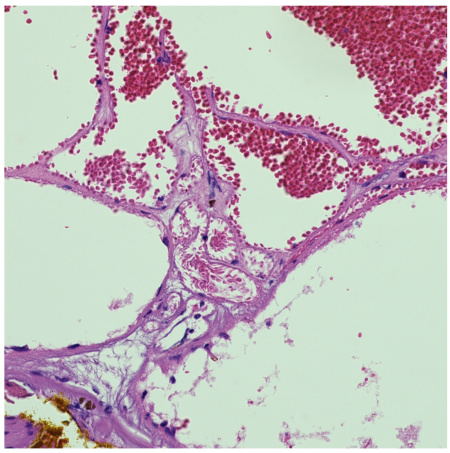

Figure 4

Abbreviations
ALS: Aminoff-Logue scale
CM: cavernous malformations
DREZ: dorsal root entry zone
MRI: magnetic resonance imaging
SHH: sonic hedgehog
WNT: wingless

Disclosures

This research did not receive any specific grant from funding agencies of public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare no conflicts of interest associated with this manuscript.