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The development of numerous radiation-induced cavernous malformations in a germ cell tumor patient: A case report

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ABSTRACT

Radiation-induced cavernous malformations (RICMs) are most commonly reported in young patients who have previously received radiotherapy. Here, we report a case of a patient with a germ cell tumor who was treated with whole brain radiotherapy (WBRT) and then incidentally found to have numerous RICMs. A 31-year-old male visited the hospital for a testicular mass. On examination, he was diagnosed with a mixed germ cell tumor with lung/brain metastases. The patient underwent a left orchiectomy and received 4 cycles of chemotherapy. He was then treated with WBRT for residual lesions in the brain and a wedge resection for the lung metastasis. Four years later, approximately 250-300 RICMs were incidentally observed in a follow-up brain image. Because the patient had not noticed any symptoms and the RICMs were small in size, he was not treated. To our knowledge, this is the first reported case of numerous (approximately 250-300) RICMs in a germ cell tumor patient after WBRT. Herein, we report details of this case and discuss the typical clinical features of RICM.

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Introduction

Testicular cancer is a relatively rare malignancy. However, it represents the most common cancer in males between the ages of 15 and 35 years old.[1] Approximately 98% of testicular cancers are testicular germ cell tumors, which are divided into seminomatous and nonseminomatous tumors.[1,2] Roughly 75%-80% of seminoma patients are diagnosed with stage I disease and have a 99% survival rate.[3] About two-thirds of patients diagnosed with nonseminomatous tumors present with stage I disease, and surgery alone successfully cures ~75% of those patients.[3] However, for patients with advanced stage disease, standard treatment consists of cisplatin-based chemotherapy (eg, bleomycin, etoposide, and cisplatin) followed by local therapy to address residual masses.[3]

Although brain metastases are rare in patients with germ cell tumors, they have a poor prognosis.[4] Further, the optimal treatment for patients with brain metastasis remains controversial. Some groups support monotherapy with radiotherapy, surgery, or chemotherapy. Other studies have encouraged combined aggressive therapy with chemotherapy and whole-brain radiotherapy (WBRT) due to the relatively poor biodistribution of chemotherapeutics to brain tissues.[4,5] However, aggressive therapy comes alongside the risk of severe toxicity. In particular, WBRT can cause early or delayed neurologic adverse effects including brain edema, somnolence, and neurocognitive degeneration.[6] Close monitoring of patients who have received WBRT can help enable early detection of these adverse effects.

In this report, we describe a patient who was diagnosed with a mixed germ cell tumor with initial lung and brain metastases. He was treated with chemotherapy, surgery, and WBRT. However, multiple cavernous malformations were found 4 years after treatment.

Case presentation

A previously healthy 31-year-old male visited our hospital with complaints of a testicular mass. After examination, including chest and abdomen computed tomography (CT), laboratory examination, and a biopsy of the primary site, he was suspected to have a left testicular germ cell tumor with multiple lung and brain metastases. The initial tumor markers were alpha fetoprotein 13,834.17 ng/mL, lactate dehydrogenase 263 Iu/L, and human chorionic gonadotropin <3 mIU/mL. Pathologic examination revealed that the mixed germ cell tumor consisted of a yolk sac tumor (90%) and immature teratoma (10%). An operation was performed to remove the testicular mass. He subsequently received 4 cycles of chemotherapy with bleomycin, etoposide, and cisplatin. Follow-up CT and brain magnetic resonance imaging (MRI) determined that the patient had a partial response to treatment, according to the RECIST criteria 1.1, but we observed residual tumors in the lung and brain.[7] The patient was thus treated with WBRT at a radiation dose of 25 Gy in 10 fractions to address the brain metastasis and with a wedge resection for the lung metastasis. Four years after receiving WBRT, the patient returned for a regular follow-up MRI, which revealed approximately 250-300 radiation-induced cavernous malformations (RICMs) (Figure). The susceptibility-weighted image revealed that the patient had evidence of numerous old microbleeds in the bilateral cerebrum and cerebellum. The patient reported no symptoms and was not treated at this stage, but continues to receive regular MRI follow-ups to monitor the RICMs.

Discussion

In this case report, we describe a 31-year-old patient who developed asymptomatic RICM 4 years after receiving WBRT. In previous reports, most germ cell tumor patients with RICM

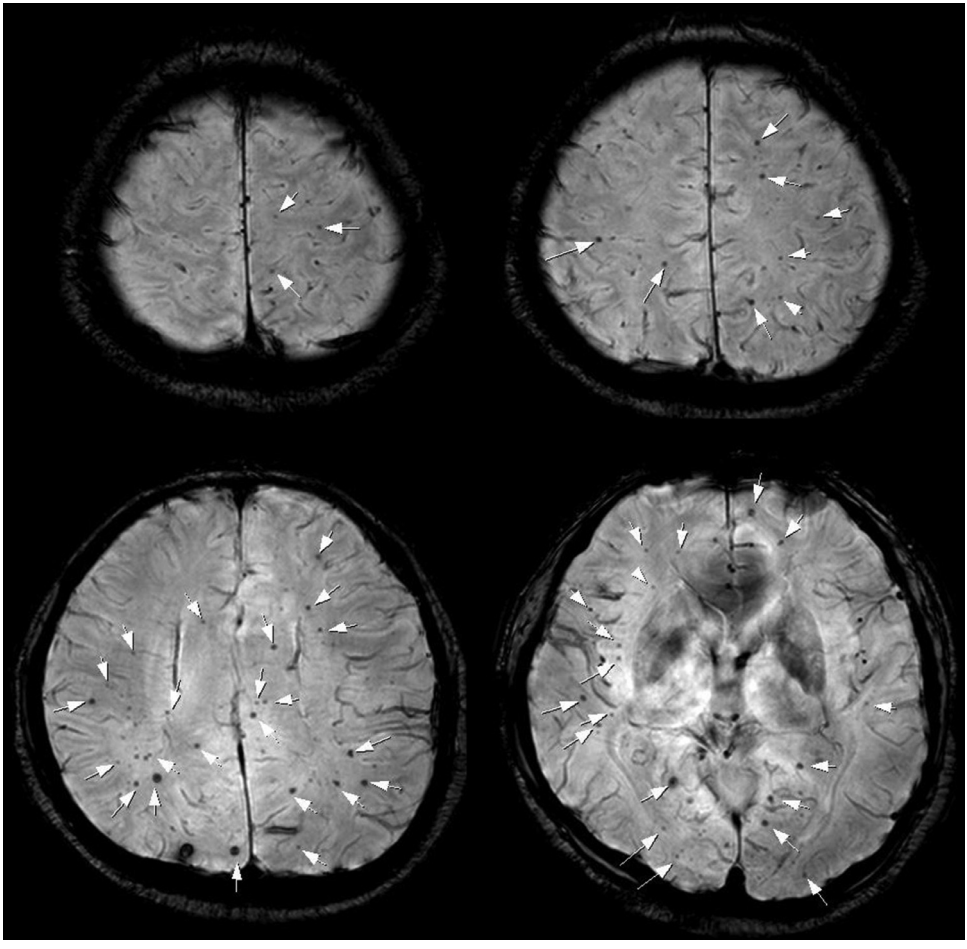

Figure. Susceptibility-weighted brain magnetic resonance imaging showed numerous old microbleeds in the bilateral cerebrum and cerebellum, suggestive of radiation-induced cavernous malformation.

have been reported to have 1-3 lesions; however, our patient presented with numerous lesions.[8,9]

Cavernous malformations are vascular structures with thin-walled, dilated capillary spaces without intervening brain tissues.[9] Cavernous malformations are primarily seen as a congenital abnormality. However, RICM has been suspected since as early as 1994.[9] A retrospective study by Jain et al reported that patients who received radiation during their childhood (3-16 years) were are risk of developing RICM in the irradiated field 3-41 years later.[9] Other studies have reported that, although children younger than 10 years old at the time of irradiation are at increased risk of RICM, it has also been observed in adults, with a direct correlation of risk with the radiation dose and a variable latency (0.7-17 years).[8,10] According to a previous analysis of pertinent literature, most patients (57%) who eventually develop RICM previously received a high dose of radiation (40-60 Gy), and most cases (65%) occur within 10 years of radiation.[11] The most common primary malignancies are medulloblastoma, malignant hematopoietic neoplasms, and low-grade gliomas.[11]

The mechanism of RICM is not well understood; however, it has been suggested that hypoxia inducible factor 1 (HIF-1) and vascular endothelial growth factor (VEGF) may play important

roles in the development of RICM. Radiation induces endothelial proliferation with hyalinization and fibrinoid necrosis of the vascular wall, causing narrowing of the vascular lumen. This leads to ischemia and activates HIF-1, which induces VEGF and causes reactive angiogenesis. Notably, the expression of HIF-1 and VEGF decreases with age, potentially explaining why RICM more frequently occurs in young patients.[8,10]

Generally, it is important to distinguish RICM from hemorrhagic metastasis. On T2-weighted MRI imaging, RICM shows a reticulated core with heterogeneous signal intensity and a surrounding rim of a decreased signal intensity, giving a typical "popcorn" appearance.[12,13] In the case of Zabramski classification of a cerebral cavernomas type 4 (as is observed in our case), it is poorly seen, or not visualized at all, on T1- and T2-weighted images. However, it is visualized as punctuated hypointense lesions on susceptibility-weighted images.[14] Because RICM shares similar imaging characteristics with hemorrhagic metastasis on MRI imaging, it is important to carefully distinguish between the 2 conditions.[13] If the patient presents with complaints of related signs and symptoms (eg, evidence of brain edema, a mass effect, or a rapid increase in size), metastasis should be considered. It is also important to distinguish RICM from treated brain metastases. The brain metastases typically present as iso- or hypointense on T1, and as hyperintense on T2-weighted images. They are occasionally surrounded by a perilesional edema with a high signal intensity on T2-weighted images and with a low signal intensity on T1-weighted images.[15,16] The tumor volume tends to decrease along with the surrounding edema, causing the margin to appear blurred over time.[17] Therefore, it may be helpful to compare images before and after treatment. In some cases, radiation necrosis may have occurred. This often presents as an enhanced lesion with a central area of necrosis on T1-weighted images. On T2-weighted images, this presents as a solid portion showing a low signal intensity and a central necrotic portion showing an increased signal intensity, which are called the "soap bubble" and "Swiss cheese" signs.[18]

The treatment of cavernous malformation mainly depends on clinical presentations. In most cases, 1-3 lesions of RICM have been observed, but sometimes multiple lesions could also be observed.[8,19] Typically, about 50% of patients remain asymptomatic despite the presence of multiple lesions. However, patients with symptoms commonly present with seizures, bleeding, headache, and focal neurologic deficits.[8,20] In asymptomatic cases incidentally diagnosed with RICM, regular MRI follow-ups may be sufficient.[8] However, close observation is required, because patients with RICM may be at an increased risk to develop hemorrhagic events.[9,21] It is currently unclear what triggers hemorrhagic events or for the RICM to increase in size, but this may be caused, in part, by the flow dynamics of cavernous malformations.[21] In the case of hemorrhagic events, neurologic symptoms (eg, headache, seizure, or impaired consciousness) may also occur, which may require surgical resection.

Microsurgical resection can be considered in patients presenting with multiple hemorrhages in high-risk areas, deteriorating neurologic deficits, refractory seizures, or who are experiencing severe symptoms.[20] Additionally, stereotactic radiosurgery can be a safe and effective method for surgically inaccessible RICM. However, the long-term effects of stereotactic radiosurgery treatments remain the subject of some debate.[20]

Conclusion

In conclusion, the possibility of RICM should be suspected when new brain lesions are identified in patients who have previously undergone radiation therapy. RICM is often asymptomatic and may simply be monitored over time. However, symptomatic cases may require treatment, depending on the location and severity of the symptoms. In this case report, we described a germ cell tumor patient who achieved long-term cure after WBRT in his early 30s. Germ cell tumors most frequently occur in young patients, and further studies are required to develop improved methods for the detection and management of RICM in asymptomatic patients who have achieved long-term cure.

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