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Case Report

Thigh leiomyosarcoma-derived brain metastasis with intracerebral hematoma: A case report and literature review

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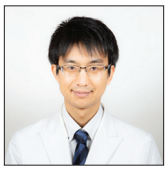

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ABSTRACT

Background: Brain metastases with hematoma are clinically important as they indicate the potential for rapid neurological deterioration. Non-uterine leiomyosarcoma-derived brain metastases are particularly rare, and their clinical features, including the bleeding rate, are unclear. Herein, we present a rare case of thigh leiomyosarcoma-derived brain metastasis with intratumoral hematoma and review previous case reports.

Case Description: A 68-year-old man with a right thigh leiomyosarcoma presented with multiple brain metastases. The patient received stereotactic radiotherapy; however, he reported sudden right-sided hemiparesis. We found a right frontal irradiated lesion with intratumoral hemorrhage and performed gross total tumor resection. Histopathological examination showed highly atypical cells with prominent necrosis and hemorrhage. Abnormal thin-walled vessels were prominent within the brain tumor, and vascular endothelial growth factor was diffusely expressed immunohistopathologically. To date, 11 cases of brain metastasis from non-uterine leiomyosarcoma, including the present case, have been reported. Of note, six patients had hemorrhage. Three out of six patients presented with hemorrhage before therapeutic intervention, three cases were from residual sites after surgery or radiation.

Conclusion: More than half the patients with non-uterine leiomyosarcoma-derived brain metastases presented with intracerebral hemorrhage. Furthermore, these patients are at risk of developing rapid neurological deterioration due to intracerebral hemorrhage.

Keywords: Brain metastasis, Hemorrhage, Non-uterine leiomyosarcoma

INTRODUCTION

Brain metastases occasionally present with intratumoral bleeding, especially in renal cell carcinoma and malignant melanoma.[3,15] This is clinically important because an acute hemorrhage can cause rapid neurological deterioration. Leiomyosarcoma is a soft-tissue sarcoma that rarely metastasizes to the brain.[4] However, the frequency of bleeding in leiomyosarcomas is unknown due to its rarity. Here, we report a case of thigh leiomyosarcoma-derived brain metastasis with rapid neurological deterioration due to tumor hemorrhage. A literature review revealed that over half of the brain metastases from non-uterine leiomyosarcoma exhibited intratumoral hemorrhage.[2,5,6,8-10,12,13] Here, we present a rare case of non-uterine leiomyosarcoma-derived

brain metastasis with intratumoral hematoma and review past case reports to understand the clinical characteristics and establish a therapeutic strategy.

CASE REPORT

A 68-year-old man presented with swelling on the right thigh. Magnetic resonance imaging (MRI) revealed a contrast-enhanced tumor with a hemorrhagic and unclear border [Figure 1a]. An open biopsy was performed, and the tumor was diagnosed as leiomyosarcoma. Subsequently, the patient underwent extensive tumor resection of the right thigh leiomyosarcoma. Microscopically, a dense proliferation of tumor cells comprising spindle and epithelioid cells with pleomorphic nuclei was observed. Necrosis and hemorrhage were also observed [Figures 1b and c]. As pathological examination revealed no tumor cells at the resection margin, the patient did not receive additional therapy. However, 1 year after surgery, computed tomography (CT) revealed multiple lung metastases. Although four courses of adriamycin were administered as first-line chemotherapy, the lung lesions progressed. Unfortunately, pazopanib as second-line chemotherapy did not stabilize the disease. Two years after the initial surgery, MRI revealed multiple brain tumors in the frontal and temporal lobe, and brain stem [Figures 2a and b]. Treatment with eribulin and stereotactic radiotherapy for brain metastases was performed. Two months later, the patient suddenly complained of the left-sided hemiparesis. CT and MRI demonstrated a progressive tumor of the right frontal lesion, which was 50 mm in maximum diameter, including peritumoral hemorrhage [Figures 2c-e]. On the other hand, the other three brain metastases disappeared. To avoid further neurological deterioration, we performed an *en bloc* tumor and hematoma resection [Figure 2f]. Macroscopic findings indicated that the tumor had extended to the subpial surface and was surrounded by hemorrhage [Figure 3a]. Microscopic examination revealed spindle and epithelioid cells with marked nuclear pleomorphism and necrosis and hemorrhage [Figures 3b-d]. Tumor cells were present in the hematoma [Figure 3c]. Immunohistochemical analysis demonstrated that the tumor cells were positive for smooth muscle markers (desmin and caldesmon), and the Ki-67 index was approximately 15% [Figures 3e-g]. These pathological findings were similar to those of the primary lesion and were compatible with brain metastasis of thigh-derived leiomyosarcoma. In addition, vascular endothelial growth factor (VEGF) was diffusely expressed in the tumor cells [Figure 3h], and abnormal blood vessels with thin walls were prominent within the tumor [Figure 3i]. After surgical resection, the hemiparesis improved, and the patient was discharged from the hospital. However, 3 months after surgery, the patient died due to the deterioration of his general condition.

DISCUSSION

Leiomyosarcoma is a soft-tissue sarcoma that occurs in the uterus, gastrointestinal tract, blood vessels, and extremities.[4,7] Because uterine leiomyosarcoma is the most common subtype, it accounts for the single site-specific subtype.[1] Uterine leiomyosarcoma harbors distinct methylation and mRNA signature patterns compared to other soft tissue leiomyosarcomas.[7] On the other hand, due to its rarity and biological aspects, leiomyosarcomas other than the uterine have been reported as non-uterine leiomyosarcomas.[2,3] Since soft-tissue sarcomas often metastasize to the lung and pelvis but rarely to the brain,[4] brain metastases of non-uterine leiomyosarcomas are particularly rare. To the best of our knowledge, 11 cases of brain metastasis from non-uterine leiomyosarcoma have been reported, including the current case [Table 1]. Primary lesions included those in the extremities, duodenum, liver, and retroperitoneum.[2,5,6,8-10,12,13] Five patients had a single brain metastasis, whereas six showed multiple lesions. In addition, ten out of 11 patients had metastases in tissues other than the brain, eight of which were in the lungs. Furthermore, two patients had leptomeningeal dissemination.[12] These

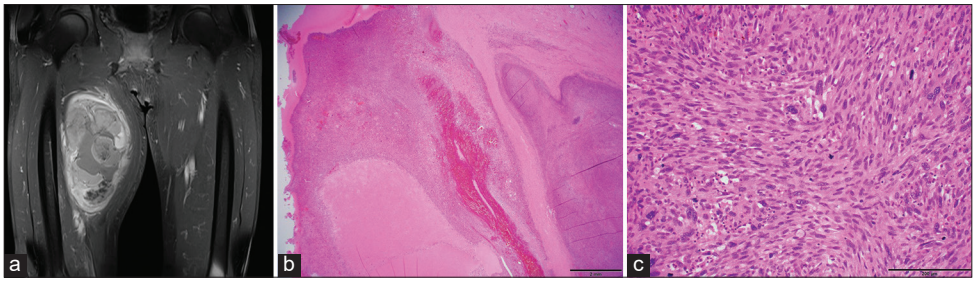

Figure 1: Clinicopathological features of the thigh leiomyosarcoma. Gadolinium-enhanced T1-weighted magnetic resonance imaging demonstrating a heterogeneously enhanced tumor in the right thigh (a), hematoxylin and eosin staining indicate dense tumor cell proliferation with necrosis and hemorrhage (b), and tumors showing spindle cells with highly pleomorphic nuclei (c).

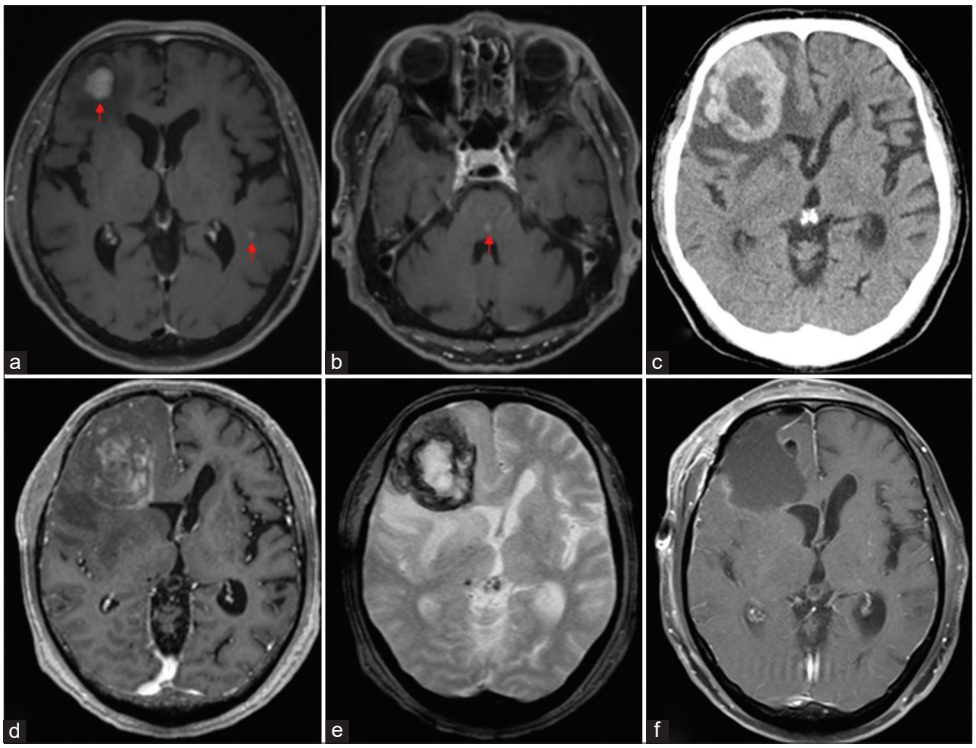

Figure 2: Radiographic features of the metastatic brain tumor derived from leiomyosarcoma of the thigh. Gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) demonstrating multiple brain tumors (a and b, arrows). Computed tomography and MRI showing the right frontal tumor with a surrounding hematoma (c-e). MRI indicating total resection of the tumor (f).

Table 1: Cases of non-uterine leiomyosarcoma-derived brain metastasis.

Authors	Age	Sex	Primary site	Brain lesions	Intracerebral hemorrhage	Other metastatic sites	Treatment	Outcome
Gercovich *et al.*	37	M	Thigh	Parietal lobe	+	Lung	PR→WBRT	Death, 5 weeks
Feeney *et al.*	63	M	Unknown	Occipital lobe	+	Lung	GTR→WBRT	Response, 6 months
Haykal *et al.*	30	F	Skin	Cerebellum	-	Lung, Heart	Resection	NA
	50	F	Liver	Temporal lobe	-	-	RT	Response
Isobe *et al.*	74	M	Duodenum	Multiple	+	Liver, Adrenal gland	Biopsy→WBRT	Death, 2 months
Kawahara *et al.*	61	F	Retroperitoneal	Multiple	+	Lung, Liver	Resection→SRS	NA
Kaduri and Tampieri	40	F	Retroperitoneal	Multiple, Leptomeningial	+	Lung	WBRT→Resection	NA
	57	F	Thigh	Multiple, Leptomeningial	-	Lung	Resection	NA
Gautschi *et al.*	65	M	Arm	Frontal lobe	-	Lung	GTR→RT	Death, 8 months
Dietel *et al.*	61	M	Arm	Multiple	-	Pancreas, Vertebral	Resection→WBRT	NA
Present case	69	M	Thigh	Multiple	+	Lung	SRS→Resection	Death, 3 months

F: Female, GTR: Gross total resection, M: Male, PR: Partial resection, RT: Radiotherapy, SRS: Stereotactic radiosurgery, WBRT: Whole-brain radiotherapy

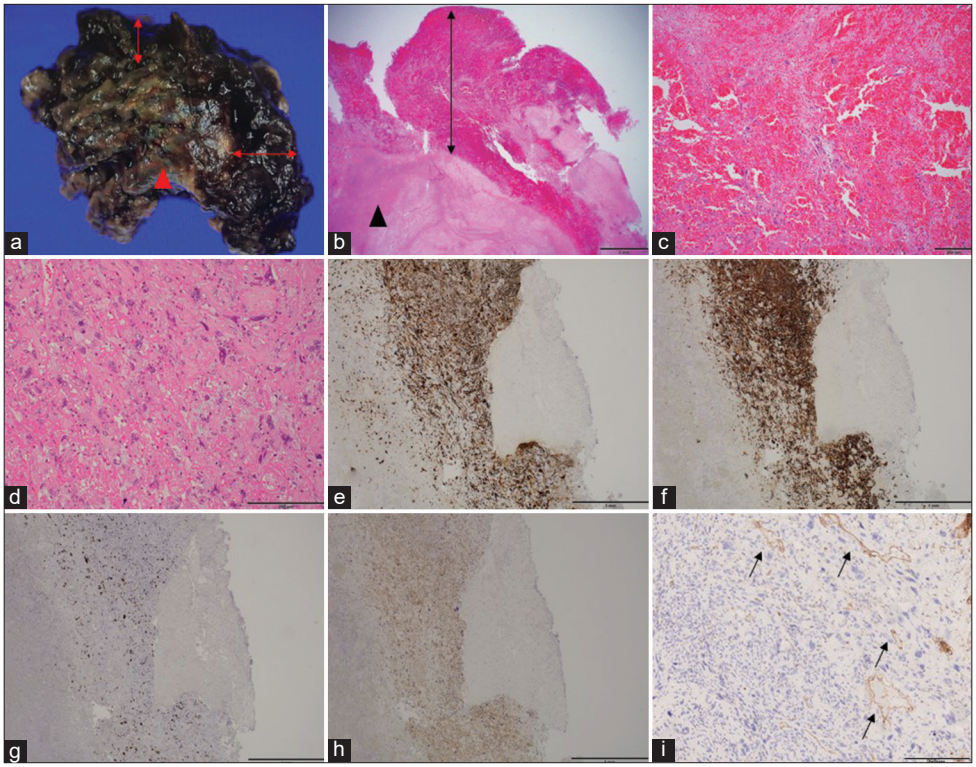

Figure 3: Pathological characteristics of the metastatic brain tumor derived from leiomyosarcoma of the thigh. Macroscopic view showing the tumor (arrowhead) and the surrounding hematoma (arrows) (a). Hematoxylin and eosin staining indicates diffuse growth of atypical cells with necrosis (arrowhead) and hemorrhage (arrows) (b). Hemorrhage comprising tumor cells (c). Tumor cells showing spindle and epithelioid features with highly pleomorphic nuclei (d). Immunostaining for desmin (e), caldesmon (f), Ki-67 (g), vascular endothelial growth factor (h), and CD31 (i). Thin-walled vessels are prominent within the tumor (i, arrows).

characteristics indicate that brain metastasis in non-uterine leiomyosarcoma is clinically challenging.

Notably, six (54.5%) patients demonstrated co-occurrence of brain metastases with hemorrhagic components.[5,8,10,12,13] Three patients presented with hemorrhage before treatment.[5,12,13] In one patient, three other lesions hemorrhaged after a biopsy, resulting in a decreased level of consciousness.[10] The patient in this report had tumor bleeding after radiotherapy. Similarly, a patient from a previous report underwent whole brain irradiation after partial resection but died due to hemorrhaging at the residual site 5 weeks after surgery.[8] The bleeding frequency in this type of metastasis is relatively higher than that in other primary site-derived brain metastases, considering that 19% of non-small lung cancers and 34% of renal cell carcinoma/melanoma exhibit intratumor hemorrhage.[3] Therefore, non-uterine leiomyosarcoma-derived brain metastases may yield a risk of acute hemorrhage, which results in rapid neurological deterioration.

Although the underlying mechanisms of hemorrhage within brain tumors are unclear, abnormal tumor vessels, such as thin-walled, poorly formed, or dilated vessels, may contribute to intratumoral hemorrhage.[16] A part of abnormal vessels with loss of vascular integrity is induced by VEGF, which is activated by hypoxic signals.[11] Of interest, non-uterine leiomyosarcoma has a more prominent hypoxia-inducible factor-1α signaling signature than uterine leiomyosarcoma.[7] Indeed, the brain lesions in our patient demonstrated tumor bleeding, high expression of Ki-67 and VEGF, prominent thin-walled vessels, and necrotic components, suggesting rapid tumor growth and angiogenesis. Leiomyosarcomas are often rich in angiogenesis, which is partly induced by VEGF.[14,17] Therefore, intratumor hemorrhage due to abnormal vessels might be more likely to occur in non-uterine leiomyosarcoma-derived brain metastasis.

In our patient, the small lesions disappeared after stereotactic radiotherapy, except for a 2 cm lesion in the right frontal lobe. Similarly, whole-brain irradiation controlled the small lesions, but the most significant lesion, measuring 2 cm, grew and required resection.[12] Three patients, including the current one, had bleeding from the residual tumor,

resulting in acute neurological deterioration.[8,10] Together, they are sensitive to radiotherapy; however, residual lesions may be at risk for hemorrhage. In addition, the prognosis of multiple brain metastases patients was poor, whereas the two patients with single brain metastasis survived for more than 6 months, even with lung metastases.[5,6] Therefore, multiple systemic metastases may not hesitate treatment with surgical removal and radiotherapy to control brain metastases.

CONCLUSION

We reported a rare case of thigh leiomyosarcoma-derived brain metastasis. The majority of non-uterine leiomyosarcoma-derived brain metastases present with intracerebral hemorrhage even after treatment. These findings suggest that non-uterine leiomyosarcoma-derived brain metastases may pose a risk of rapid neurological deterioration due to intracerebral hemorrhage and require early therapeutic intervention.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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