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CASE REPORT

Extramedullary skeletal muscle metastasis of glioblastoma: A case report and literature review*

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Abstract

Objective The aim of the study was to explore the clinicopathologic, immunophenotypic, and diagnostic features of extramedullary metastases of glioblastoma.

Methods One case of extramedullary skeletal muscle metastasis of glioblastoma was studied, including the clinical, histological, and immunohistochemical features.

Results A 24-year-old man underwent surgical resection for glioblastoma (WHO grade IV) in the left temporal parietal region followed by radiotherapy and temozolomide therapy. One year and nine months later, he developed an extramedullary skeletal muscle metastasis in L4, and the histology was remarkably different from that of the primary glioblastoma specimen. The immunohistochemical analysis also showed changes. In the metastasis, the small cells were negative for GFAP; weakly positive for S-100; and positive for nestin, NSE, and CD56, with 60% of cells positive for p53 and 40% positive for Ki-67. The giant cells showed strong positivity for GFAP and S-100, and weak expression of p53, Ki-67, nestin, NSE, and CD56. The primary glioblastoma specimen showed strong positivity for GFAP and S-100 and was negative for NSE, nestin, and CD56, with around 25% of the tumor cells positive for p53 and a Ki-67 labeling index of 20%.

Conclusion Extraneural metastasis (ENM) is a rare complication of glial tumors and glioma stem cells may be related to the metastasis. Since extraneural metastasis may occur in patients without central nervous symptoms, any unusual signs during the follow-up of patients diagnosed with glioblastoma should not be underestimated.

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Extraneural metastasis (ENM) is a rare complication of tumors of the nervous system [1–3]. ENMs affect only 0.96% of those with tumors of the nervous system [4]. Among these, ENMs of glioblastomas are also a rare finding, and lungs and lymph nodes are particularly susceptible to extraneural spread [5]. Here we report on a patient with an extramedullary skeletal muscle metastasis from a World Health Organization (WHO) grade IV glioblastoma.

Case history

A 24-year-old man presented with headaches and vomiting. A brain magnetic resonance imaging (MRI) scan revealed a left temporal parietal occupied lesion (Fig. 1a–1c). Complete resection of the lesion was performed and pathological examination revealed a WHO grade IV glioblastoma. Subsequently, the patient was treated with TomoTherapy radiotherapy combined with temozolomide. Routine MRI scans of the brain performed every 2 months did not show any local recurrence.

Approximately 1 year and 9 months later, the patient experienced backache. An MRI scan of the lumbar vertebra showed a mass in the canalis vertebralis, spinal marrow, and right rear muscle of L4. The lesion spread backward to the bilateral accessory and spinous process and showed marked homogeneous enhancement (Fig. 1g–1j). An MRI scan of the brain showed a local recurrence (Fig. 1d–1f).

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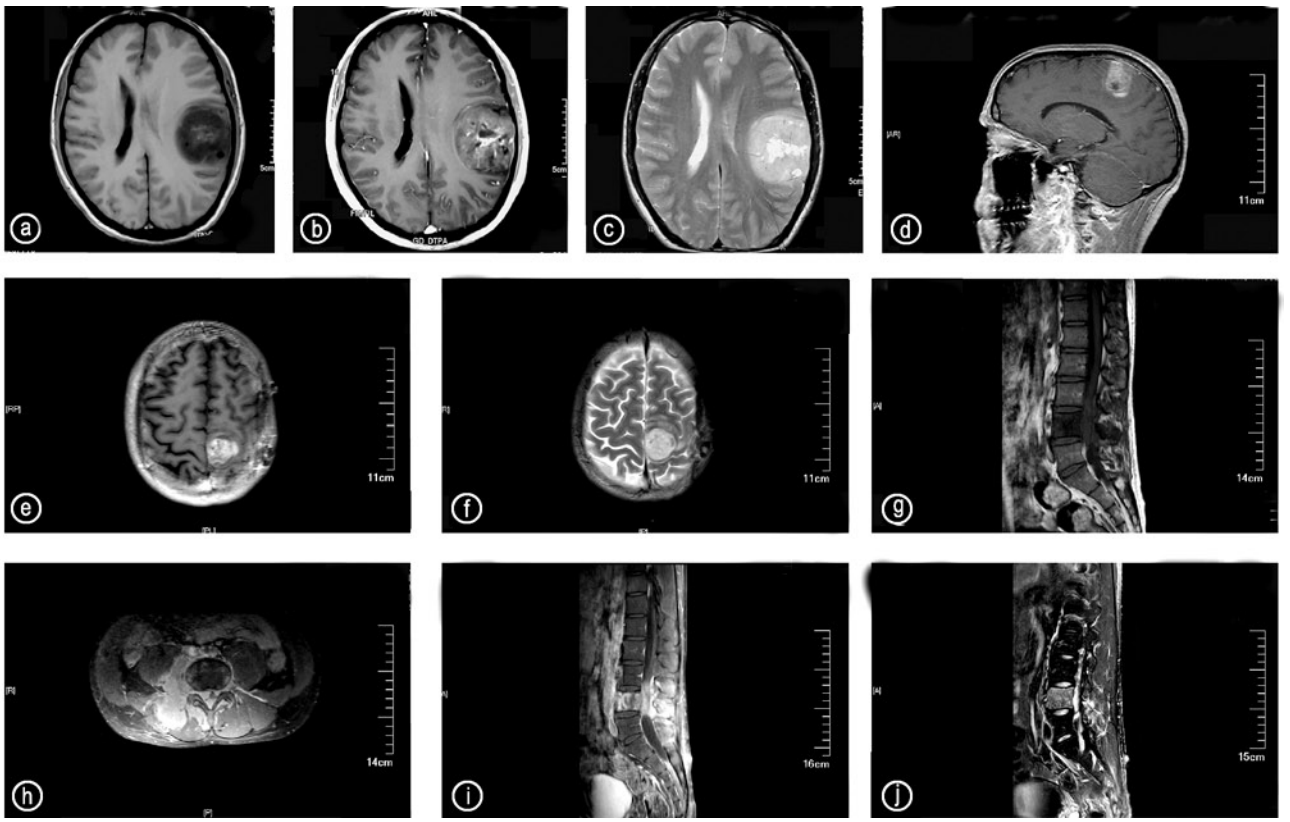

Fig. 1 MRI scans of the different tumor locations. (a–c) The tumor preoperative of brain: T1 axial MRI (a), T1-weighted axial MRI (b) and T2 axial MRI (c); (d–f) A year and nine months later, MRI scan of the brain showed a local recurrence: T1-weighted coronal MRI (d), T1-weighted axial MRI (e) and T2 axial MRI (f); (g–j) MRI scan of the lumbar vertebra showed the metastasis: T1 coronal MRI (g), T1 axial MRI (h), T1-weighted coronal MRI (i) and T2 coronal MRI (j)

Resection of the lesions in L4 was performed and we found the tumor, measuring around 10 cm × 7 cm, had invaded the endorhachis and both sides of the psoas, erector spinae, and quadratus lumborum. The tumor was diagnosed as an extramedullary skeletal muscle metastasis of a WHO grade IV glioblastoma. Subsequently, the patient received radiotherapy combined with temozolomide and irinotecan-cisplatin chemotherapy. The patient died 1 year and 3 months after surgical resection of the metastasis.

Pathological findings

Primary glioblastoma

Histopathologically, the specimen consisted of brain tissue with diffuse infiltration of atypical cells with oval pleomorphic hyperchromatic nuclei in a fibrillary background. The cells were arranged densely and demonstrated increased mitotic activity and necrosis and microvascular proliferation. Immunohistochemically, the tumor cells showed strong positivity for GFAP (almost all of the tumor cells were positive) and S-100. No positivity for mutant IDH1 (R132H), EGFR, AE1/3, CD99, CgA, Syn, NSE, LCA, nestin, CD56, or CD133 was found. About 25% of the tumor cell nuclei showed positive reactions for p53. The Ki-67 labeling index was 20% (Table 1). The pathological diagnosis of the primary tumor was glioblastoma (WHO grade IV; Fig. 2a and 2b).

L4 metastasis

For the submitted surgical specimen taken from L4, the histopathology showed that numerous atypical cells were infiltrated as solid nests among the skeletal muscle tissues. The tumor cells were different from those seen in the primary tumor. On hematoxylin and eosin staining, the tumor was composed of two different cell morphologies: uniform small round cells with oval nuclei and unremarkable nucleoli, and giant cells similar to glioblastoma composed of highly anaplastic giant and syncytial cells. Immunohistochemically, the staining pattern also differed between the two cell types. The small cells were negative for GFAP, weakly positive for S-100, had more cells (around 60%) positive for p53, a Ki-67 positive index of 40%, and some demonstrated positive expression of the neural stem cell (NSC) marker nestin and the neuro-

blast cell markers NSE and CD56. The giant cells showed strong positivity for GFAP and S-100 and lower expression of p53, Ki67, nestin, NSE, and CD56. All of the tumor cells were negative for mutant IDH1 (R132H), EGFR, LCA, and CD133 (Table 1). The tumor was diagnosed as an extramedullary skeletal muscle metastasis of a WHO grade IV glioblastoma (Fig. 2c–2h).

Table 1 Summary of immunohistochemical findings

Antibodies	Primary tumor	Small cells in the metastasis	Giant cells in the metastasis
GFAP	+++	–	+++
S-100	+++	+	+++
p53	25%	60%	10%
Ki67	20%	40%	10%
Nestin	–	++	+
CD56	–	+++	++
NSE	–	++	+
CgA	–	–	–
Syn	–	–	–
CD133	–	–	–
IDH1 (R132H)	–	–	–
LCA	–	–	–
EGFR	–	–	–
AE1/3	–	–	–
CD99	–	–	–

+++, Strong reactivity; ++, Moderate reactivity; +, Week reactivity; –, No reactivity

Discussion

Metastatic spread from a cranial primary tumor is unusual, especially for glial tumors. Possible explanations include [6]: the absence of lymphatic vessels in the brain; presence of the blood-brain barrier; survival duration in cases of malignant gliomas is too short to develop metastases; glial tumor cells may require a special metabolic environment found only in the central nervous system; and the immunological response of the host organ to glial tumor cells may prevent growth outside of the central nervous system. Neurosurgical operations, especially ventriculoperitoneal shunts and multiple craniotomies, have been suggested to increase the risk of ENMs [2, 6, 7].

Extracranial metastases from glioblastoma have been detected for many years, with the first documented case in 1928 [8]. In a meta-analysis by Lun *et al* [9], 83 published cases of extracranial metastases from glioblastoma were found in the period from 1928 to 2009. In a single institution experience of extracranial metastasis in glioma by Amitendu *et al* [10] from the Brain Tumor Database of the National Neuroscience Institute of Singapore, between September 2004 and October 2009, the incidence of metastasis was 2.7% (4 of 148 patients). Extracranial metastases have been observed almost exclusively in cases of high-grade (III and IV) gliomas, but there has been no discrimination between WHO grade III and IV tumors in published cases [2]. Metastases from well-differentiated gliomas are very uncommon [11]. Of those that metastasize extraneurally, metastases to the vertebral bodies repre-

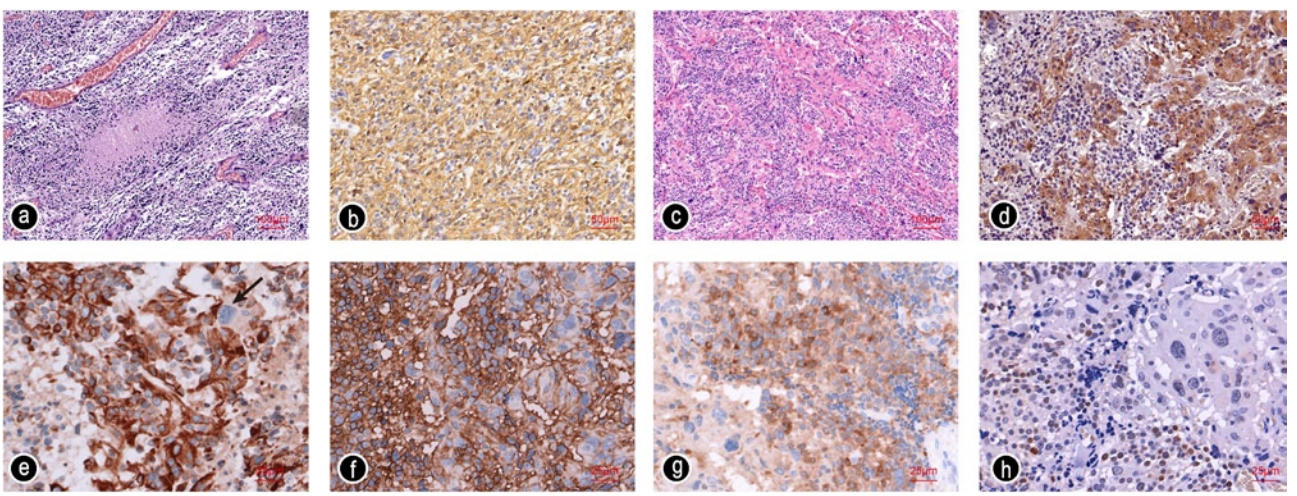

Fig. 2 Histopathological appearance of the different tumor locations. (a and b) Fist surgical brain tumor resection showing diffuse infiltration of atypical cells with oval hyperchromatic nuclei in a fibrillary background with necrosis and pathological microvascular proliferations by H & E staining (a) and strong positivity for GFAP by immunohistochemistry (b); (c–h) The surgical specimen in L4 showing the tumor was composed of two different cell morphologies: one is uniform small round cells with oval nuclei and unremarkable nucleoli; the other is composed of highly anaplastic giant and syncytial cells on H & E stain (c); Immunohistochemically, the component of small cells was negative for GFAP while the part of giant cells showed strong positivity for GFAP (d); There were more strong positive cells for nestin in small cells part than that in giant cells (e), also for CD56 (f), NSE (g) and p53 (h); The arrow showed negative expression for nestin in a giant cell

sent a significant proportion. Goodwin *et al* [12] reviewed 28 cases from the published literature of glioblastoma multiforme metastasis to the vertebra and found the mean age at presentation was 38.4 years with an average overall survival duration of 26 months. Patients were either asymptomatic with metastasis discovered at autopsy or presented with varying degrees of pain, weakness of the extremities, or other neurologic deficits. Hematogenous spreading is equally important as cerebrospinal fluid spread for ENM [13].

In our case, although our patient underwent surgical resection followed by radiotherapy and temozolomide therapy, neither a ventriculoperitoneal shunt nor multiple craniotomies were performed, and the time to recurrence was short (only 1 year and 9 months). The intravasation of tumor cells during the intraoperative injury of blood vessels may be associated with ENM. In addition, many researchers have demonstrated that in tumor tissue the blood brain barrier is not intact, which can promote ENM [5, 7]. Furthermore, based on an admittedly small number of cases, adjuvant radiation therapy may reduce the dura tightness, facilitating transdural tumor cell migration.

Intrinsic molecular properties of tumor cells may be involved in the process of extraneural spread. The increased expression of EGFR and mutations in the p53 and IDH1 genes may play a role in ENM of glioblastomas [5, 14–16]. In our case, we found neither the primary lesion nor the metastatic tumor expressed EGFR or had mutant IDH1 (R132H) expression, but the positive expression rate of p53 and Ki-67 in the metastasis doubled in comparison with the original lesion.

Interestingly, the pathological morphology and immunohistochemical expression of GFAP, p53, and Ki-67 had changed greatly in the metastatic lesion. The primary specimen consisted of similar uniform atypical cells, which almost all showed strong positivity for GFAP. The metastatic tumor was composed of two different cell morphologies, uniform small round cells negative for GFAP expression, higher mutant p53 expression, and a higher Ki-67 labeling index; and anaplastic giant and syncytial cells with GFAP expression, less mutant p53 expression, and a lower Ki-67 labeling index. This interesting phenomenon indicated the possible existence of glioma stem cells [17, 18].

Glioma stem cells account for a fraction of the tumor cell population, with stem cell-like properties including multi-potency, self-renewal, and tumorigenesis [19–21]. We speculated the small, uniform, round, GFAP-negative tumor cells in the metastasis might be related to glioma stem cells, and with the microenvironment and metabolic changes (from the left temporal parietal to extramedullary skeletal muscle), this group of cells differentiated into GFAP-positive giant tumor cells that were different from the primary lesion. Further research including immunohistochemical analysis with the neural stem cells marker nestin [22–24] and neuroblast cell markers NSE and CD56 showed the small cells were positive for nestin, NSE, and CD56, while the giant cells showed weaker expression of these markers.

Conclusion

ENM of glioblastoma is extremely rare. Because patient survival has increased these days, the incidence of this atypical presentation is likely to increase. Because ENM may occur in patients with a short disease history and without any central nervous symptoms, any unusual symptom occurring during the follow-up of these patients should not be underestimated. The best treatment for these tumors is excision of the mass followed by radiotherapy and chemotherapy.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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