GBM skin metastasis: a case report and review of the literature

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Glioblastoma (GBM) is the most common type of malignant tumor found in the brain, and acts very aggressively by quickly and diffusely infiltrating the surrounding brain parenchyma. Despite its aggressive nature, GBM is rarely found to spread extracranially and develop distant metastases. The most common sites of these rare metastases are the lungs, pleura and cervical lymph nodes. There are also a few case reports of skin metastasis. We present the clinical, imaging and pathologic features of a case of a GBM with metastasis to the soft tissue scar and skin near the original craniotomy site. In addition, we discuss the details of this case in the context of the previously reported literature.

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Glioblastoma (GBM) is the most common type of malignant tumor found in the brain, accounting for up to 25% of all primary CNS tumors [1]. GBM behaves very aggressively by quickly and diffusely infiltrating the surrounding brain parenchyma. As a result, the natural history of the disease is short and patient survival is limited. However, despite its aggressive nature, GBM is rarely found to spread extracranially and develop distant metastases [2,3]. The most common sites of these rare metastases are the lungs, pleura and cervical lymph nodes [4,5]. There are also a few case reports of skin metastasis, with reports as early as 1960 [4,6]. We present the clinical, imaging and pathologic features of a case of a GBM with metastasis to the soft tissue scar and skin near the original craniotomy site.

Case presentation

The patient was a 47-year-old woman who initially presented with a several month history of dizziness, headaches and nausea. Her symptoms progressed to the point that she was unable to walk due to balance difficulties. MRI of brain with and without contrast revealed a cystic enhancing lesion in the left medial cerebellar hemisphere extending to the vermis, with a nodular focus of enhancement in the posterior region of the fourth ventricle. She underwent a gross total resection, and the pathology was consistent with a GBM, *IDH1*-wt, with an unmethylated *MGMT* promoter. The patient underwent treatment, consisting of radiotherapy to a total dose of 60 Gy in 30 divided fractions with concurrent daily temozolomide (75 mg/m² of body surface area), followed by three cycles of adjuvant temozolomide (150 mg/m²) for 5 days every 28 days. She also received subcutaneous

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IFN- β (300 million units every other day for 3 doses with each cycle) during cycles 2 and 3 of adjuvant temozolomide. At this time, the patient began to notice a soft tissue mass protruding from the back of her neck (at the site of her surgical scar) that initially measured approximately 0.5 cm. An MRI of the brain and spine with and without contrast revealed enhancing lesions in the leptomeninges and fourth ventricle. In addition, there was abnormal signal in the cervical vertebrae consistent with drop metastases and leptomeningeal disease. MRI C-spine with and without contrast also showed enhancing soft tissue nodules in the subcutaneous fat of the suboccipital neck measuring 0.7 and 0.6 cm. Clinically, the patient noticed her mass continued to increase in size to 6 cm. She underwent craniospinal irradiation to a dose of 36 Gy in 15 fractions with concurrent daily temozolomide (75 mg/m²) and thymalfasin (1.6 mg subcutaneous two-times a week). Temozolomide and thymalfasin were subsequently discontinued due to pancytopenia. Throughout this time, the patient reported that her mass had decreased in size during the second radiation course. However, after she finished radiotherapy, she noted that the mass began to increase in size, causing her significant pain. All parts of her initial diagnosis, treatment and management were performed at an outside institution in her home country of China.

She then presented to our institution for a second evaluation. Repeat MRI C-spine with and without contrast showed stable leptomeningeal disease. It also showed that the suboccipital subcutaneous masses now measured 1.7 and 2.5 cm. On our initial physical examination, the patient exhibited a subcutaneous mass measuring approximately 3 cm located in the suboccipital region (under her surgical scar) that was confirmed with CT imaging (Figures 1 & 2). On neurologic examination, she had 4/5 strength in both lower extremities, unsteady gait and a positive Romberg sign. The patient's Karnofsky Performance Score (KPS) was 50. The patient was offered radiotherapy for her mass, as a partial response was reported with previous radiotherapy. After weighing the different treatment options, the patient decided to proceed with surgical excision of the soft-tissue mass due to increasing and severe pain. She underwent incision and radical excision of the mass by neurosurgery and plastic surgery. During the surgery, the neurosurgeon noted that the tumor had

infiltrated into the dermis of the skin but all of the mass appeared to be above the cervical fascia.

Pathologic examination of the soft tissue mass showed an infiltrative, small round blue cell tumor with elevated mitotic activity, nuclear molding, apoptotic bodies and necrosis suggestive of a primitive neuroectodermal tumor (Figure 3). The majority of the tumor cells were positive for synaptophysin and *p53* immunohistochemical stains. Rare scattered neoplastic glial elements were also highlighted with GFAP immunohistochemical stain. The material from the soft tissue mass was compared with the original material resected from the cerebellum, which showed a GBM with a subset of tumor cells that were positive for synaptophysin consistent with a morphologic pattern of GBM recognized by the WHO 2016 Classification as GBM with a primitive neuronal component [7]. The tumor present in the soft tissue was consistent with the primitive neuronal component of the GBM seen in the original tumor upon comparison.

Discussion

Skin and soft tissue metastases from GBM are rare, with less than 20 published case reports as of 2016 (Table 1) [4]. Most cases were adults, and one was a child [8]. Given the aggressive clinical course of GBM, it is intriguing for its low propensity to metastasize. Some possible explanations include a short survival time and an effective immune response to malignant glial cells outside of the CNS [4,9].

In previous reports, skin and soft tissue metastases from GBM have occurred at the craniotomy scar [4] and at the site of stereotactic biopsy [10,11] as soon as 6 weeks after diagnosis and treatment of the primary, or as long as 4 years (Table 1). A comprehensive meta-analysis of patients with extracranial metastasis at any site found a median time of 9 months from initial diagnosis to the diagnosis of metastasis [9]. Our patient developed her metastases approximately 5 months after her initial diagnosis. Skin and soft tissue metastases have been reported as isolated areas of disease, synchronous with other metastases, or concurrently with intracranial recurrence. However, it appears that the most common presentation is skin and soft tissue metastases concurrent with intracranial recurrence. The exact mechanism is unknown but it could result from subcutaneous implantation of tumor cells during surgical removal or cell escape along the excision/biopsy tract through the dura toward

Figure 1. Photo of the soft tissue mass in the radiation treatment position.

the skin. It is unclear if surgical technique plays a role. GBM can be resected by en bloc resection or by an ‘inside-out’ approach in which the surgeon enters the solid tumor as an initial step in the resection and then proceeds to perform a piecemeal removal directed toward the edge of the lesion [25]. Intuitively, a piecemeal approach would be concerning for tumor cell escape, but this has not been studied in detail.

The most appropriate management of skin and soft tissue metastases from GBM has not been determined. Biopsy can be performed either via

subtotal/total resection or via fine-needle aspiration (FNA) biopsy. However, a full patient history and physical examination should be obtained, as other diagnoses (squamous cell carcinoma, melanoma, etc.) on the differential should not be diagnosed via FNA biopsy. If an FNA biopsy is performed, the histology should be confirmed when surgical excision is completed, particularly because some immunohistochemical stains (e.g., S100) may be present in melanoma and GBM. As presented in [Table 1](#), the majority of patients underwent surgery in combination radiotherapy and/or

Figure 2. Computed tomography imaging of the mass (white crosshairs) in axial and sagittal views.

Figure 3. Hematoxylin and eosin stained sections show a diffusely infiltrating high grade blue cell tumor with mitotic activity (A), molding (B), and necrosis (C). Immunohistochemical stains showed that the tumor cells were positive for synaptophysin (D). The majority of the tumor cells showed p53 expression (E) and only rare cells were positive for GFAP (F).

chemotherapy [4]. Chemoradiation alone has also been used, but Senetta and associates found better local control with surgery plus radiotherapy compared with biopsy plus radiotherapy with adjuvant temozolomide [12]. Therefore, surgery may be an integral part of treatment for these recurrences. Review of previous cases (Table 1) highlights a wide range of survival outcomes (2 weeks to 1 year) after development of cutaneous disease, with the longest survival seen in a patient treated with surgery and radiation. For extracranial GBM metastases

at any site, Pietschmann *et al.* reported a median survival of 6 months after metastasis diagnosis [6].

Our patient's clinical case has some other unique features. At the time of disease recurrence, she had failure at her initial site of disease, leptomeningeal spread and soft-tissue and skin metastases. Leptomeningeal disease in GBM is not common, with an estimated prevalence of 2–4% [26,27]. It is possible that our patient was at higher risk for leptomeningeal disease due to the involvement of the cerebellum and

fourth ventricle at the time of diagnosis. One study found early development of leptomeningeal metastasis in patients with primary disease in the cerebellum [26]. The proper management of leptomeningeal spread in GBM is not clear, but previous reports have found that the use of chemotherapy and radiation (as our patient received) tended to have better results compared with single modality treatment [26,28,29].

In this case, the microscopic examination of the tumor sample revealed features that possibly explain its clinical behavior. The tissue diagnosis was GBM with a primitive neuronal component, a subtype of classic-appearing GBM. These areas can resemble a medulloblastoma or other CNS embryonal tumor due to synaptophysin and *p53* staining, as well as a reduction in GFAP staining compared with classic-appearing GBM. This subtype has a high rate of cerebrospinal fluid (CSF) dissemination (30–40%) and can often harbor *MYCN* or *MYC* gene amplifications

(40% of cases) [7]. The *IDH1* (R132H) mutation is uncommon in this subtype; it is seen in only 15–20% of cases [7]. The molecular profile of our patient's original cerebellar tumor was *IDH1/IDH2* wild-type, *1p/19q* not codeleted, and *MGMT* promoter unmethylated, which fits this description. Given that this subtype has a higher propensity for CSF dissemination, it unsurprising that our patient had developed leptomeningeal disease. Had this subtype been identified at initial diagnosis, the patient may have benefited from complete CNS staging with craniospinal imaging and CSF analysis (especially given the cerebellar location). Given this higher rate of CSF dissemination, one must also consider whether this subtype is also more prone for extraneural metastasis as well, although this has not been reported previously.

In addition, our patient received adjuvant IFN- β in combination with temozolomide as part of her initial treatment at an outside

Table 1. Published cases of glioblastoma with metastasis to skin or soft tissue.

Study (year)	Patient's age (years)	Patient's sex	Therapy of primary	Time until cutaneous disease (months)	Therapy of cutaneous lesion	Survival
Matsuyama <i>et al.</i> (1989)	68	M	Surgery (GTR), RT, CT	Unknown	Unknown	5 months
Wallace <i>et al.</i> (1996)	41	M	Surgery (GTR), RT, CT	3	Local RT and CT	8 months
Houston <i>et al.</i> (2000)	32	M	Surgery (STR), RT, CT	6	Excision	13 months
	19	M	Surgery (STR), RT (brachytherapy), CT	10	Local RT and CT	17 months
Hata <i>et al.</i> (2001)	Unknown	Unknown	Surgery, RT, CT	Unknown	Unknown	Unknown
Figueroa <i>et al.</i> (2002)	34	F	Surgery (STR), RT, CT (via Ommaya Reservoir)	8	Excision	13 months
Allan (2004)	60	M	Surgery, RT	12	None	14 months
Moon <i>et al.</i> (2004)	35	F	Surgery, RT	48	CT	52 months
Jain <i>et al.</i> (2005)	49	F	Surgery, RT	10	Excision	12 months
Schultz <i>et al.</i> (2005)	74	F	Surgery, RT, CT	12	Excision	13 months
Bouillot-Eimer <i>et al.</i> (2005)	60	F	Biopsy, RT, CT	11	Partial Excision	12 months
Saad <i>et al.</i> (2007)	13	M	Surgery, RT, CT	Unknown	CT	10 months
Mentrikoski <i>et al.</i> (2008)	58	F	Surgery, RT, CT	16	Biopsy	Unknown
	41	M	Surgery, RT (Brachytherapy)	2	Unknown	Unknown
Senetta <i>et al.</i> (2009)	48	F	Surgery, RT, CT	14	Excision and RT	26 months
	53	F	Surgery, RT, CT	14	Biopsy and focal RT	25 months
Miliaras <i>et al.</i> (2009)	63	M	Surgery	7	Biopsy	10 months
Ginat <i>et al.</i> (2013)	62	M	Surgery (STR), RT, CT	10	Excision and CT	14.5 months
Bathla <i>et al.</i> (2015)	51	M	Surgery (GTR), RT, CT	1.5	None	2 months
Elena <i>et al.</i> (2015)	30	M	Surgery, RT, CT	74	Excision	10 weeks
	43	M	Surgery (GTR), RT, CT	20	None	3 weeks

CT: Computed tomography; GTR: Gross total resection; RT: Radiotherapy; STR: Subtotal resection.

Data taken from [3,8,10–24].

institution in her home country. IFN- β is not part of the standard of care for GBM but some data have suggested that IFN- β with temozolomide can improve outcomes [30–32]. There are several proposed mechanisms of action, including downregulation of the MGMT DNA repair enzyme (resulting in increased sensitivity to temozolomide) and stimulation of the immune system response to tumor cells [31,33–34]. Our patient also received thymalfasin (also known as thymosin- α 1 or Talphal) as part of her initial management, which has not been studied as much as interferon in the treatment of GBM. Thymalfasin is a synthetic analog of a naturally occurring hormone that circulates in the thymus and stimulates thymocyte growth and differentiation [35]. Animal studies have shown some potential benefit in combination with carmustine against GBM and glioma cells [13,36].

Conclusion

Skin and soft tissue metastases are rare complications of GBM despite the aggressive natural history of the disease. The exact mechanism of occurrence is unknown but likely represents implantation of tumor cells after surgical instrumentation, coupled with a molecular subtype that can survive extracranially. We propose that GBM with primitive neuronal component is one such variant responsible for extracranial seeding, as tumors with this subtype have an increased proclivity for CSF dissemination and thus merit full CNS staging. Further study is needed to determine whether this subtype's

increased propensity for CSF dissemination is associated with an increased ability to survive extraneurally.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Informed consent disclosure

The authors state that they have obtained verbal and written informed consent from the patient/patients for the inclusion of their medical and treatment history within this case report.

EXECUTIVE SUMMARY

- Glioblastoma (GBM) is the most common type of malignant tumor found in the brain, accounting for up to 25% of all primary CNS tumors.
- However, despite its aggressive nature, GBM is rarely found to spread extracranially and develop distant metastases.
- The most common sites of these rare metastases are the lungs, pleura and cervical lymph nodes.
- There are only a few case reports of skin metastasis.
- Some possible explanations for GBM's low metastatic potential include a short survival time and an effective immune response to malignant glial cells outside of the CNS.
- The exact mechanism of occurrence of these rare skin and soft tissue metastases is unknown but likely represents implantation of tumor cells after surgical instrumentation, coupled with a molecular subtype that can survive and thrive extracranially.
- We propose that GBM with primitive neuronal component is one such molecular variant responsible for extracranial (and possible extraneural) metastasis.
- The most appropriate management of skin and soft tissue metastases from GBM has not been determined but combined modality treatment with surgery, chemotherapy and radiation is a reasonable option.

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