Rare disease

Skin spread from an intracranial glioblastoma: case report and review of the literature

Ignacio Jusué Torres,¹ Pilar Jerez Fernández,¹ Jose Ortega Zufiría,¹ Jose María Rodríguez Barbero²¹Department of Neurosurgery, Hospital Universitario de Getafe, Madrid, Spain;²Department of Pathology, Hospital Universitario de Getafe, Madrid, Spain**Correspondence to** Dr Ignacio Jusué Torres, ignaciojusue@gmail.com**Summary**

Extracranial metastases secondary to intracranial neoplasm are extremely rare. The incidence of extraneural metastases of brain tumours is estimated to be less than 0.4%. The authors report a case of postoperative intracranial glioblastoma spreading to the skin in an adult patient. In this case, the radiological images and surgical findings suggest that the potential dissemination mechanism is as a result of infiltration through the surgical wound site. The primary tumour—upon coming into contact with the dura and the skin—mimicked the characteristics of both tissues. This case supports the theory of risk of spread through the durotomy site, although this phenomenon is extremely rare. Both the specific pathogenic mechanisms as well as the ideal and effective management have not been established yet and require further investigation.

BACKGROUND

Despite their aggressive behavior, extracranial metastases secondary to intracranial neoplasm are considered extremely rare. While brain metastases secondary to malignancies in other organs are rather common and occur in approximately 10% of cases, the opposite is much rarer. The incidence of extraneural metastases of brain tumours is estimated to be less than 0.4%. Large autopsy series have reported that the frequency of primary central nervous system (CNS) tumours spreading to areas outside the craniospinal axis is 0.4–0.5%.¹

Gliomas are the most frequent primary intracranial neoplasm. They account for almost half of all CNS tumours, among which glioblastoma is the most aggressive subtype. However, the most common malignancies found in the CNS are, by far, secondary tumours, which are approximately 10 times more common than primary tumours.² Despite continuous and renewed efforts in the treatment of high-grade gliomas, the likelihood of long-term survival has remained poor and stable over the last three decades, with a 2–4% 5-year survival in patients with glioblastoma.

The most common sites where glioblastoma metastases have been diagnosed are lungs and pleura, followed by lymph nodes, bone marrow and liver. By far, the most common metastasis site among patients with non-shunt-related metastases is the lung. On the contrary, there is a greater tendency toward visceral dissemination and bone metastases in shunt-related cases.³

Isolated skin metastases secondary to glioblastomas are extremely rare. To the best of our knowledge, at least about a dozen cases of skin metastasis secondary to glioblastoma have been reported (table 1). We report a case of an intracranial glioblastoma spreading to skin. In our case, the radiological images and surgical findings suggest that the potential mechanism of dissemination was infiltration through the surgical wound site.

CASE PRESENTATION

A 63-year-old female with hypertension, type 2 diabetes and dyslipidemia developed left upper limb apraxia over the past month. In the physical examination, the patient presented with minimal left upper limb paresis and no

Figure 1 Preoperative images from gadolinium-enhanced cranial MRI: lesion with contrast uptake in the right superior frontal gyrus.

Table 1 Reported cases of high-grade glioma in skin

Authors & year	Age (years)	Sex	Histopathology (WHO grade)	Primary site	Degree of 1st surgery	Time from 1st surgery to skin metastasis	Radiation therapy prior to skin metastasis	Chemotherapy	2nd line chemotherapy
Shuangshori (1988) ⁶	69	Female	Meningioma and glioblastoma (WHO IV)	Left parieto-occipital area	Subtotal excision	Before surgery	Not specified	Not specified	-
Carvalho (1991) ⁹	26	Female	Glioblastoma (WHO IV)	Right temporal lobe	Subtotal resection	Not specified	+	Not specified	-
Figuerola (2002) ¹⁰	34	Male	Glioblastoma (WHO IV)	Left temporal lobe	Partial resection	7 months	+	-	-
Santos (2003) ¹³	42	Male	Glioblastoma (WHO IV)	Left Fronto-parietal area	Gross total resection	36 months	+	Not specified	-
Allan (2004) ⁷	60	Male	Glioblastoma (WHO IV)	Not specified	Not specified	12 months	Not specified	Not specified	-
Jain (2004) ¹¹	49	Male	Glioblastoma (WHO IV)	Right temporo-parietal area	'Decompression'	10 months	+	-	-
Bouillot (2005) ⁸	60	Female	Glioblastoma (WHO IV)	Left parietal lobe	Stereotactic biopsy	8 months	+	Carmustine (BICNU)	-
Schultz (2005) ¹⁶	74	Female	Glioblastoma (WHO IV)	Left temporal lobe	Partial resection	12 months	+	-	Stereotactic DTI-Q15
Saad (2007) ³	13 ½	Male	Glioblastoma (WHO IV)	Left frontal lobe	Subtotal resection	9 months	+	Temozolomide	Thalidomide, Celebrex, Etoposide
Mentrikoski (2008) ¹²	41	Male	Anaplastic oligodendroglioma (WHO III)	Not specified	Not specified	2 months	-	-	-
Mentrikoski (2008) ¹²	58	Female	Glioblastoma (WHO IV)	Left frontal lobe	Not specified	16 months	+	Temozolomide	Bevacizumab
Millaras (2009) ⁵	63	Male	Glioblastoma (WHO IV)	Left fronto-parietal area	Gross total resection	7 months	+	Temozolomide	-
Senetta (2009) ¹⁴	48	Female	Glioblastoma (WHO IV)	Right fronto-parietal area	Gross total resection	Not specified	+	Temozolomide	-
Senetta (2009) ¹⁴	54	Female	Glioblastoma (WHO IV)	Left frontal lobe	Partial resection	Not specified	+	Temozolomide	-
Present report	63	Female	Glioblastoma (WHO IV)	Right frontal lobe	Gross total resection	6 months	+	Temozolomide	1. Carmustine implants 2. Bevacizumab and irinotecan

other neurological focus. A diffusion MRI of the brain and proton spectroscopy showed a space-occupying lesion of 2.7 cm in diameter at the level of the right upper frontal gyrus with irregular but intense contrast uptake and areas of necrosis, surrounded by significant vasogenic edema causing mild subfalcial herniation (figure 1). The lesion showed spectroscopic data suggestive of overt neuronal destruction, with accelerated cell exchange (significantly decreased N-acetylaspartate as well as reduced creatine and very high levels of choline, combined with lactate and lipid peaks), which may indicate a very high mitotic activity. The extension study was negative.

The patient underwent surgery involving a right frontal craniotomy and apparently total intraaxial tumour resection. The intraoperative and definitive histopathological findings confirmed the diagnosis of a glioblastoma. It was a solid tumour made up of markedly pleomorphic cells. It had different areas: gemistocytic cells, multinucleated giant cells and small fusiform cells with hyperchromatic nuclei. There was marked endothelial hyperplasia and areas of necrosis with peripheral palisade. The mitotic index was high, with a 10% Ki 67, and markedly positive p53 expression. Subsequently, a follow-up cranial MRI was performed which showed no surgical site complications. The patient completed treatment according to the Stupp protocol with cranial radiotherapy and chemotherapy with temozolomide.

OUTCOME AND FOLLOW-UP

Six months after surgery, the patient developed slowly progressive weakening of the left side of the body. The cranial MRI showed tumour recurrence at the surgical margins with dural infiltration in falx cerebri, convexity and superior sagittal sinus. Of note, there was a contrast-enhanced, 15 mm soft tissue tumour located in scalp and subcutaneous cell tissue, close to the craniotomy edge (figure 2). This lesion was not present in the postoperative MRI.

Seven months later, surgery was performed in which the craniotomy was reopened and the lesion was excised with the assistance of cortical mapping with Ojemann's neurostimulation; the preservation of the supplementary motor area was verified and carmustine implants were subsequently placed in the surgical site. The skin lesion was excised (figure 3). At the time of surgery, this lesion was not suspected to be glioblastoma. During the immediate post-operative period, the patient experienced left hemiplegia associated with potential supplementary motor area syndrome, since the cranial CT scan showed no complication and it resolved within the first 48 h. The pathophysiological diagnosis was high-grade glial tumour with mesenchymal differentiation consisting of relapsing glioblastoma in brain tissue involving the dura and dermis. The immunohistochemical study of the skin specimen showed that proliferating cells were mostly positive for vimentin and smooth muscle actin, but there were also very wide areas which were positive for glial fibrillar acidic protein (figure 4). One month after surgery the patient was started on bevacizumab and irinotecan. The 6-month follow-up cranial MRI indicated that the intracranial lesion was absent.

DISCUSSION

Primary malignant brain tumours are characterised by poor prognosis despite their low rate of extraneural spread.

Figure 2 Cranial MRI images showing local intracranial recurrence with a contrast-enhanced skin lesion. Both are linked by a thin, contrast-enhancing bridge.

Figure 3 Picture from the OR showing the skin lesion before resection.

Paradoxically, many somatic tumours are much more circumscribed and yet show metastases much more frequently. The reason why glioblastomas rarely metastasise is not clear, but some theories have been described by different authors.²

1. The absence of a real lymphatic system connecting the CNS to the rest of the body.
2. The presence of a resistant outer dura mater.
3. Brain vascularisation with thick basal membranes (blood-brain barrier) and intracranial venous sinuses contained in a dense dural membrane.
4. Brain tumour cells do not survive easily within other organs which are morphologically different, perhaps due to the immune response generated by host tissues against tumour cells. However, little is known yet about the specific immunological behavior against brain tumour cells in the periphery.
5. The lack of local disease control does not allow for survival which is long enough to allow the development of extraneural metastases.

Nevertheless, some experiments have shown that primary brain tumours can grow outside the CNS.⁴ There are

several papers reflecting large number of cases of systemic spread of CNS tumours reaching more than 250 cases reported.¹⁻⁵ In 1988, Shuangshoti published the first case of skin metastasis of a surgically removed glioblastoma.⁶ About a dozen cases of skin metastases have been published to date (table 1).^{3, 5-14}

The pathophysiological mechanisms of such metastases are still not fully understood. However, in the overwhelming majority of cases of extraneural metastasis, they occurred after surgery, particularly after craniotomies. Moreover, there are very few published cases in the literature where remote metastases of glioblastomas occur with no previous surgical manipulation.¹⁵

Our case supports what these authors have described. Even though the skin tumour was not known to be a glioblastoma during surgery, when the free bone flap was raised, it was possible to see that there was some firm fibrous tissue around the suspension points, which could not be differentiated from the dura and formed some fine cylinders around these points. After opening the dura, it was possible to see that this tissue was the same color and consistency as the recurring glioblastoma, since the tissue had mimicked the

Figure 4 H&E-stained slides of the skin specimen. (a) 100x image showing infiltration of dermal collagen. (b) 100x image of the tumour with necrosis and glomerular vascular proliferation. (c) 400x image showing significant cell atypia and abundant mitosis.

characteristics of the dura (mesenchymal differentiation) after coming into contact with it. The same phenomenon occurred with the skin lesion. After the pathophysiological diagnosis, we reviewed the MRI and it was possible to see how the contrast enhanced both the intracranial and skin tumours and that both were linked by a narrow tumour bridge, also enhanced by contrast. Therefore, in this case, a direct extension is described both in the radiological images and in the surgical procedure. In agreement with the authors mentioned above, we suppose that the glioblastoma found some way to use the dural incision, the suspension points and the anchoring holes in the bone flap to spread into the skin at the surgical wound site.

Learning points

- ▶ Extraneural metastases of glioblastomas are a rare but well-described complication.
- ▶ The long debate on whether primary brain tumours have the potential to metastasize and grow in peripheral tissues is yet to be put to rest.
- ▶ Both the specific pathogenic mechanisms as well as the ideal and effective management have not been established yet and require further investigation.
- ▶ This case supports the theory of risk of spread through the durotomy site, although this phenomenon is extremely rare.

Competing interests None.

Patient consent Obtained.

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