Subcutaneous Dissemination in Highly Aggressive Intracranial Glioblastoma: Case Report and Literature Review

Glioblastoma (GBM) is a highly invasive and incurable primary central nervous system (CNS) tumor. Despite its aggressive behavior, extracranial metastases are rare, with an estimated incidence of less than 2%. In our literature review, we found only 21 reported cases of skin and soft tissue dissemination. We report a case of an early (two and a half months) postoperative skin and muscle flap-associated dissemination of a temporal glioblastoma.

The particular aspect of this case, besides its rarity, is that the clinical presentation, the image reports and even the surgical findings were always in favor of a postoperative subdural empyema and epicranial abscesses. The diagnosis of soft tissue dissemination was only possible after negative microbiological cultures and histopathological confirmation of muscle and skin invasion by the tumor. This case illustrates the rare but potential risk of myocutaneous flap tumor dissemination through the durotomy/craniotomy site that can mimic a much more common, post-surgical infection.

O glioblastoma é um tumor do sistema nervoso central extremamente invasivo e incurável. Apesar do comportamento agressivo desses tumores, a metastização extracraniana é rara, apresentando uma incidência inferior a 2%. A nossa revisão da literatura revelou apenas 21 casos descritos de disseminação de glioblastoma para a pele e tecidos moles. Nós descrevemos um caso de disseminação precoce de um glioblastoma temporal para o retalho miocutâneo associado à cirurgia, cerca de 2 meses e meio após a intervenção. Além da raridade, este caso é peculiar, uma vez que tanto a forma de apresentação clínica quanto a descrição imagiológica e os achados intraoperatorários foram sempre muito sugestivos de um empiema subdural e de abcessos epicranianos. O diagnóstico definitivo de disseminação tumoral para os tecidos moles apenas foi possível após o resultado negativo das culturas microbiológicas e a confirmação histológica de invasão do músculo e da pele pelo tumor. Este caso ilustra o raro, mas potencial risco de disseminação tumoral de um glioblastoma através do retalho miocutâneo de acesso cirúrgico e do local de craniotomia/durotomia, que se pode facilmente confundir com uma situação mais frequente de infecção após cirurgia.
**Introduction**

Glioblastoma (GBM) is a highly malignant tumor typically associated with a poor prognosis, with a 5-year survival rate of 4.7%.1-6 While brain metastases secondary to neoplasms in other organs are quite common and occur in ~10% of cases, the opposite is much less frequent. Like the majority of the primary brain tumors, GBM does not frequently metastasize outside of the central nervous system (CNS). Death usually occurs as a consequence of the growing mass within the skull, resulting in increased intracranial pressure and herniation.

There are few reports of extracranial metastasis from GBM, and most mention an overall occurrence rate of less than 2%.1-5 Metastases are postulated to occur by hematogenous dissemination or direct extension of the tumor.7 The reported sites of metastases include lung and pleura, bone, bone marrow, lymph node, and liver.8

Skin metastases secondary to GBM are extremely rare. To the best of our knowledge, ~21 cases have been reported in the literature so far (Table 1).9-22

In our case, the review of the radiological and intraoperative findings points to the hypothesis of soft tissue tumor dissemination through the surgical wound site.

**Case Report**

**Presentation** A 36-year-old woman with dyslipidemia, esophageal reflux and smoker of 1 pack of cigarettes a day, presented with a 3-week persistent headache. The neurological examination was normal. A computed tomography (CT) scan revealed an intra-axial irregular ring contrast-enhanced right temporal lesion (Fig. 1).

**Treatment** The patient was submitted to surgery, and a gross total resection was accomplished. The histopathological exam confirmed giant cell GBM (grade IV). It was a solid tumor made up mainly of pleomorphic cells, with frequent multinucleated giant cells, extensive necrosis and microvascular proliferation. The mitotic index was high, and there was a markedly positive expression for vimentin, NSE, p53 and EGFR. There was no MGMT methylation or IDH1 mutation.

**Outcome and follow-up** The patient fulfilled the Stupp Protocol, but 3 months after surgery she had a recurrence of symptoms, with strong headaches and a right hemicranial and facial mass with an associated edema. Image studies showed the recurrence of a previous lesion in the temporal lobe, a new right frontal lobe hemorrhagic lesion, and an extra-axial antero-inferior frontal lesion with peripheral enhancing signal extending epicranially through the craniotomy, suggesting an empyema and small epicranial abscesses (Fig. 2A-C). The differential diagnosis included abscesses, radiation-associated necrosis and soft tissue tumor dissemination.

A second surgery was performed with the enlargement of the craniotomy and the removal of purulent and necrotic subcutaneous/subdural and intra cerebral tissue. The microbiological tests were negative, with no confirmation of abscesses.

After one month, the patient was submitted to a third surgery because of extensive local recurrence with mass effect. Magnetic resonance imaging (MRI) showed extensive tumor invasion of the subcutaneous tissue and temporal muscle (Fig. 3A-C). The surgical intervention consisted of the reopening of the previous surgical wound with extensive removal of the tumor infiltrating the temporal muscle and a wide resection of tumor recurrence in the temporal and frontal lobes.

The histology finally confirmed duramater, temporal muscle and subcutaneous tissue invasion by GBM cells (Fig. 4B). The immunohistochemical analysis revealed no MGMT methylation, no IDH1 mutation, but there was EGFR amplification.

She repeated the treatment with temozolomide, but died before completing it, seven months after the initial diagnosis.

**Discussion**

Extracranial metastases of high-grade gliomas, especially to soft tissue, skin or muscle are truly rare. They are estimated to occur in less than 2% of patients. The first report in 1988 by Shuangshioti23 described a case of skin metastasis in a surgically removed GBM. About 21 cases of skin and soft tissue metastases have been published to date (Table 1).

The average time for recognition of metastases since the initial tumor diagnosis has been reported to be 12.1 months.24

In the majority of cases of GBM extracranial metastases previously described in the literature, patients had already undergone a neurosurgical procedure, especially craniotomies. However, there is one case of GBM metastasis outside the central nervous system, without previous surgical procedures.25

There are several theories on why GBM is hardly ever correlated with extracranial metastases:

1. Because of the aggressiveness of the tumor, patients die of the primary illness before metastasis can occur.2
2. The presence of physical barriers, exclusive to the brain, as the thick dura and thickened basement membranes on blood vessels preclude both hematogenous and lymphatic spreads.6,26
3. Glioma malignant cells may lack the capacity to disseminate through connective tissue and blood vessels outside the central nervous system, because within the brain parenchyma there is no collagen and fibronectin.7,27 Since these cells do not have the means necessary to invade connective tissue situated outside the central nervous system, they lack the ability to develop systemic metastases.

The pathophysiology of extracranial metastases is still not fully understood. The common feature of the majority of cases reported in the literature is that most patients were previously submitted to surgery. The surgical procedure does provide a break in the physical barrier, allowing seeding or hematogenous dissemination. Moreover, Müller et al28 recently described that ~20% of GBM patients have significant
Table 1 Review of the case reports of subcutaneous and soft tissue metastasis of high-grade intracranial gliomas presented in the literature

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>1st surgery</th>
<th>Histology (WHO grade)</th>
<th>Metastatic site/region</th>
<th>Time* (mo.)</th>
<th>Radiation/chemotherapy</th>
<th>Second line chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shuangshoti et al(^2)</td>
<td>F</td>
<td>69</td>
<td>Subtotal resection</td>
<td>GBM (IV) NS</td>
<td>Before Su.</td>
<td>NS/NS</td>
<td>–</td>
</tr>
<tr>
<td>Carvalho et al(^9)</td>
<td>F</td>
<td>26</td>
<td>Subtotal resection</td>
<td>GBM (IV) Temporal/parietal areas of the scalp</td>
<td>16</td>
<td>+/- NS</td>
<td>–</td>
</tr>
<tr>
<td>Figueroa et al(^10)</td>
<td>M</td>
<td>34</td>
<td>Partial excision</td>
<td>GBM (IV) 2 cm posterior to the frontal scalp line</td>
<td>7</td>
<td>+/-</td>
<td>–</td>
</tr>
<tr>
<td>Santos et al(^11)</td>
<td>M</td>
<td>42</td>
<td>GT resection</td>
<td>GBM (IV) Skin/subcutaneous tumor seeding</td>
<td>36</td>
<td>+/- NS</td>
<td>–</td>
</tr>
<tr>
<td>Allan(^11)</td>
<td>M</td>
<td>60</td>
<td>NS</td>
<td>GBM (IV) Scalp over craniotomy</td>
<td>12</td>
<td>NS/NS</td>
<td>–</td>
</tr>
<tr>
<td>Jain et al(^12)</td>
<td>M</td>
<td>49</td>
<td>“Decompression”</td>
<td>GBM (IV) Adjacent to scar</td>
<td>10</td>
<td>+/-</td>
<td>–</td>
</tr>
<tr>
<td>Bouillot-Eimer et al(^13)</td>
<td>F</td>
<td>60</td>
<td>ST biopsy</td>
<td>GBM (IV) Subcutaneous occipital region</td>
<td>8</td>
<td>+/- Carmustine</td>
<td>–</td>
</tr>
<tr>
<td>Schultz et al(^14)</td>
<td>F</td>
<td>74</td>
<td>Partial excision</td>
<td>GBM (IV) Left parietal scalp</td>
<td>12</td>
<td>+/-</td>
<td>Stereotactic DTI-015</td>
</tr>
<tr>
<td>Saad et al(^15)</td>
<td>M</td>
<td>13</td>
<td>Subtotal resection</td>
<td>GBM (IV) Scalp through skull defect, spinal leptomeninges</td>
<td>9</td>
<td>+/- Temozolomide</td>
<td>Thalidomide; celecoxib; etoposide</td>
</tr>
<tr>
<td>Mentrikoski et al(^7)</td>
<td>M</td>
<td>41</td>
<td>NS</td>
<td>Anap Olig (III) Adjacent to the craniotomy site</td>
<td>2</td>
<td>+/-</td>
<td>–</td>
</tr>
<tr>
<td>Mentrikoski et al(^7)</td>
<td>F</td>
<td>58</td>
<td>NS</td>
<td>GBM (IV) Adjacent to the craniotomy site</td>
<td>16</td>
<td>+/- Temozolomide</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Miliaras et al(^16)</td>
<td>M</td>
<td>63</td>
<td>GT resection</td>
<td>GBM (IV) Scapular subcutaneous mass</td>
<td>7</td>
<td>+/- Temozolomide</td>
<td>–</td>
</tr>
<tr>
<td>Senetta et al(^17)</td>
<td>F</td>
<td>48</td>
<td>GT resection</td>
<td>GBM (IV) Scapula metastasis close to the surgical scar</td>
<td>NS</td>
<td>+/- Temozolomide</td>
<td>–</td>
</tr>
<tr>
<td>Senetta et al(^17)</td>
<td>F</td>
<td>54</td>
<td>Partial excision</td>
<td>GBM (IV) Scapula, 2 cm away from the surgical scar</td>
<td>NS</td>
<td>+/- Temozolomide</td>
<td>–</td>
</tr>
<tr>
<td>Torres et al(^16)</td>
<td>F</td>
<td>63</td>
<td>GT resection</td>
<td>GBM (IV) Scalp/subcutaneous tissue near the craniotomy scar</td>
<td>6</td>
<td>+/- Temozolomide</td>
<td>Carmustine implants; bevacizumab; irinotecan</td>
</tr>
<tr>
<td>Armstrong et al(^18)</td>
<td>F</td>
<td>30</td>
<td>Partial excision</td>
<td>GBM (IV) Below scalp, several centimeters posterior to the craniotomy scar</td>
<td>NS</td>
<td>+/- Temozolomide</td>
<td>Sorafenib; erlotinib; irinotecan; bevacizumab</td>
</tr>
<tr>
<td>Guo et al(^19)</td>
<td>F</td>
<td>19</td>
<td>NS</td>
<td>GBM (IV) Ipsilateral posterior cervical region</td>
<td>8</td>
<td>+/- Temozolomide</td>
<td>–</td>
</tr>
<tr>
<td>Dawar et al(^27)</td>
<td>F</td>
<td>57</td>
<td>GT resection</td>
<td>GBM (IV) Subcutaneous pre-auricular mass</td>
<td>57</td>
<td>+/- Temozolomide</td>
<td>Mesna; doxorubicin; ifosfamide</td>
</tr>
<tr>
<td>Ginat et al(^20)</td>
<td>M</td>
<td>62</td>
<td>Subtotal resection</td>
<td>GBM (IV) Subcutaneous, adjacent to the craniotomy</td>
<td>10</td>
<td>+/- Temozolomide</td>
<td>Bevacizumab; lomustine; erlotinib</td>
</tr>
<tr>
<td>Forsyth et al(^21)</td>
<td>F</td>
<td>59</td>
<td>NS</td>
<td>GBM (IV) Bone, subdermal over the craniotomy</td>
<td>6</td>
<td>+/- Temozolomide</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Ray et al(^22)</td>
<td>M</td>
<td>29</td>
<td>Subtotal resection</td>
<td>Anap Olig (III) Posterior neck mass</td>
<td>13</td>
<td>+/- Procarbazine; lomustine; vincristine</td>
<td>–</td>
</tr>
<tr>
<td>Ferreira et al()</td>
<td>F</td>
<td>36</td>
<td>GT resection</td>
<td>GBM (IV) Subcutaneous and temporal muscle over the craniotomy site</td>
<td>3</td>
<td>+/- Temozolomide</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: Anap Olig; F, female; GBM, glioblastoma; GT, gross total; M, male; NS, non specified; ST, stereotatic; Su., surgery.

*Time from first surgery to metastasis (months).
levels of circulating tumor cells (CTC) in their blood, which supports their potential for extra-CNS dissemination. Even more relevant, these CTCs were discovered both before and after surgical intervention, thus revealing that the presence of CTCs does not depend on surgical manipulation.

The pathogenic dissemination mechanism most commonly described in previous reports is the seeding of tumor cells after surgical treatment.

Additionally, reported cases of sarcomatous transformation of the tumor allows for successful implantation and growth in a non-neuronal environment. The current case, however, did not show any evidence of sarcomatous features.

In our case, there was an initial misdiagnosis of subdural empyema and soft tissue abscesses over the craniotomy site. This was based on the three-month previous clinical manifestations of our patient, with facial/cranial mass and edema, and also with neuroradiology reports suggesting local infection. Due to this high suspicion of infection, demanding urgent surgery, no MRI was obtained before the surgical procedure. During the second surgery, we removed a lot of necrotic tissue and what seemed to be purulent tissue invading the subcutaneous tissue and temporal muscle. After

Fig. 1 Post-contrast axial CT scan showing a right temporal intra-axial irregular ring contrast-enhanced mass lesion, suggesting a high-grade glioma.

Fig. 2 Post-contrast axial CT scans depicting a recurrence of the previous lesion in the temporal lobe (A), a new right frontal lobe hemorrhagic lesion (B), and an extra-axial antero-inferior frontal lesion with the peripheral enhancing signal extending epicranially trough the craniotomy, suggesting an empyema and small epicranial abscesses (C).
Fig. 3  Post-contrast axial (A), coronal (B) and sagittal (C) MRI showing new right temporal tumor recurrence with direct extension and invasion of the subcutaneous tissue and temporal muscle, through the borders of the craniotomy.

Fig. 4  Photomicrographs (H&E) showing a giant cell glioblastoma with multinuclear cells with a bizarre aspect (A) and soft tissue infiltration by the same tumor (B).
opening the previous cranial flap and the dura, we could see the same kind of tissue continuing to the subdural space and also invading the temporal and frontal lobes.

We were quite convinced by the smell and consistency of the tissue removed that it was most likely an infection, so the collected sample was only sent to microbiological analysis, and no pathological analysis was made in this second procedure.

The microbiology results were negative, and one month later the patient was submitted to a third surgery because of extensive local recurrence with mass effect. Magnetic resonance imaging showed extensive tumor invasion of the subcutaneous tissue and temporal muscle that was linked to the intracranial tumor through the margins of the cranietomy. There was no diffusion restriction of the soft tissue lesions, and they were similar to the intracerebral lesions in all MRI sequences, excluding the possibility of abscesses and thus confirming the presence of extracranial metastases of the known glioblastoma (Fig. 3A-C). Histology confirmed dura, temporal muscle and subcutaneous tissue invasion by the tumor (Fig. 4A,B). The immunohistochemical analysis in our case revealed no MGMT methylation, as well as no IDH 1 mutation, but there was EGFR amplification. This last genetic marker seems to promote the extracranial growth of GBM, and it has been previously associated with circulating GBM tumor cells.28

The same way that MGMT methylation29 and IDH 1/2 mutations30 are known to be associated with long-term survival and better treatment responses, their absence, associated with other specific molecular factors, such as EGFR amplification, as it happened with our patient, may predict the potential for metastatic dissemination. All of these molecular signatures should probably be routinely searched in each patient in the near future, since there is a higher chance for tumor metastases with prolonged survival.

Our case illustrates the rare occurrence of soft tissue dissemination in a patient submitted to surgery for a glioblastoma. As most of the previous reported cases, the most likely mechanism of dissemination points to a migration of the glioblastoma tumor cells trough the durotomy incision and the cranietomy, spreading into to the temporal muscle and subcutaneous tissue. The similar tumoral aspect of the dura and soft tissue over the cranietomy site also supports the previous described theories of possible mesenchymal differentiation of the tumor when in contact with other tissues.

Thus, greater awareness of the potential for GBM metastases can contribute to the development of surgical protocols to minimize seeding, namely watertight dural closing, calvarial reconstruction, or altering instruments between the intradural and extradural parts of the surgical procedure.31

Furthermore, an important lesson learned is that one should consider the possibility of extracranial metastases of these tumors in the differential diagnosis of the more common surgical complications of wound infection, abscesses and subdural empyema. For this matter, an MRI exam is better than the contrast-enhanced CT scan, and should be obtained before proceeding with the surgical intervention.

Conclusions

Soft tissue dissemination in GBM is rare, and seems to be associated with younger ages and even more aggressive tumoral lesions.

The possibility of GBM soft tissue metastases should always be considered in the differential diagnosis of a possible post-surgical infection, and an MRI exam is mandatory to help with diagnosis.

The pathogenesis of GBM soft tissue metastases, the best treatment to offer to these patients and possible preventive surgical measures to avoid this complication are issues to consider for further investigation.

Disclosure

The authors have no conflicts of interest to declare. The patient's family has consented to the submission of the case report to the journal.

References

Subcutaneous Dissemination in Glioblastoma  Ribeiro da Cunha et al. 53

31 Allan RS. Scalp metastasis from glioblastoma. J Neurol Neurosurg Psychiatry 2004;75(4):559