Metastatic Glioblastoma: A Case Report and Review of the Literature

William T. Harrison, Christine M. Hulette, Cynthia Guy, Thomas Sporn and Thomas Cummings
Duke University Medical Center, Department of Pathology, USA

Abstract

Glioblastoma, the most common and aggressive primary glial tumor, has a median survival time of approximately 3 months without medical treatment. Surgical resection, radiotherapy, and chemotherapy are the main methods of treatment and have been shown to increase life expectancy 1 to 2 years. The tumor has an infiltrative growth pattern that distorts the normal anatomy and can extend to distant parts of the brain along white matter tracts. While glioblastoma commonly infiltrates surrounding brain tissue and intracranial metastases to the meninges and spinal cord are frequently reported, extra-cranial metastases are extremely rare. This is most probably due to the lack of lymphatic vessels in the brain and inability of the malignant cells to invade blood vessels. We present a case of a 56-year-old female with a history of right temporal glioblastoma, who was found to have biopsy proven metastases to the lung. The patient presented for a chest x-ray, as part of a requirement for a clinical trial, and was found to have bilateral lung nodules; a subsequent chest computed tomography (CT) scan showed numerous pulmonary nodules and low density lesions in the liver. The patient underwent right thoracoscopic wedge resection. Frozen section and permanent sections were diagnostic of metastatic glioblastoma.

Introduction

Glioblastoma is the most aggressive primary brain neoplasm. Despite surgical resection, chemotherapy, and radiation, local recurrence occurs with high frequency [1]. This is, in part, due to the infiltrative growth pattern of the tumor, which often obviates any chance for complete surgical resection. While usually centered in the white matter of the cerebral hemispheres, infiltrating tumor cells frequently are present in an adjacent lobe or the opposite hemisphere as the tumor extends along the white matter tracts of the centrum semiovale, corpus callosum, and internal capsule [2,3].

A diagnosis of glioblastoma requires histological examination of the tumor [4]. Hallmark features include hypercellularity, nuclear pleomorphism, microvascular proliferation and intravascular thrombosis [5]. Necrosis is usually present, often with tumor cells clustering around necrotic foci, in a pseudopalisading pattern. Glioblastoma cells are immunopositive for glial fibrillary acid protein (GFAP). An immunohistochemical stain for Ki-67 (Mib-1) often shows an elevated (>10%) proliferation-related labeling index [5].

While direct extension and local recurrence of glioblastoma are typical, metastases outside of the CNS are exceedingly rare with a reported rate of less than 2% [6]. In almost all cases of reported metastatic glioblastoma, patients had undergone surgical resection, which suggests that iatrogenic seeding of the tumor cells could have occurred after there was potential local intravascular exposure of the tumor cells. Herein, we present a case of a 56-year-old woman who underwent resection of a right temporal glioblastoma. Fifteen months after resection, she was found to have bilateral pulmonary nodules, which were histologically proven to be glioblastoma metastases.

Case Report

A 56-year-old woman began to have increased migraine headaches. They became constant and were localized to the right temporal, parietal and vertex regions. Three months later she had progressive headaches, fatigue, irritability, anxiety and cognitive issues. She also had an episode where she could not find her way home or to work. A magnetic resonance image (MRI) scan of the brain was performed and showed a large cystic enhancing right temporal lobe lesion (Figure 1A).

Figure 1: A) T1 weighted MRI image with contrast demonstrating a right temporal enhancing mass. B) H&E stained sections of the patient's original brain biopsy demonstrating a high grade glioma (100X). C) Glial fibrillary acid protein (GFAP) staining of the brain tumor (400X). D) Ki-67 (Mib-1) labeling index of the brain tumor (100X).

She underwent craniotomy and resection and her pathology showed the lesion to be a classical glioblastoma, large cell variant (Figure 1B),
with a Ki-67 labeling index of 20% (Figure 1D). The tumor cells were immunopositive for glial fibrillary acid protein (GFAP) (Figure 1C).

She was then enrolled in a clinical trial at an outside institution for treatment. The clinical trial investigated whether the therapeutic regimen of paclitaxel poliglumex (PPX) and radiation improved progression-free survival when compared to standard therapy with temozolomide and radiation. Follow-up MRI four months later showed a right to left midline shift, an increase in size of the mass, and uncal herniation. Clinically, she developed left sided hemiparesis and homonymous hemianopsia. She was then treated with temozolomide and bevacizumab and completed 8 cycles of chemotherapy. After completion of this therapy she was then enrolled in another clinical trial. One of the primary objectives of this trial was to determine the maximum tolerated dose of CTO (carboxamidotriazole orotate) when combined with standard dosing of bevacizumab among patients with recurrent malignant glioma (WHO grade 3 or 4) that have previously failed bevacizumab. As part of the initial workup for the trial, she received a chest x-ray which showed small nodular opacities in the bilateral lungs. A follow up CT scan demonstrated numerous pulmonary nodules and low density lesions were visualized in the liver (Figures 2A and 2B). She underwent a right lung wedge resection and a diagnosis of metastatic glioblastoma was confirmed. The tumor cells were immunopositive for GFAP and were negative for cytokeratin, supporting this diagnosis (Figures 3A and 3B).

Within a few months, there was intracerebral, pulmonary, and hepatic disease progression. After continued systemic chemotherapy the patient died approximately 23 months after the initial cranial glioblastoma surgery. Permission for autopsy was declined by the next of kin.

### Figure 2
A) Computed tomography (CT) imaging demonstrating a subpleural nodule later biopsied to show metastatic glioblastoma. B) Computed tomography (CT) image showing a hypodense liver lesion.

### Figure 3
A) H&E stained section of the pleural nodule demonstrating pseudopalisading necrosis (100X). B) Glial fibrillary acid protein (GFAP) stained section of the nodule (400X).

### Discussion
Extra-cranial metastases of glioblastoma are rare with a reported incidence of less than 2% [6,7]. Metastases occur most often in the lungs and pleura (found in 60% of patients with metastatic glioblastoma) but also in the regional lymph nodes (51%), bones (31%), and liver (22%) [6]. In most instances multiple organs are found to be involved. There are several reasons that account for the rarity of such extracranial spread; the brain does not have lymphatic vessels, which along with the presence of the blood-brain barrier, greatly reduces the potential for distant tumor spread. Also, the cerebral sinuses are lined by dense dura mater, which makes penetration and subsequent venous spread by tumor cells difficult [6,7]. Additionally, glioma cells have a poor affinity for arterial walls, which makes direct vascular invasion more difficult, and there is no direct connection between the subarachnoid space and the systemic circulation [7].
There is a virtual lack of collagen and fibronectin within the central nervous system and, in general, glioma cells do not express fibronectin \[8,9\]. This lack of fibronectin expression is thought to inhibit vascular endothelial invasion and subsequent extracranial seeding. Furthermore, most patients who develop glioblastoma have a median survival time of 14.6 months \[6\], and the rapid lethality of glioblastoma decreases the likelihood that individuals would have time to develop clinically detectable distant metastases \[3,6\].

Most documented cases of metastatic glioblastoma have been reported in patients who had either a stereotactic biopsy or open craniotomy. This suggests that iatrogenic exposure of glioblastoma cells to extra-cerebral tissue via defects in meningeal and parenchymal blood vessels from surgical interventions accounts for most reported cases of extracranial spread \[7\]. Additionally, in other incidences of metastatic glioblastoma, patients had therapeutic shunts made connecting the cerebrospinal fluid (CSF) to either the peritoneum or pleura. The presence of a direct shunt offers a mechanical explanation for metastases in these cases. Distant metastases of medulloblastomas and glioblastomas have been reported in multiple instances in patients with ventriculoperitoneal shunts \[10,11\].

There have been reported cases of individuals with glioblastoma with no history of cranial surgery or shunt placement that developed extra-cranial metastases. A 1970 review by Anzil showed that there was no documented surgical intervention in more than 10% of patients with metastatic glioblastoma \[12\]. In these cases, the mechanism of extra-cranial spread is not fully understood. Malignant glioblastoma cells may directly invade the thin-walled CNS venules \[7\]. These venules are not as large and dense as the dural sinuses and may be more susceptible to invasion by tumor cells \[13\]. Additionally, it is well known that one of the defining features of glioblastomas is microvascular proliferation, which may represent microscopic alterations in the normal blood-brain barrier and provide direct access to systemic circulation \[7\].

Muller et al suggested that glioblastoma cells may circulate in the peripheral blood more frequently than the reported incidence of extracranial metastases implies. They analyzed the peripheral blood for glioblastoma cells by immunohistochemical staining for GFAP in 141 patients with glioblastoma. Circulating tumor cells (CTCs) were found in 29 of the patients. Interestingly enough, they did not observe significantly different rates and counts of glioblastoma cells before, during, or after tumor resection; however, all patients in the study carried a histologically proven diagnosis of glioblastoma before any peripheral blood samples were analyzed, meaning that all participants in the study had already had a diagnostic biopsy. Additionally, they observed an association with the release of CTCs and amplification of epidermal growth factor receptor (EGFR), suggesting that EGFR signaling may support the extracranial spread of glioblastoma cells \[14\]. However, this not fully understood at this time.

The potential of extra-cranial metastases may be low, but it should be recognized as a potential risk in organ transplantation. Historically, patients who died with a primary central nervous system neoplasm were considered to be potentially good solid organ donors as it was generally accepted that gliomas do not spread outside the CNS \[15\]. Summaries of tumor registry reports by Penn and Buell suggested that organs from individuals with a central nervous neoplasm need not be categorically rejected and may be used in recipients with a short-life expectancy \[16,17\]. However, the development of extracranial glioblastoma foci in transplanted lungs, kidneys, and livers from previously treated donors have been documented \[18-21\]. In many of these reported cases the recipients developed widely metastatic disease and died. The malignancy subcommittee of the disease transmission advisory committee (DTAC) for the United Network for Organ Sharing (UNOS) suggested that low grade (WHO grade I and II) CNS neoplasms may have relatively low transmission rates and organs from such donors may be acceptable and usable in recipients at significant risk without transplant \[15\]. However, higher grade (WHO III and IV) primary CNS neoplasms, including glioblastoma, as well as any CNS tumor from individuals who had any kind of percutaneous, peritoneal, or pleural metastases of a glioblastoma multiforme to the pleura, small bowel and pancreas. J Clin Neurosci 13: 677-681.

Conclusion

A patient with glioblastoma of the brain was found to have pulmonary and hepatic nodules and the rare occurrence of histological confirmation of extra-cranial metastases to the lung is reported. While the mechanism of metastasis is not fully understood, a review of the literature suggests that iatrogenic seeding of tumor cells following surgical intervention may account for the vast majority of instances. As the life expectancy is gradually increasing for patients with newer therapies for glioblastoma, the incidence of extracranial metastases may increase and this rare phenomenon may become more common and clinically relevant.

Conflicts of Interest

All authors agree there are no conflicts of interest to disclose.

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