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Clinical Study

Bone marrow metastases from glioblastoma multiforme – A case report and review of the literature

Vandana Rajagopalan[1], Francois G. El Kamar[2], Rose Thayaparan[3] and Michael L. Grossbard[1,4]
[1]*Hematology–Oncology Unit, St. Luke's–Roosevelt Hospital Center, New York, USA;* [2]*Division of Neuro-Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA;* [3]*Department of Pathology, St. Luke's–Roosevelt Hospital Center, New York, USA;* [4]*Hematology–Oncology Unit, Beth Israel Medical Center, New York, USA*

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Summary

Clinically detected extra-cranial metastases from glioblastoma multiforme (GBM) are quite rare, with an incidence of <2% reported in the published literature. Among the various reported sites of systemic metastases from GBM, there are few cases of clinically symptomatic bone marrow metastasis. The case of a patient developing systemic dissemination of a GBM is described. A 60-year-old man with GBM who developed back pain, thrombocytopenia and subsequently neurological deficits was found to have extensive bony and bone marrow metastases. Previously reported cases of extra-cranial systemic spread of GBM and attempts made in the literature to explain the possible routes of extra-neural dissemination are reviewed.

Introduction

In 2004, there will be an estimated 18,400 new diagnoses of malignant brain tumor in the United States, accounting for approximately 12,690 deaths [1]. Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults. Despite advances in surgical and radiation techniques, the prognosis of GBM remains dismal, the median survival ranging from 40 to 70 weeks [2]. Clinically detected extra-cranial metastases from GBM are rare occurring in 0.2–2% patients reported in available literature [3]. We present a case of a 60-year-old man with GBM who developed extensive bony and bone marrow metastases with back pain, cytopenias and subsequent neurological deficits.

Case report

A 60-year-old right handed white male presented in November 2002 with a 1 month history of worsening headaches, and rapidly progressing left hemiparesis. A brain MRI with gadolinium revealed a 5 cm right parietotemporal hypodense lesion surrounded by vasogenic edema (Figure 1). In December 2002 he underwent a right temporal craniotomy and a sub-total resection. The pathologic diagnosis was GBM (Figure 2). A post-operative MRI of the brain showed a rim of residual enhancement in the resection cavity consistent with residual tumor. His headaches resolved but he had persistent mild left arm weakness.

In January 2003, he was treated with one cycle of high dose Irinotecan (375 mg/m^2 weekly 2 weeks on 1 week off for 6 weeks) and Celecoxib (200 mg orally twice a day for 6 weeks) as part of a phase II protocol for GBM. A follow-up MRI revealed progressive disease. Temozolomide (150 mg/m^2 × 5 days) was started and radiation therapy with a 3D conformal approach was planned. A dramatic clinical and radiological worsening led to a re-resection of his recurrent disease in March 2003. Post-operative chemoradiotherapy with BCNU (200 mg/m^2 day 1 q8wks) and 60 Gy limited field external beam radiation (XRT) was completed in May 2003. He was continued on BCNU.

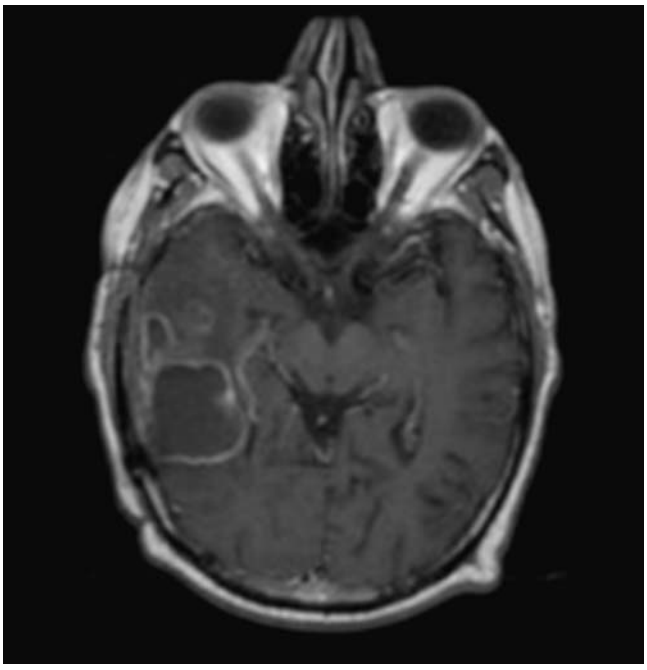

Figure 1. Contrast enhanced axial MRI scan of the brain showing the GBM.

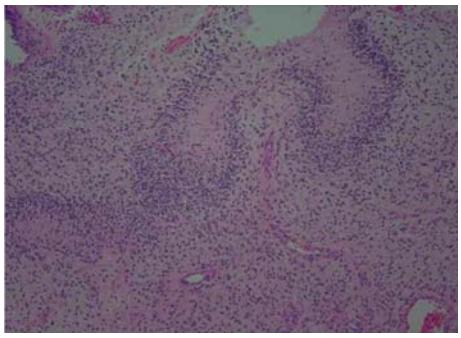

Figure 2. Hematoxylin and Eosin stain from the original brain tumor resection specimen showing palisading necrosis typical of GBM.

In July 2003 he presented with 2 weeks of rapidly worsening low back pain. A contrast enhanced MRI scan of his lumbo-sacral spine showed a heterogenous marrow signal in the lumbar vertebrae with an L4 epidural soft tissue mass mildly effacing the thecal sac. (Figure 3a and b). Laboratory values were significant for 20,000 platelets per microliter (normal range: 150–400 K/μl), and a hemoglobin (Hb) level of 8.0 g/dl (normal range: 13.5–17.5 g/dl). A Fluoroscopy guided bone biopsy from the lesion seen at the L4 level of the spine done on July 28th revealed metastatic GBM in the bone marrow (Figure 4). Immunohistochemical studies for glial fibrillary acidic protein (GFAP) were positive (Figure 5). He rapidly worsened thereafter and developed bilateral lower extremity paresis with bladder/bowel incontinence despite palliative radiotherapy to the lumbo-sacral spine. He expired in August 2004.

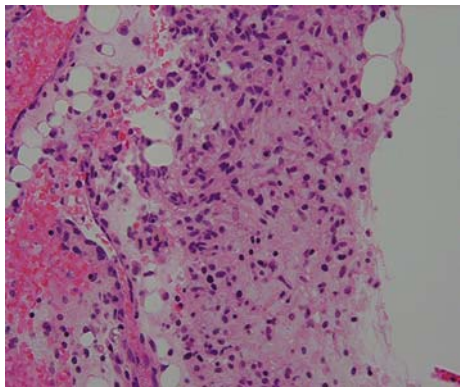

Figure 4. Hematoxylin and Eosin stains from the L4 vertebra biopsy showing the involvement of the bone marrow by GBM cells.

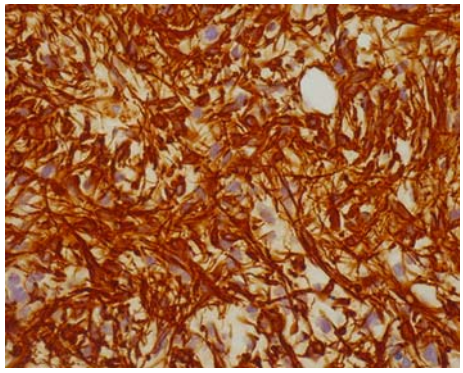

Figure 5. Glial fibrillary acidic protein (GFAP) stain of the bone marrow biopsy showing diffuse positivity.

Discussion

Extra-cranial metastases from GBM occur rarely with an incidence of 0.2–1.2% in the reported literature [3–5]. They are usually asymptomatic and found only at autopsy [6]. Smith et al. [7] reported 23 cases of extra-neural metastatic GBM in 8000 cases of CNS neuro-ectodermal tumors.

The sites of metastasis in decreasing order of frequencies are the pleura and lungs, lymph nodes, bones and liver. The most common sites of bone metastases are the vertebral spine and the thoracic cage [8,9] (Table 1).

Leptomeningeal spread from GBM is more common than extra-neuraxial spread [10], occurring in 15–25% cases of supratentorial GBM [11, 12] and up to 60% in infra-tentorial GBM [13]. The most common sites of spinal metastasis are involvement of the nerve roots, the cauda equina, nerve root sleeves, and the fundus of the thecal sac [14]. There are very few cases of spinal cord involvement with neurological deficits secondary to vertebral body metastases with epidural extension as in our case [7,15].

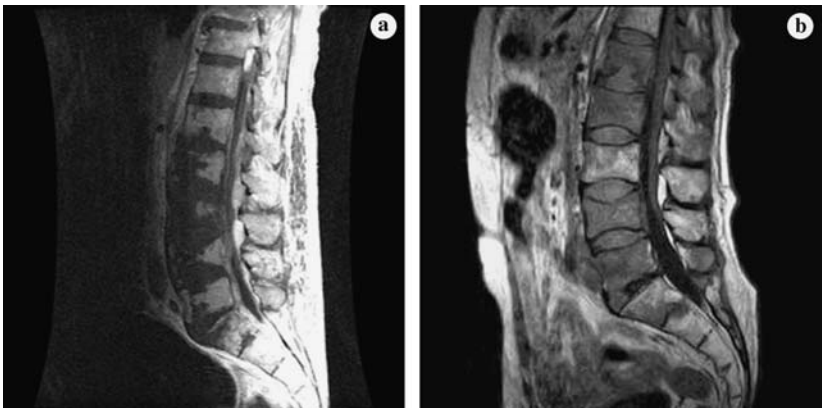

Figure 3. (a, b) T1 and T2 sequences of a sagital MRI scan of the LS spine, showing the tumor involvement of the bone marrow.

Table 1. Reported frequencies of metastatic involvement by organ in GBM Based on 72 cases of extraneural metastases from Pasquier et al. [8]

Metastatic site	Frequency (%)
Lung/pleura	60
Lymph nodes	51
Bone	31
Vertebral Spine	73
Ribs	23
Sternum	18
Skull	14
Acetabulum	9
Liver	22

Only 19 cases of bone marrow metastases from gliomas have been reported, 13 due to GBM [3,9, 16–24]. The age group involved ranges from 11 to 60 years. The median time of presentation of the metastasis was 4–12 months after diagnosis of the intracranial GBM. One patient had bone marrow metastases at the time of diagnosis of the brain tumor [23]. The prognosis after detection of bone marrow metastasis has been uniformly poor. The presentation in most cases was with back pain and cytopenias as in our case (Table 2).

GBM cells are believed capable of migration and metastasis because of their high levels of proteases such as urokinase type plasminogen activator and lower levels of their inhibitors [25]. Transmission of glioblastoma through allogeneic organ transplants also seems to validate the idea that GBM can spread to distant organs [26–28]. Although GBM lesions rarely have an intact blood brain barrier (BBB), only 12 cases of extra-cranial spread without any prior surgical intervention have been reported [4,29]. This suggests that the relative integrity of the BBB is critical in limiting extra-cranial metastases [23,30–38]. In addition to prior surgery, peritoneal metastases may follow ventriculo-peritoneal (VP) shunts [39] and a few reports describe transmission after stereotactic biopsies [40]. Thus, invasive procedures may release tumor cells into blood or CSF [39–40]. The proposed pathways of extra-cranial spread of a GBM are via venous invasion through lepto-meningeal sinuses or intra-cerebral veins; direct invasion through the dura mater and bone; and cellular migration via ventricular drainage tubes [41,42].

It has been proposed in 1976 that the short survival of patients with GBM accounts for the low incidence of clinically detected symptomatic extra-cranial metastases [43]. The incidence of metastatic GBM reported in earlier autopsy series was much higher (4–20%) [6] suggesting that the true incidence of metastases is significantly higher than those that are clinically apparent. The relative increase in the frequency of reported symptomatic extra-cranial metastases from GBM in the recent years (14 cases from 1992 to 1999 as against just 22 cases from 1955 to 1992) [44] may be the result of improved survival, a higher index of suspicion and better diagnostic tools.

Both MRI with gadolinium imaging as well as technetium-99m sestamibi SPECT imaging are sensitive in detecting extra-cranial especially bony/bone marrow metastases in GBM [1,43,45]. Histopathologic confirmation of any extra-neural metastasis is necessary due to its relative rarity. Immunohistochemical staining with GFAP is a sensitive and specific marker for glial-derived tumors and is useful in confirming the glial origin of extracranial metastases [46]. Tissue samples too small in size or markedly anaplastic tumors may result in a false-negative result [47].

Symptomatic extracranial metastases from GBM are not as rare as previously believed. With improving diagnostic tools and improved survival of these patients due to improvements in surgical and radiation therapy techniques with a better integration of chemotherapy and targeted therapies, we may witness an increase in the incidence of symptomatic systemic metastasis from

Table 2. Bone marrow metastasis from GBM in literature

Reference	Year	Age (years)	Back pain	Cytopenia	Prior Sx-resection	Biopsy-proven metastasis	Survival from diagnosis
Terheggen [16]	1977	12	+	Anemia	+	No	4 months
Mousavi [17]	1980	55	No	Pancytopenia	+	Yes	5 months
Yung [18]	1983	24	+	Thrombocytopenia	Subtotal	Yes	2 months
Yung [18]	1983	57	+	Thrombocytopenia	Subtotal	Yes	Shortly after
Newman [19]	1984	40	+	Pancytopenia	Biopsy	Yes	NR
Pasquier [20]	1986	55	+	Pancytopenia	No	Yes	3 months
Friedman [21]	1987	52	No	Anemia, thrombocytopenia	Subtotal	No	3 months
LoRusso [9]	1988	41	No	Anemia, thrombocytopenia	+	Yes	7 months
Haddon [22]	1989	31	+	None	Subtotal	Yes	3 weeks
Gamis [23]	1990	11	+	None	Shunt	Yes	2 months
Kleinschmidt-Demasters [24]	1996	58	+	Thrombocytopenia	Subtotal	Yes	2 months
Kleinschmidt-Demasters [24]	1996	60	+	Thrombocytopenia	+	Yes	2 weeks
Hsu [3]	1998	13	+	Pancytopenia	+	Yes	10 months
Present	2004	60	+	Anemia, thrombocytopenia	Subtotal	Yes	1 month

this disease. Patients with GBM presenting with back pain, anemia and/or thrombocytopenia, should be evaluated for extra-cranial dissemination [48].

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Address for offprints: Michael Grossbard, MD, St. Luke's–Roosevelt Hospital Center, 1000 10th Avenue Suite 11G, New York, NY 10019, USA; Tel.: +1-212523-5419; Fax: +1-212-523-2004; E-mail: mgrossbard@chpnet.org