TOPIC REVIEW

Metastatic glioblastoma: case presentations and a review of the literature

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Abstract Extracranial metastases from glioblastoma
(GBM) are uncommon with an estimated incidence of less
than 2%. We report two cases of metastatic GBM seen
within an 8-week period followed by a literature review.
We attempted to identify common factors or a causative
mechanism. Factors that predominated among the reviewed
cases included male gender, tumor location, and younger
age. Causative mechanisms were not apparent. While
metastatic disease remains rare, it might be occurring with
increasing frequency. This trend might be due to increased
diagnosis, better imaging, a more extensive physician
workup, or an increase in survival. Metastatic GBM can
present and progress quite rapidly, and repeat evaluations
of persistent or worsening complaints among GBM patients
are warranted. Early diagnosis of metastatic disease spread
can help to expedite alleviation of patients' discomfort, in
an already aggressive disease process.

Keywords GBM · Metastases · Extracranial

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Introduction

Extracranial metastases from glioblastoma (GBM) are
uncommon with an estimated incidence of less than 2%
[1]. Case reports and small series bespeak the rarity of this
complication, none of which have reported the identifiable
mode for metastatic spread. Most malignant tumors have a
propensity for metastases; this rarity is curious for GBM. It
might be related to short survivals for GBM patients, issues
intrinsic to the central nervous system (CNS) such as the
blood brain barrier (BBB) or the lack of lymphatics. We
report two cases of metastatic GBM seen within an 8-week
period followed by review of literature in attempt to
identify common factors, high-risk patients or a causative
mechanism.

Case 1

A 72 year-old man with a history of hyperlipidemia and
sleep apnea presented after 1 week of left sided weakness,
dysarthria, and personality changes. His exam was normal
except for a left facial droop with a left upgoing toe. CT
and MRI revealed right temporal and right temporal/
occipital enhancing mass lesions. A gross total resection of
both masses was performed; pathology was consistent with
GBM. He was treated with radiation therapy (RT) and
temozolomide. Eight months later, he developed focal
seizures and repeat MRI showed tumor progression. He
was started on bevacizumab and follow-up MRI showed
improvement in tumor enhancement. However, the patient
progressively developed worsening behavioral and cogni-
tive changes, so carmustine was added to the bevacizumab.
Two months later he began to complain of rib/chest, hip
and back pain requiring admission for work up. Chest

imaging revealed no evidence for pulmonary embolism, but instead destructive osseous lesions with a soft tissue component invading the spinal canal and pulmonary nodules suspicious for metastatic lesions. MRI of his spine revealed multifocal bony lesions to cervical, thoracic, and lumbar spine with some extension into midline paraspinal muscles. Fine needle biopsy of the paraspinal mass revealed pathology similar to his primary GBM (positive for glial fibrillary acidic protein (GFAP)). The patient was transferred to hospice, dying 19 months after his initial diagnosis and about 9 months after his diagnosis of metastasis.

Case 2

A 31 year-old woman with no significant past medical history presented after 2 weeks of headache and 1 week of nausea/vomiting and gait ataxia. On exam she had left facial droop, upward gaze palsy and left greater than right limb ataxia. MRI revealed heterogeneously enhancing mass in the left cerebellum and vermis with obstructive hydrocephalus. MRI of spine was unremarkable with no evidence of leptomeningeal spread. Ventriculostomy was placed and subsequent gross total tumor resection was done; the ventriculostomy was removed after surgery. Pathology was read as GBM. She was started on RT and temozolomide after which she was treated with erlotinib/bevacizumab. Four months after her initial diagnosis, her MRI brain showed progression of the cerebellar lesion and she began experiencing low back pain. MRI of the spine was performed to evaluate for leptomeningeal dissemination, but revealed extensive osseous disease in the cervical, thoracic, lumbar, and sacral spine. She underwent a CT chest/abdomen/pelvis that had no other signs for metastatic disease except for a breast lesion that was biopsied and found to be benign. Biopsy of an osseous lesion was histologically similar to the cerebellar GBM pathology (GFAP positive). She was treated with palliative RT to the spine followed by temozolomide and bevacizumab. Six months after initial diagnosis, she had a bone scan that revealed diffuse progression of her bony disease. The patient died 9 months after her initial diagnosis and 5 months after diagnosis of metastasis.

Materials and methods

We searched PubMed for reports of extracranial metastatic GBM that was confirmed by biopsy or autopsy. Search terms used were extracranial GBM, extraneural GBM, and metastatic GBM. We only used reports from 1960 to 2010 and excluded cases with patients less than 18 years of age

or non-English reports. Data collected was as follows: age, gender, location of primary GBM, treatment of initial GBM, local recurrence of initial GBM, location of metastatic disease, time to diagnose metastatic disease, treatment of metastasis, survival from time of diagnosis of metastatic disease, and overall survival (OS).

Results

Seventy-nine cases were found that met our criteria (Table 1) [1–45]. Forty percent (32 patients) of these cases were reported between 1960 and 1980. The median age was 42 (range 18–74). Eighty-five percent of the patients were less than 60 years of age and seventy-seven percent of the patients were men.

We divided initial tumor location into left or right hemisphere and lobe(s) of involvement. Fifty-five percent of patients had right hemisphere involvement compared to 45% on the left. The two most common sites of primary GBM location were right temporal lobe (32%) and left frontal lobe (20%) followed by right parietal lobe, left temporal and right frontal lobe in 14% each.

Forty-four percent of the patients had local tumor recurrence at some point in the course of the disease; of these, 55% had local tumor recurrence prior to the diagnosis of metastatic disease. The median time to diagnosis of metastatic disease was 9.5 months. The diagnosis of metastatic disease was made at autopsy in 6% of the cases.

Organs with metastatic disease included bone, bone marrow, lymph nodes, eyes, lungs, spleen, liver, parotid gland, adrenal gland, subcutaneous tissue, skin, heart, pancreas, diaphragm, kidney, stomach, pelvis, and thyroid. The four most common organs were bone (38%), lymph nodes (37%), lungs (32%), and liver (18%). Most patients had one (62%) or two (28%) organs affected by metastases, then there was a drop-off with three to four metastatic sites (6%) and more than four sites (4%).

The median OS time for patients with metastatic GBM was 13 months (Table 2). Median survival based on the number of organ systems involved was: 14 months for one system, 11 months for two, 14 months for 3–4 and 17 months for >4 systems. The median survival time for patients from the time of their diagnosis of metastatic disease was 5 months (Table 3). In patients with metastasis to one site the median OS from the time of diagnosis of the metastasis was 6 months. It was 5 months for patients with sites or 3–4 sites and 1 month if >4 sites.

Wilcoxon rank-sums were used to evaluate for the effect of GBM treatment type on OS. Total resection compared to subtotal resection of GBM did not significantly affect OS in those with metastatic disease ($P = 0.17$). RT alone or

Table 1 Reported cases of Metastatic GBM

Case no.	Reference	Age	Sex	Location primary	Location met
1	[2]	48	M	R temporoparietal	Bone
2	[3]	27	F	R frontal	Lymph node
3	[4]	29	M	L frontal	Lymph node, bone
4	[5]	39	M	R parietal	Lymph node
5	[6]	41	M	R frontal	Lymph node, eye
6	[7]	51	M	L frontal	Lung
7	[8]	54	M	R temporal	Bone
8	[9]	47	F	R temporooccipital	Spleen, lung
9	[10]	42	M	R temporal	Bone
10	[11]	30	M	R temporal	Bone
11	[12]	25	M	R frontoparietal	Lung
12	[13]	33	M	L frontal	Parotid gland
13	[14]	60	M	R temporoparietal	Bone
14	[15]	74	M	R temporooccipital	Bone, spleen, LN, lung
15	[16]	25	M	R frontoparietal	Lymph node, bone
16	[17]	58	F	L frontal	Skin
17	[18]	58	M	R temporal	R parotid, R orbit; at autopsy: lung, lymph node, bone, liver, heart
18	[19]	39	M	L frontal	Pancreas
19	[20]	66	M	R frontal	Lung
20		74	F	R temporal	Liver
21		67	F	L frontal	Bone
22		72	M	R occipital	Lung
23		63	M	R temporal	Lung
24		70	F	R frontal	Lymph node
25		69	M	R temporal	Lung
26	[21]	31	M	R occipital	Bone
27	[22]	40	M	R temporoparietal	Neck
28	[23]	58	M	L frontal	Bone
29		60	M	L temporal	Bone
30	[24]	31	M	L hemisphere	Bone
31		31	M	R frontotemporal	Neck, bone
32		27	M	R temporal	Lung
33		25	F	R frontoparietal	Skin, parotid
34		60	M	L frontal	Bone
35	[25]	57	M	L temporooccipital	Bone marrow, bone
36		24	F	R frontal	Bone marrow
37	[26]	22	F	L occipital	Subcutaneous tissue, lungs, lymph nodes, bone marrow, liver
38	[27]	47	M	L parietooccipital	lymph nodes
39	[28]	52	M	L frontoparietal	Lung, lymph node
40		38	M	L hemisphere	Lymph node
41		24	M	R parietal	Lung
42		43	M	R temporal	Liver
43		45	M	R temporal	Liver
44		58	M	L temporal	Liver
45		29	M	L temporal	Lung, lymph node
46		22	M	R parietal	Lung, lymph node
47		55	M	R temporal	Bone
48		54	M	R, L frontal	Lung

Table 1 continued

Case no.	Reference	Age	Sex	Location primary	Location met
49		45	M	L occipital	Lymph node
50		36	M	L frontal	Bone
51		63	M	R temporal	Adrenal, lung
52		49	M	R temporal	Liver
53		49	M	R frontal	Liver, pancreas, lymph node, bone
54		42	M	L temporal	Lungs, lymph node
55		63	F	L frontal	Lungs, bone
56		42	M	L parietal	Lymph node
57		38	M	L parietal	Lung, lymph node
58		36	F		Bone, lymph node
59		64	M	R temporal	Liver, lung
60		36	M	L temporal	Bone
61	[29]	54	F	L frontoparietotemporal	Liver, bone
62	[30]	35	F	L frontal	Lymph node
63	[31]	28	M	L temporal	Orbit
64		22	M	R temporooccipital	Lymph node
65	[32]	40	M	R temporooccipital	Lung, lymph node, bone
66	[33]	31	M	L frontal	Bone
67	[34]	22	M	L thalamus	Lungs, pleura, pericardium, diaphragm
68	[35]	63	M	R temporoparietal	Lung, lymph node, bone
69	[36]	21	F	L temporal	Lymph node, liver
70	[37]	42	M	R temporal	Bone
71	[1]	40	M	L frontal	Parotid gland
72	[38]	58	M	R temporal	Liver, spleen
73	[39]	42	M	L temporal	Subcutaneous tissue, LN, bone, kidney, pancreas, liver, lung, epicardium
74	[40]	21	M	R parietal	Lymph nodes, lung
75	[41]	18	F	Frontal	Omentum, stomach, abd wall, pelvis
76	[42]	35	F	R parietal	Lymph nodes
77	[43]	33	F	L frontoparietal	Bone
78	[44]	55	F	L temporoparietal	Bone marrow, liver
79	[45]	18	M	R parietal	Lung, thyroid, LN

Table 2 Effect of number of organ systems with metastasis on OS (months)

Number or systems with metastases	N	Median
1	45	14.00
2	18	10.50
3–4	5	14.00
>4	3	17.00

Table 3 Effect of number of organ systems with metastasis on survival from time of metastasis diagnosis (months)

Number or systems with metastases	N	Median
1	30	6.00
2	5	5.00
3–4	2	5.00
>4	2	1.25

RT with resection did not affect OS ($P = 0.73$ and $P = 0.26$, respectively). However, chemotherapy, either alone or given with RT and resection, was associated with an increase in median OS compared to those who did not receive chemotherapy. The median OS in patients who were treated with chemotherapy alone was approximately 22 months compared to 11 months in those who did not ($P = 0.02$). The median OS in those who underwent resection, had RT and chemotherapy was 24 months compared to 14 months in those who did not have all three forms of treatment ($P = 0.03$).

Wilcoxon rank-sums were again used to assess how GBM treatment affected time to diagnosis of metastatic disease. Neither resection alone nor RT alone significantly prolonged the time to diagnosis of metastatic disease. Chemotherapy did show a statistically significantly longer time to metastatic GBM diagnosis (15 months) compared to those who received no chemotherapy (12 months) ($P = 0.049$). This significance decreased in the presence of resection, RT, or both resection and RT.

Discussion

There has been an increase in the number of reported cases of metastatic GBM in the literature in the time period we reviewed. In 1969, it was reported that 0.44% of patient developed extracranial metastatic GBM [28]; more recently it is thought that the frequency may be as high as 2% [20]. From our literature review, the majority of patients with metastatic GBM were reported after 1980. This trend might be due to increased diagnosis, better imaging, a more extensive physician workup, or an increase in survival. We restricted our review to GBM, but reports of metastases from other gliomas exist [46] and would increase the number of cases reported.

Why the incidence of extracranial metastases is low remains unclear given the aggressive nature of GBM. However, it occurs but who is at risk and why remains unknown. Using our criteria 79 cases were identified over a 50 years period. Given that in the U.S. alone there are 10,000–12,000 cases of GBM per year, the incidence of metastatic GBM is almost certainly far below the reported 2%. The goal of this review was to better assess the common factors among those patients who develop metastatic disease. We are unable to define risk factors for the development of metastatic disease as the number of cases known is only what has been published and this may be an underestimate of cases; we would also need to know all the patients with GBM diagnosed in a given time period to determine "true" risk factors and also incidence.

The median time to diagnosis of metastatic disease was about 10 months. Perhaps the increasing survival times of GBM patients in modern times allows for the development of metastatic disease, explaining the increasing frequency of reported cases in more recent decades; although we would expect even higher numbers. Six percent of the cases reviewed were diagnosed at autopsy, which might have been documented pre-mortem with better diagnostic tools and clinical awareness.

The two most widely accepted modes of spread are hematogenous and lymphatic [16]; in some cases direct extension of tumor is the cause. Hematogenous seeding may occur during surgery or if there is vascular invasion from the tumor. Using the former hypotheses, it would be expected that the greater the resection the more likely the risk but three reported cases had only a biopsy, suggesting vascular invasion may be a feasible explanation [18] [20]. Lymph nodes were among the most frequently metastasized sites. Given the absence of lymphatics in the CNS this is curious, but lymphatic tumor seeding during resection is a possible explanation but we would then expect an earlier occurrence of metastatic disease. Dissemination into the cerebrospinal fluid and then extracranially is another hypothesis, but usually only occurs with ventricular shunts so there is a communication from CSF to extracranial structures (peritoneal cavity). Explanations for the rarity of metastatic GBM include absence of lymphatic vessels in the CNS, the lack of communication between intracranial and extracranial perivascular spaces [20], short survival time of patients, and undiagnosed metastatic disease [18].

Factors that predominated among the reviewed cases included a male sex, tumor location, and younger age at presentation. In general, 60% of GBM cases are in men. However, the proportion of male patients with metastatic GBM was higher than expected with no clear reason. The majority of patients with extra-cranial disease were less than 60 years of age (median 42 years). Age is a well-known prognostic factor, with decreased survival based on age, so increased survival may place some patients at higher risk. Other relevant factors are primary tumor proximity to the ventricular system, whether or not the tumor is multifocal [47], and the functional status of patients at the time of GBM diagnosis. We considered these factors but available data was insufficient for analysis.

The OS times when developing extracranial GBM did not seem to differ from expected survival in patients without metastatic disease. Median OS for patients with GBM is approximately 12–15 months [48], compared to 13 months among the patients reported here with metastatic GBM. Patients with local intracranial tumor recurrence reportedly have a median OS of 7.5 months [49]. Furthermore, according to our data, the median survival time from the time of extracranial disease diagnosis was 5 months. A study looking at median survival from time of intracranial, extraparenchymal spread of GBM (subependymal or subarachnoid space) was found to be 9.25 months [50]. It is difficult to compare these patterns of spread, but the diagnosis of extracranial spread compared to intracranial, extraparenchymal spread seems to carry with it a shorter survival time. However, intracranial, intraparenchymal recurrence seems to carry a poorer prognosis compared to extracranial metastatic disease.

Systemic chemotherapy, regardless of type, was the only treatment that significantly lengthened OS in patients with metastatic GBM. Additionally, it was the only treatment

that significantly extended the time to metastatic disease diagnosis. If chemotherapy has a true impact on survival, it is likely a function of local and systemic effects.

Although extracranial GBM does not appear to drastically shorten survival time of patients with GBM, physicians should be aware of its existence. Bone, lymph nodes, and lung were among the most commonly affected organ systems and any symptoms referable to these areas should be evaluated. Bone pain may be commonly mistaken for complications of steroid therapy like avascular necrosis or compression fractures but in our cases, bone pain was the initial manifestation of disease. Likewise, lung metastases causing chest pain or respiratory complaints may be mistaken for pulmonary embolus or pneumonia. Similarly, enlarged lymph nodes should be carefully evaluated for evidence of GBM invasion. The two cases outlined here earlier demonstrated that metastatic disease can present and progress quite rapidly. Repeat or frequent evaluations of persistent, and worsening, complaints among GBM patients are warranted. Early diagnosis of metastatic disease spread can help to expedite alleviation of patients' discomfort, in an already aggressive disease process.

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