Metachronous Osseous Metastases From Gliobliostoma Mutiforme: An Unusual Presentation

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Abstract

Metastasis occurs very rarely in glioblastoma cases. Diagnosing metastatic glioblastoma has to follow a strict protocol to avoid misdiagnosis. Weiss’s 1935 criteria, which is in prevalence, needs to be modified to include current standards of investigation. We report an interesting case of metachronous osseous metastasis from a primary glioblastoma with a complete response at a local site. We also suggest modifications to Weiss’ criteria, which may improve its utility in establishing the diagnosis of metastatic glioblastoma.

Introduction

Since glioblastoma multiforme (GBM) was first described in 1864 by Virchow [1], this group of tumours have remained the most common primary malignant tumour of the central nervous system in adults. It constitutes more than one-third of all primary brain tumours [2]. Gliomas rarely metastasize, although they are locally aggressive tumours. Extracranial metastasis is much rarer, accounting for only around 0.2% - 0.3% of cases [1]. Even after the first case of metastatic GBM was reported as early as 1928 by Davis [1], only around 200 patients have been reported worldwide [3], as of 2021. Bone (24%) is the most common site of extracranial metastasis from GBM, followed by lung (22%), lymph nodes (12%), neck (9%), liver (9%) and other systemic sites (24%) [1].

We report a case of osseous metastasis from primary GBM in the absence of local relapse, considering its rarity, and the need for more cases to get an insight into the tumour biology of metastatic GBM.

Case Presentation

A 36-year-old female presented with a single episode of loss of consciousness one week before presentation, along with intermittent, generalised headache and a few episodes of vomiting over one week. She had a positive family history on her maternal side with one first-degree relative, three second-degree relatives and two third-degree relatives having abdominal malignancy. MRI Brain revealed a 6.5 x 5.0 cm T1 isointense and T2 hyperintense lesion in the right frontal lobe, involving and effacing surrounding parenchyma, corpus callosum with mild perilesional oedema. There was a midline shift of 10 mm to the left. The lesion was provisionally diagnosed as a subacute haemorrhage with mass effect (Fig. 1).
FIGURE 1: MRI Brain (T2W) - 6.5 x 5.0 cm heterogeneous, T2 hyperintense lesion in the right frontal lobe, involving and effacing surrounding parenchyma, corpus callosum with mild perilesional oedema. There was a midline shift of 10 mm to the left.

The patient underwent a right frontal craniotomy and a near-total excision of the lesion was performed. An ill-defined, highly vascular, greyish, suckable growth was seen in the right frontal lobe involving the corpus callosum and extending to the left side. A histopathological examination of the lesion showed polymorphous tumour cells, arranged in sheets, with round nuclei having coarse chromatin and clear cytoplasm. Brisk mitotic activity was observed. Gemistocytic cells and spindle cells were also seen. Microvascular proliferation and necrosis were seen but no calcifications were observed, consistent with glioblastoma multiforme. In molecular analysis, O6-methylguanine-methyltransferase (MGMT) promoter methylation was not detected; IDH1 and IDH2 (isocitrate dehydrogenase) were not mutated. Also, it was negative for 1p-19q codeletion.

She was started on adjuvant chemoradiotherapy (CCRT). Contouring was done following European Organization for Research and Treatment of Cancer (EORTC) guidelines [4]. She received external beam radiotherapy by Intensity-modulated radiation therapy (IMRT) and concurrent temozolomide. She further received six cycles of adjuvant temozolomide. Because of minimal toxicity, the patient was continued on temozolomide for six more cycles. Follow-up MRI showed no intracranial residual lesion. After the completion of adjuvant chemotherapy, she complained of right-sided hip pain. A bone scan showed multiple osteolytic lesions involving multiple cervical, thoracic, lumbosacral vertebrae; left clavicle, left seventh rib, bilateral scapula, pelvic bones and proximal femora. CT thorax and abdomen showed multiple skeletal metastases and a diffuse enlargement of the thyroid gland.

Biopsy from the right iliac blade lesion reported metastatic glioblastoma multiforme. Immunohistochemistry (IHC) showed diffuse positivity of GFAP (glial fibrillary acidic protein), p53 positivity and a Ki67 labelling index of 15% - 20%. In addition, there was a loss of expression of ATRX, and IHC analysis was negative for PanCK, CK-7, CDX-2 (Fig. 2). Fine needle aspiration cytology (FNAC) was done from the thyroid lesion which showed follicular neoplasm (Fig. 3). Suspecting metastasis from the thyroid, IHC analysis for TTF-1 was also done on the specimen from the right iliac blade, which showed a negative result (Fig. 2).
FIGURE 2: Biopsy from the metastatic lesion in the iliac blade

A&B- Biopsy shows viable tumor cells arranged around the blood vessels along with scant tumor necrosis at the periphery (40X & 100X); C- Higher magnification shows nuclear pleomorphism with atypical mitosis (red arrow) (400X); D- Tumor cells expressing GFAP (glial fibrillary acidic protein) immunohistochemistry (400X); E- Tumor cells expressing strong PS3 overexpression (200X) F- Ki67 showing increased proliferative activity (400X); G&H- Tumor cells immunonegative for pan cytokeratin and TTF-1 (400X)
The patient was planned for palliative radiation to the symptomatic bone metastases followed by bisphosphonates and combination chemotherapy with bevacizumab and irinotecan.

Discussion

The rarity of extracranial metastases in GBM (0.4% - 0.5% of all GBM cases) is hypothesised to be due to two major reasons. First, the survival of GBM was low giving a little window for any metastatic disease to present [3,5]. The median survival as noted by the initial RPA (recursive partitioning analysis) in 1993 was as low as 4.6 - 17.9 months (depending on the RPA class). This hypothesis is supported by the fact that the number of reported cases per decade has been increasing over time [6] due to the improvement in the survival of patients, secondary to the development of better surgical, radiation techniques and the use of chemotherapy. Second, the physical barriers restrict any communication between the intracranial and the extracranial compartment - including the dura mater, the thick basement membrane, and the blood-brain barrier. Also, there is no direct communication between the intracranial (glymphatic system) and extracranial lymphovascular spaces [3]. Finding offsetting this hypothesis include the presence of circulating tumour cells (CTCs), which are found in 20% - 40% of all GBM patients (depending on the method used to identify them) [7,8]. Other hypothesised reasons for the rarity of extracranial metastases in GBM allude to the intrinsic property of the glial filaments, lack of specific extracellular matrix proteins in the extracranial mesenchymal tissue, and the role of the immune system in eliminating the extracranial tumour cells [3].

Even with these temporal, physical and molecular hurdles, there are a few cases that develop metastases outside the CNS. They are believed to occur by haematogenous spread (neovascularisation caused by the growth of the tumour mediated by vascular growth factors; potential accentuation by radiation by increasing vascular permeability, promoting neovascularisation [3,9]); lymphatic spread (invasion of intradural lymphatics); local invasion of disease to extend beyond the physical barriers; invading areas with good lymphatic drainage; sarcomatous metaplasia of the GBM tumour cells [10]; spontaneously acquired mutations, which may be radiation induced.

Establishing the diagnosis as metastatic GBM has to be done carefully since GBM is observed to have low rates of metastasis. Weiss, as early as 1955 [11], had laid out criteria to reasonably ascertain this. This includes four prerequisites: i) Histologically characteristic single tumour in the CNS; ii) Clinical history corroborative of this as the primary tumour; iii) Complete autopsy to be done to rule out any other potential primary lesion; and iv) Morphology of the primary CNS lesion and the metastatic lesion to be identical with due allowance for variation in the degree of anaplasia.

We find that our case fits Weiss’s criteria to be labelled as metastatic GBM except for the autopsy criteria. However, it is suitable to note that science has progressed so much that we have other methods to satisfactorily rule out the presence of other primaries. Reviewing the Weiss criteria in the current timeframe, it seems prudent to modify the criteria keeping the essence intact. We suggest the following modifications to the Weiss criteria:
a combination of both have a nine-month overall survival of 43% with lomustine alone, 38% with bevacizumab alone and 59% with combination with bevacizumab is a reasonable option with phase II studies showing the combination regime is, however, phase II data and did not show a significant overall survival difference. Lomustine alone or in addition to other chemotherapy in the recurrent setting increases the 6-month progression-free survival in combination with irinotecan in recurrent glioblastoma (PFS) from 9% - 15% (without bevacizumab) to 40% - 50% (with bevacizumab) [14,15]. Use of bevacizumab as monotherapy or in addition to other chemotherapy in the recurrent setting increases the 6-month progression-free survival (PFS) from 9% - 15% (without bevacizumab) to 40% - 50% (with bevacizumab) [15]. Irinotecan with bevacizumab has been attempted in two-weekly as well as six-weekly regimens in recurrent glioblastoma [14,16]. In our study, we used this combination because it gives a six-month PFS advantage of around 8% and a six-month ORR (objective response rate) advantage of around 10% over bevacizumab alone [14]. This is, however, phase II data and did not show a significant overall survival difference. Lomustine alone or in combination with bevacizumab is a reasonable option with phase II studies showing the combination regime have a nine-month overall survival of 45% with lorustine alone, 58% with bevacizumab alone and 59% with a combination of both [17].
Procarbazine, lomustine and vincristine (PCV) chemotherapy has also been tried in the recurrent setting (post-progression on temozolomide) [18]. Regorafenib is another drug studied for its utility in recurrent GBM. According to phase II studies, both have higher toxicities; PCV has lower survival rates, regorafenib may have a benefit over lomustine [19,20].

All treatment options described here are studied in recurrent localised GBM and not in a metastatic setting. But due to the rarity of metastasis in GBM and the unavailability of established guidelines in the metastatic setting, this management may be extrapolated to a metastatic setting.

**Conclusions**

Better treatment techniques and options have afforded improved survival for GBM patients. This has clinically translated to a higher proportion of them presenting with metastases. Any complaints of GBM patients are to be evaluated with the possibility of metastasis in mind.

Consider aggressive treatment of GBM with metastasis taking into account the age, the functional status of the patient, since aggressive management may have a survival advantage. Bevacizumab is the common factor among regimens in the recurrent setting which can give maximum benefit. Bevacizumab based chemotherapy is to be considered in the recurrent setting. To put things in perspective, the best available care after recurrence may provide an overall survival that is comparable to an RPA Class V GBM. In the absence of any recommendations, metastatic GBM may be managed following the principles of recurrent gliomas as is described in this report and review.

**Additional Information**

**Disclosures**

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