Diagnosis and Management of Spinal Metastasis of Glioblastoma

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ABSTRACT: Background: When patients with cranial glioblastoma develop weakness, a rare differential diagnosis is spinal metastases. Methods: Chart and literature reviews were performed. Results: The reported patient had delayed onset spinal drop metastasis that was only detected by magnetic resonance imaging (MRI). A 48-year-old patient had supratentorial glioblastoma, treated with radiotherapy (RT) and concurrent temozolomide followed by six cycles of adjuvant temozolomide. Four years after completion of all treatments (62 months from initial presentation), he developed low backache and weakness in both legs. Positron emission tomography/computed tomography scans demonstrated intracranial recurrence only. Spinal drop metastases were detected only by MRI scan. Local spinal RT 40 Gy in 20 fractions with concurrent and maintenance temozolomide were given. Because of disease progression after nine cycles of temozolomide, systemic therapy was changed to bevacizumab, which greatly improved his symptoms for 4 months before deterioration of mental status. He is still alive with disease at 22 months after diagnosis of spinal metastases (84 months from initial glioblastoma diagnosis). Conclusions: MRI is the diagnostic imaging of choice for spinal metastases. This illustrative case of delayed-onset spinal metastases shows unusual slow progression. Local RT, temozolomide, and targeted therapy may improve survival. This illustrative case is the first report of bevacizumab as a second-line therapy in drop metastasis of glioblastoma.

CASE REPORT

A 48-year-old Caucasian man noted pressure on the right side of his head by the end of 2007. Then the headaches worsened with new onset of blurring of vision. By spring 2008, a computed tomography (CT) and magnetic resonance imaging (MRI) scans revealed a $6.3 \times 5.4 \times 4.6 \text{cm}^3$ mass in the genu of the corpus callosum. Patients with spinal metastasis from glioblastoma are diagnosed at a relatively young mean age of 44 years and survival of 17.8 months from the initial cranial diagnosis.\(^1\) In the literature, the median time of glioblastoma to spinal metastasis is 10-13 months, with a median time of 3-4 months from spinal metastasis to death.\(^2\) Only one patient survived 20 months after treatment.\(^3\) Although 6% patients with hemispheric glioblastomas have spinal seeding at autopsy, only 0.4-2% presented with symptoms while alive\(^4\) because patients do not live long enough for small tumor implants to grow to a symptomatic size.\(^5\)

In the literature, there are only a few rare examples of delayed recurrence.\(^6\) To our knowledge, the following patient has the longest duration of onset of spinal recurrence from glioblastoma: 62 months from initial presentation.
callosum. He underwent stereotactic biopsy. The pathology was astrocytoma grade III. There was no necrosis seen in the material submitted. Soon after that, he received a gross total resection and the pathology was grade IV per World Health Organization classification. The resected specimen showed extensive necrosis. The viable tumor had generally moderate but with focally high cellularity and was composed of a mixture of small cells with little cytoplasm and gemistocytic forms. Microvascular and endothelial proliferation was identified. The Ki67 labeling index

Figure 1: MRI of the brain (T2 scan) and lumbar spine at recurrence in July 2014.

Figure 2: MRI of the brain (T2 scan) in December 2014. The patient was started on bevacizumab after this.

Figure 3: MRI of the brain (T2 scan) and spine in April 2015. The brain primary had grown and there were a few more small spinal metastases.
was approximately 10%. Immunohistochemistry with MIB-1 antibody revealed a large number of immunopositive cells in the proliferative phase of the cell cycle. A neuropathologist reviewed the slides as well and concurred with the glioblastoma diagnosis. Tests at the Mayo Clinic detected mutation of isocitrate dehydrogenase 1, but not of promoter methylation of O6-methylguanine-methyltransferase in the resection specimen.

A shunt was put in on the sixth day postoperatively because of persistent high intracranial pressure. The patient then received adjuvant three-dimensional conformal radiation to 60 Gy in 30 fractions and chemotherapy (temozolomide at 75 mg/m²/day, given 7 days per week during the entire duration of radiotherapy). After a 4-week break, he received six cycles of adjuvant temozolomide according to the standard 5-day schedule every 28 days for 6 cycles, completed in early 2009. Regular follow-up MRI and positron emission tomography (PET)/CT scans did not show any tumor.

About 4 years after completion of all treatments, in the summer of 2013, the patient developed a low backache with paraesthesia. Initial PET/CT did not show any abnormality in the spine, although intracranial recurrence was seen. Later, a 3-Tesla MRI of the lumbar spine revealed four intradural enhancing nodules between L1 and L3. The largest nodule was 0.7 × 0.7 × 0.6 cm³ at the L2 level (Figure 1). At the same time, the T2 MRI head scan showed a mass-like heterogeneous solid and cystic 1.7 × 1.2 × 1.3 cm³ hyperintensity of the right parasagittal frontal lobe, posterior and superior to the resection cavity. It demonstrated irregular peripheral and minimal central enhancement. Palliative high-dose radiation to the L-spine of 40 Gy in 20 fractions was completed in the fall of 2013 with concurrent temozolomide followed by nine cycles of maintenance doses.

An MRI spine scan in early 2014 showed stability of drop metastases and a shrinkage of the recurrent primary tumor. By December 2014, the primary in the brain progressed (Figure 2). Since October 2014, the patient was on dexamethasone 4 mg once daily. In December 2014, chemotherapy was changed to bevacizumab. He could no longer walk and needed a total lift and wheelchair. His symptoms and quality of life were improved with bevacizumab. He could no longer walk and needed a total lift and wheelchair. His symptoms and quality of life were improved with bevacizumab. He could no longer walk and needed a total lift and wheelchair. His symptoms and quality of life were improved with bevacizumab. He could no longer walk and needed a total lift and wheelchair. His symptoms and quality of life were improved with bevacizumab. He could no longer walk and needed a total lift and wheelchair. His symptoms and quality of life were improved with bevacizumab.

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There were only 3/42 (7%) lesions involving the cauda equina/conus medullaris in a previously reported series.3

Multifocal spread of glioblastoma within the central nervous system can occur at initial presentation, but delayed symptomatic spinal drop metastasis is uncommon in the literature because most patients die early from the intracranial primary. Our patient corroborates the literature with symptomatic spinal metastases more commonly occurring in younger patients, as in Table 1.11-14

As for treatment of spinal drop metastases, different options include resection if the lesions can be localized. Steroids and focal radiotherapy have been used, with little clinical benefit.7 No treatment strategy has offered a therapeutic advantage because patients deteriorated rapidly regardless of intervention.15 Modern treatment with chemotherapy and targeted therapy is available and accounts for the long survival of our patient. Inotocan had been reported by St. Jude Children’s Hospital for pediatric glioblastoma16; this may be tried in the future as second- or third-line therapies.

Routine prophylactic craniospinal axis irradiation as part of initial therapy is not indicated for infratentorial glioblastoma because of the rarity of spinal metastasis and its overall poor prognosis (8% 3-year survival), and with almost all recurrences being local in the cranium.17 However, the pattern of recurrence may be changing to out-of-radiation fields with concurrent temozolomide and bevacizumab.18 As for the best management in gliosarcoma to prevent spinal metastases, further investigations are needed.19,20

In conclusion, the slow progression of our case is unique. Despite the rarity of spinal metastases in glioblastoma, it should be included in the differential diagnoses of causes for symptoms in the back and lower limbs. MRI is the diagnostic imaging of choice. PET scan has corroborated the literature with symptomatic spinal metastases of infratentorial glioblastoma: clinical characteristics and pathomechanism relating to GFAP expression. J Neurooncol. 2011;101:329-33.


