

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.

RÉSUMÉ: *Diagnostic et prise en charge de métastases spinales d'un glioblastome.* *Contexte:* Quand des patients atteints d'un glioblastome cérébral présentent de la faiblesse, le diagnostic différentiel doit inclure des métastases spinales, bien que celles-ci soient rares. *Méthode:* Nous avons effectué une revue de dossiers ainsi que de la littérature à ce sujet. *Résultats:* Le patient âgé de 48 ans, dont nous rapportons les observations, a présenté tardivement des métastases spinales d'un glioblastome détectées seulement par imagerie par résonance magnétique (IRM). Il était porteur d'un glioblastome sus-tentorial traité simultanément par radiothérapie (RT) et témozolomide, suivi de six cycles de traitement adjuvant par le témozolomide. Quatre ans après la fin du traitement (62 mois après la consultation initiale), il a présenté une lombalgie et de la faiblesse au niveau des deux membres inférieurs. Des scans par tomographie par émission de positons/tomodensitométrie n'ont montré que la récurrence intracrânienne de la tumeur. Des métastases spinales ont été détectées au scan par IRM. Il a été traité par RT spinale locale 40 Gy en 20 fractions avec administration simultanée et à long terme de témozolomide. À cause de la progression de la maladie après neuf cycles de témozolomide, le traitement systémique a été modifié. Le bévacizumab a amélioré considérablement la symptomatologie pendant 4 mois avant que le patient ne présente une détérioration de son état mental. Il est toujours vivant 22 mois après le diagnostic des métastases spinales (84 mois après le diagnostic initial de glioblastome). *Conclusions:* L'IRM est la technique d'imagerie de choix pour détecter les métastases spinales. Il s'agit d'un cas où l'apparition de métastases spinales a été tardive, avec une lenteur inhabituelle de la progression. La RT locale, le témozolomide et un traitement ciblé peuvent améliorer la survie. Ceci constitue le premier cas rapporté de traitement par le bévacizumab administré en seconde intention pour des métastases spinales d'un glioblastome.

Keywords: Brain tumors, glioma, neuroimaging, neuro-oncology - medical, radiation, radiation oncology

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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 alive⁴ 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.

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 × 5.4 × 4.6 cm³ mass in the genu of the corpus

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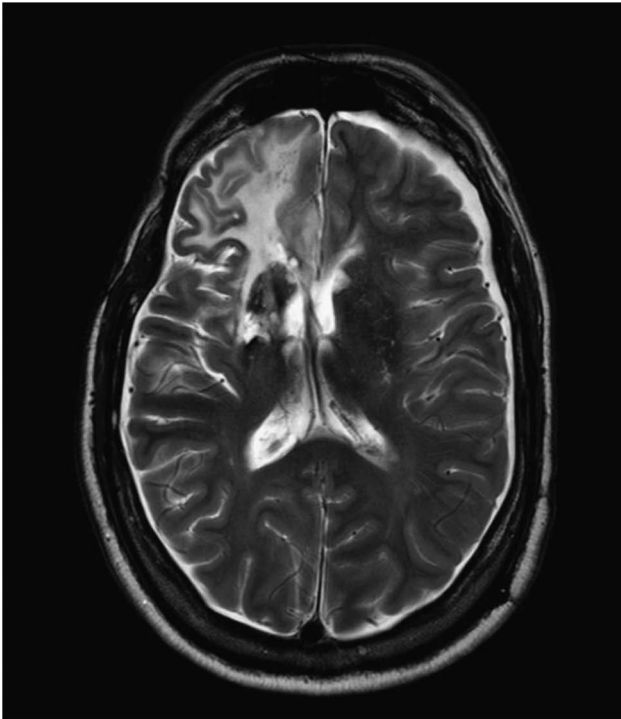


Figure 1: MRI of the brain (T2 scan) and lumbar spine at recurrence in July 2014.

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

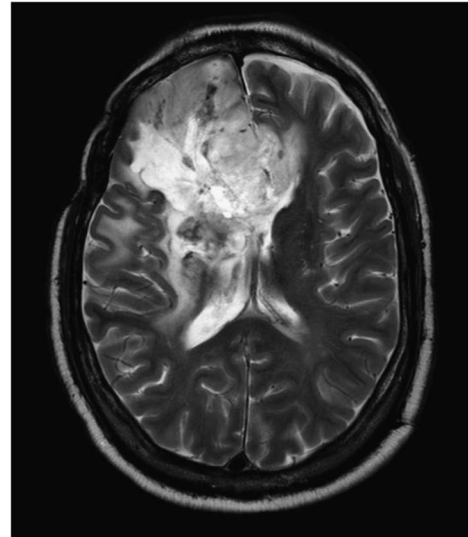


Figure 2: MRI of the brain (T2 scan) in December 2014. The patient was started on bevacizumab after this.

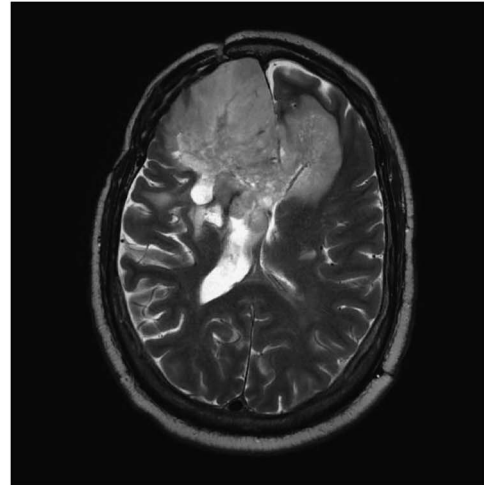


Figure 3: MRI of the brain (T2 scan) and spine in April 2015. The brain primary had grown and there were a few more small spinal metastases.

was approximately 10%. Immunocytochemistry 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 promotor 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 paraparesis. 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 in spring 2015. He was more alert, with improved memory and speech while the dexamethasone was tapered. He is still alive 22 months after treatment of spinal metastases and 84 months since the initial diagnosis of cranial glioblastoma. The latest MRI of the head and spine in April 2015 showed some tumor progression (Figure 3). The amount of edema around the brain primary was less than December 2014.

DISCUSSION

The mechanisms of tumor spread along cerebrospinal fluid pathways include perivascular growth, invasion of choroid plexus, or cortical surface and subpial spread. The incidence of spinal drop metastases was 0.4-2.0% in the literature.⁷ Clinical symptoms are due to the compression of the spinal cord, conus medullaris, or cauda equina, especially if left untreated. Diagnosis used to be made with myelogram and is now made with enhanced MRI of the spine, cerebrospinal fluid cytology, and/or PET scan.⁸ Perhaps because of the limitation of resolution of PET scan as in this case, it has a low sensitivity for leptomeningeal or drop metastases. Not all cases have positive cerebrospinal fluid cytology.⁹ The location of symptomatic spinal metastases is more frequently leptomeningeal (14%) than intramedullary (1.1%).¹⁰

Table 1: Examples of spinal metastasis from cranial glioblastoma, modified from Lawton et al³

Author	Age	Sex	Primary treatment	Interval to metastases	Metastasis management	Interval from metastasis to death
Onda, 1986	42	M	NS	NS	C5-T1 laminectomy, RT to C1-T8	12 months
Vertosick, 1990	21	F	NS	60 months	Decompressive laminectomy and spinal RT 25 Gy	2 months
Vertosick, 1990	43	M	NS	20 months	Spinal RT 40 Gy	2 months
Chang, 2001	51	M	S → 60 Gy RT	32 months	NS	2 months
Lindsay, 2002	42	M	Biopsy → RT	24 months	8 Gy/1 Fr to L spine and lomustine	12 months
Birbilis, 2010	57	F	Biopsy → CRT	37 months	Biopsy only	2 months
Grab, 2014	59	F	Subtotal S → CRT. During RT, cranial progression; reoperated	2 months (after two 28-day courses of maintenance temozolomide)	30 Gy/10 Fr to C3-6; T8-10	1 month
Present case, 2015	48	M	Gross total resection → CRT	53 months after adjuvant treatment	40 Gy/20 Fr to L spine and temozolomide	22+ months; still alive with disease

C = cervical; CRT = chemoradiation therapy; F = female; Fr = fraction; L = lumbar; M = male; NS = not specified; RT = radiotherapy; S = surgery; T = thoracic.

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. Irinotecan 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 a lower sensitivity for leptomeningeal metastases as in this case. Local palliative radiotherapy and systemic treatment with chemotherapy and targeted therapy may improve patient survival. Temozolomide and bevacizumab were used in this case. Bevacizumab is a useful second-line systemic therapy, and our case is the first report of its use in spinal metastases of glioblastoma.

DISCLOSURES

There are unlabeled/unapproved/experimental and/or investigational (non-Food and Drug Administration approved) use of drugs or products in the presentation. The authors declare no other disclosures.

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