Symptomatic Spinal Metastases from Intracranial High-grade Glioma – Report of Four Cases and Review of the Literature

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Abstract

Intraspinal (leptomeningeal or intramedullary) metastases from primary intracranial gliomas have been well documented in several clinical and pathological series; however, symptomatic intraspinal metastases remain rare. We conducted a retrospective search of cases of intraspinal metastases treated at our centre and report four cases of symptomatic intraspinal leptomeningeal and intramedullary metastases from an intracranial glioma. The mean age of the four cases was 43 years (range 28–55 years). The intraspinal metastases were detected after a median time of 18.5 months after onset of the disease and the median survival time of the four patients from detection of spinal metastases was one month. Median overall survival of the four patients was 19 months. One patient was treated with surgery and all received radiotherapy treatment. Radiotherapy provided good initial palliation of pain but improvement in neurological deficits was limited.Overall, prognosis in cases of leptomeningeal and intramedullary metastases from primary intracranial glioma is very poor; however, this diagnosis should be considered in patients with malignant glioma presenting with new back pain and/or associated spinal neurological signs or symptoms. Radiotherapy provided relief of pain and some improvement in neurological function but no survival advantage. Clinical awareness and recognition of this entity will become increasingly important as local control of primary malignant glioma improves and corresponding improvements in outcome and prognosis of this disease are observed.

Keywords

Intramedullary metastases, leptomeningeal metastases, glioma, radiotherapy

Disclosure: The author has no conflicts of interest to declare.
Received: 31 January 2011 **Accepted:** 5 April 2011 **Citation:** *European Oncology & Haematology*, 2011;7(3):179–82 *DOI: 10.17925/EOH.2011.07.03.179*
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Intraspinal (leptomeningeal or intramedullary) metastases from primary intracranial gliomas have been well documented in several clinical and pathological series.[1–5] Post-mortem and cytological incidence of meningeal and cerebrospinal fluid (CSF) dissemination of up to 40 % has been demonstrated in these studies. Symptomatic intraspinal metastases in patients with primary intracerebral gliomas occur rarely however – roughly 1–5 % in published series[6–9] – with the reduced incidence of symptomatic metastases primarily attributed to poor survival in this group of patients.

In this case series, we report four cases of symptomatic intraspinal leptomeningeal and intramedullary metastases from an intracranial glioma. Two cases of primary anaplastic astrocytoma, one case of glioblastoma multiforme (GBM) and one unspecified grade 3 glioma are presented. Three cases are of leptomeningeal metastases only, while one case is of simultaneous leptomenigeal and intramedullary metastases. We report the clinical findings, radiographic evaluation, treatment and subsequent clinical course of these patients.

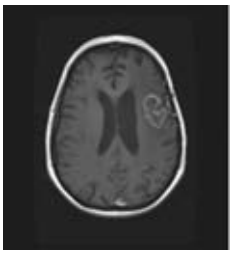
Case Reports

The mean age of the four cases in our series was 43 years (28–55 years). The intraspinal metastases were detected after a median time of 18.5 months after onset of the disease and the median survival time of the four patients from detection of intraspinal metastases was one month. Median overall survival of the four patients was 19 months.

Case 1

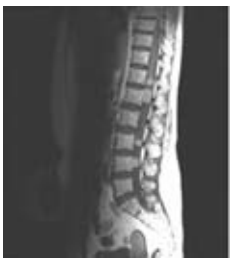
In April 1993, this 28-year-old man presented following a generalised seizure. Computed tomography (CT) head scan demonstrated a large mass in the right temporal lobe with moderate surrounding oedema and compression of the lateral ventricle. Subtotal resection was performed with histopathology demonstrating low-grade astrocytoma and no adjuvant treatment was given. He developed recurrent seizures in 1996 and clinical examination demonstrated bilateral papilloedema; he underwent a further craniotomy and debulking for recurrent high-grade astrocytoma. He proceeded to cranial radiotherapy, 60 Gy in 2 Gy fractions commencing six weeks after surgery given with concurrent procarbazine, lomustine and vincristine (PCV) chemotherapy. Post-radiotherapy CT scan showed residual disease. Chemotherapy was completed in May 1997 and four months later the patient attended his general practitioner (GP) complaining of back pain, progressive leg weakness and numbness in the legs and one week later was admitted to hospital with urinary retention. Spinal magnetic resonance imaging (MRI) scan revealed a posterior intradural mass lesion at the T8/9 level compressing the spinal cord. In October 1997 he underwent a T7–T10 thoracic laminectomy and histopathology confirmed recurrent malignant astrocytoma consistent with the histopathology of the primary tumour. Following surgery, radiotherapy was delivered to T7–T10 of the spinal cord to a total dose of 54 Gy in 30 fractions in 1.8 Gy fractions. On completion of radiotherapy improvement in back pain, leg weakness and numbness

Figure 1: Magnetic Resonance Image of Brain T1 + Contrast



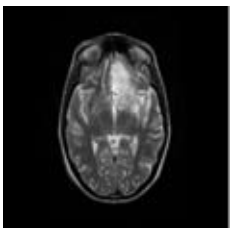
Glioma of left frontal lobe.

Figure 2: Magnetic Resonance Image of Spine T1 + Contrast



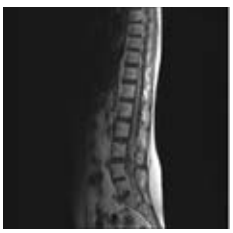
Glioma of left frontal lobe intradural thoracolumbar metastases.

Figure 3: Magnetic Resonance Image of Brain T2



Left medial frontal lobe astrocytoma.

Figure 4: Spine Magnetic Resonance Image T1 + Contrast



Diffuse spinal meningeal metastases.

was observed and bladder function returned to normal. These effects lasted for one month when his condition deteriorated and he noticed worsening leg weakness and bladder function. He was managed with best supportive care and died in January 1998, two months following completion of radiotherapy.

Case 2

In August 2002, this 55-year-old woman was admitted to hospital with a one-month history of expressive dysphasia and right facial, arm and leg weakness. Brain MRI scan demonstrated a 6 cm cystic mass structure in the left frontal lobe associated with surrounding oedema and midline shift (see *Figure 1*). She underwent craniotomy and subtotal resection and histopathology demonstrated a World Health Organization (WHO) grade 3 glioma. She received post-operative radiotherapy to a dose of 54 Gy in 30 fractions followed by four cycles of PCV chemotherapy, which was completed in June 2003; an MRI brain scan post treatment showed residual disease. In November 2003, she attended her GP surgery complaining of pain in her left buttock and leg with associated bilateral leg weakness but with no sensory level and no disturbance of bowel or bladder function. MRI scan of brain and spine showed stable intracerebral disease but several intradural metastases in the thoracolumbar spinal region (see *Figure 2*). Histopathological confirmation was not sought and she underwent a course of palliative radiotherapy planned to the thoracolumbar spine to a total dose of 50 Gy over five weeks. Pain and leg weakness initially responded; however, radiotherapy was discontinued after 14 fractions due to pancytopenia. Her leg weakness deteriorated following this and she died from progressive disease in January 2004, one month after the diagnosis of intraspinal metastases.

Case 3

This 44-year-old woman presented with light-headedness in November 2004. She received an MRI brain scan in March 2005 that revealed a left inferior frontal and medial temporal lobe lesion compatible with a glioma (see *Figure 3*). Histopathology from a stereotactic biopsy in March 2005 demonstrated a WHO grade 3 astrocytoma. She underwent radical radiotherapy, followed by four cycles of PCV chemotherapy that she completed in December 2005.

Routine MRI scan on completion of treatment demonstrated a new lesion in the contralateral right temporal lobe, within the previous radiotherapy treatment field and she underwent chemotherapy with temozolamide, completing six cycles of treatment in July 2006. MRI scan following six cycles demonstrated a partial response. She began complaining of lower back pain in November 2006 and was admitted to a local hospice in January 2007, her general condition having deteriorated significantly. She had bilateral lower limb weakness and numbness. Cerebrospinal MRI scan revealed diffuse meningeal involvement (see *Figure 4*) throughout the thoracolumbar spine but stable intracerebral disease and due to her frailty, no histological confirmation was sought. Her condition deteriorated further and she died in February 2007, less than one month following diagnosis of intraspinal disease; she did not undergo specific treatment for the spinal disease due to her poor general condition.

Case 4

This 45-year-old man presented in September 2008 with headaches, dysarthria and unsteadiness. MRI brain scan demonstrated a left temporal lobe tumour (see *Figure 5*) and he underwent subtotal debulking. Histopathological examination revealed a GBM (WHO grade IV). Adjuvant external beam radiotherapy with 60 Gy in 30 fractions with concurrent temozolamide was completed in December 2008. On completion, the patient's condition deteriorated, developing headaches with right-sided arm and leg weakness. Repeat MRI scan in January demonstrated an increase in the tumour volume and therefore, the planned sequential chemotherapy with temozolamide was converted to PCV chemotherapy. Further MRI scan post-cycle three PCV showed a reduction in the temporal lobe tumour mass. In June 2009, the patient began complaining of lower back pain with associated bilateral proximal lower limb weakness but normal

sensation. MRI brain scan showed stable intracerebral disease, but spinal MRI revealed diffuse leptomeningeal metastases, particularly over the lower thoracolumbar spinal cord and cauda equina with a further intramedullary enhancing lesion within the lower cord at T11/12 (see *Figure 6*). Due to frailty, no biopsy was performed. Radiotherapy was given to T9–S2 with a total dose of 30.8 Gy in seven fractions. Pain resolved, but very little improvement in leg power was observed and he died in August 2009, following further deterioration.

Discussion

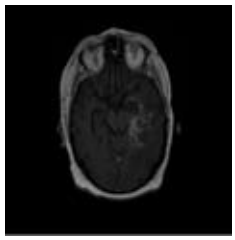
Intramedullary metastases from glioblastoma are uncommon[7,10] and may present with or without leptomeningeal metastases.[11,12] Simultaneous leptomeningeal and intramedullary metastases from glioblastoma are very rare and case 4 is one of the few such cases reported.[9,13–16] Intraspinal metastases from astrocytomas have been less commonly reported. The mechanism of metastatic spread is thought to be due to seeding of tumour cells via CSF pathways either from direct spread into the subarachnoid space or from iatrogenic spread following surgical manipulation. While surgery to the primary tumour is thought to increase the risk of drop metastases and each case in our series underwent surgery, drop metastases have also been reported in people who have not had surgery.[2]

Reported rates of intraspinal dissemination from intracerebral glioma have varied and as in cases 2, 3 and 4 in our series, intraspinal metastases have also been observed in patients with stable intracerebral disease. Typically, the incidence of symptomatic intraspinal metastasis has been lower than the incidence observed post mortem because patients do not survive long enough for small tumour implants to develop into symptomatic lesions.[4,5,16] However, with improved outcome observed from newer treatments and improved diagnostics the incidence is likely to increase in the future. Erlich et al.[4] reported leptomeningeal metastasis in five out of 20 spinal cords of patients with GBM examined post-mortem, with one suffering clinical symptoms. Awad et al.[5] conducted a retrospective review of patients with supratentorial high-grade gliomas and identified 13 out of 191 with unequivocal evidence of leptomeningeal metastases. Of these, eight patients had symptoms, but a firm diagnosis was only established pre-mortem in five cases. Vertosick et al.,[6] in 1990, reported that 11 out of 600 (2 %) patients with intracranial GBM had symptomatic intraspinal dissemination and, in 1986, Choucair et al.[17] diagnosed spinal cord metastases in five of 405 patients (1.2 %) with GBM. In 1992, Schwaninger et al.[7] summarised 22 cases from the literature along with one case of their own of symptomatic intraspinal metastases from GBM. In 2001, Hubner et al.[8] included their own series along with other published articles to increase the number of reported cases of symptomatic intraspinal metastases to 36. More recently, Scoccianti et al.[16] and Alatakis et al.[12] published case reports of patients with symptomatic leptomeningeal and intramedullary metastases from a GBM. These suggest an increase in the number of symptomatic intraspinal metastases being reported. In another series, Stark et al.[9] reported three out of 267 (1.1 %) cases of GBM who developed intraspinal drop metastases.

Intraspinal metastases typically occur in the lower thoracic, lumbar and lumbosacral spine,[12,18] possibly due to gravitational effects.[18] In our cases, the highest lesion was T8/9 and, mostly, involvement was in the lower thoracic and lumbar spine. The most common symptoms of leptomeningeal metastases are back pain, radicular pain in the upper and lower limbs, paraesthesiae and other sensory symptoms followed by motor weakness,[12,15] and symptoms often progress rapidly. Back pain associated with leg weakness was observed in each of our cases while radicular pain, sensory symptoms and urinary retention were also seen.

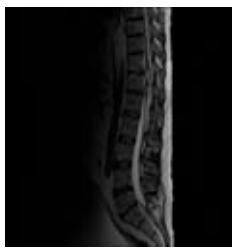
Treatment of drop metastases is solely palliative and can include neurosurgery, radiotherapy, chemotherapy or steroid therapy. One patient in our series with an isolated area of disease in the T8/9 region underwent thoracic laminectomy, surviving for three months following surgery. However, given the overall poor prognosis of these patients, along with the fact that even apparently localised disease is highly likely to have further areas of spinal microscopic involvement, surgical management is rarely suitable in these patients. Radiotherapy remains the most commonly used treatment modality, having demonstrated good symptomatic benefit. Varying total doses and dose per fraction have been reported with total doses of 20–40 Gy reported,[12,15,16] with most authors recommending hypofractionated radiotherapy with 2.5–4 Gy per fraction. Our patients were treated with a

Figure 5: Magnetic Resonance Image of Brain T1 + Contrast



Left temporal lobe glioma.

Figure 6: Magnetic Resonance Image of Spine T2 + Contrast



Leptomenigeal metastases with enhancing lesion at T11/12.

Table 1: Toxicity of Radiotherapy to the Spine

Effect	Management
Acute	
Tiredness	Advice about fatigue (e.g. moderate exercise, goal setting)
Initial flare of pain	Analgesia
Skin reaction	Aqueous cream
Diarrhoea	Loperamide
Nausea and vomiting	Antiemetics
Myelosuppression	Monitor full blood count (FBC), blood transfusion
Late	
Spinal cord damage	Warn patient
Ovarian failure	Avoid ovaries when planning treatment

total dose of 54, 50 and 30.8 Gy[8] in varying fraction sizes from 1.8 to 4.4 Gy per fraction. Good initial palliation of pain was observed in each of our cases but improvement in neurological deficits was observed less consistently. Radiotherapy to the spine has potential acute side effects (see *Table 1*), but in our series, along with the reported literature, is reasonably well tolerated. Late side effects of this treatment are less relevant in this patient group as prognosis is so poor.

Overall, the outcome in cases of leptomeningeal and intramedullary metastases is very poor, independent of treatment modality used, with median time between diagnosis of intraspinal dissemination and death previously reported as two to four months.[6,7,12,15,16] In our cases, median survival following diagnosis of metastasis was one month (range zero to three months).

In conclusion, patients with malignant glioma presenting with new back pain and/or associated spinal neurological signs or symptoms should raise the possibility of leptomeningeal and/or intramedullary spinal metastases. It is likely that with improved diagnostics the number of symptomatic metastases detected will increase. This may have a corresponding therapeutic implication, with further attention paid to the use of chemotherapeutic strategies to attempt to reduce the frequency of intraspinal metastases.

The importance of the clinical awareness and recognition of this entity will therefore increase, especially as local control of primary malignant glioma improves and corresponding improvements in outcome and prognosis of this disease are observed. Consideration should be given to symptomatic spinal radiotherapy, which can provide timely and effective palliation of pain and possible improvement in neurological function. ■

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