**Spinal cord metastasis in a patient treated with bevacizumab for glioblastoma**

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**Abstract**

Spinal metastases from glioblastoma (GBM) are extremely rare and may be misdiagnosed leading to a delay in investigation and treatment. Patient outcomes are poor with a high morbidity and mortality. Metastases are seen in the context of increasing survival due to improvements in glioblastoma therapies. We report a case of a patient developing a thoracic spinal cord metastasis while receiving anti-angiogenesis therapy with bevacizumab.

**Key words**

Glioblastoma; Bevacizumab; Vascular Endothelial Growth Factor, Spinal cord metastasis

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**Conflict of Interest statement: The authors declare that they have no conflict of interest.**

## Introduction

Glioblastoma is an aggressive, highly vascular primary brain tumor. Optimal treatment includes surgical debulking followed by radiotherapy with concomitant and adjuvant temozolomide[1]. This is associated with a survival benefit over radiotherapy alone, with overall survival at five years of 9.8% versus 1.9%, respectively[2]. Although considered extremely rare, metastases to the spine have been described, emphasising the invasive nature and difficulties of treating this high-grade tumor.

At recurrence of the primary, anti-angiogenesis agents may be utilised[3,4]. Bevacizumab is a humanized anti-vascular endothelial growth factor (VEGF) monoclonal antibody. It remains controversial how bevacizumab exerts its therapeutic effect on the tumor and that it may enhance features of tumor invasiveness.

We report a case of a patient with glioblastoma developing a metastasis involving the thoracic spine while receiving bevacizumab. This appears to be the first reported case for a patient receiving anti-angiogenesis therapy.

**Case report**

An otherwise well 44 year old man with previously resected intra-cerebral glioblastoma, presented with lower limb neurological deficits secondary to an intra-medullary spinal cord metastasis.

He had been diagnosed 18 months earlier with a left sided fronto-temporal mass. Debulking resection revealed a GBM. Post-surgical management involved standard of care concurrent radiotherapy and temozolomide chemotherapy. In addition, the patient was enrolled on a clinical trial and received fortnightly bevacizumab. Standard post-radiotherapy temozolomide was prescribed for five days every month for a total of six months. Bevacizumab was given concurrently every two weeks. At the completion of chemotherapy, bevacziumab was continued every three weeks as maintenance therapy.

The patient developed significant proteinuria after an additional six months of bevacizumab therapy and treatment was ceased. His intra-cranial disease had remained radiologically stable until immediately prior to this presentation, when he was noted to have asymptomatic gradual disease progression on MRI.

At this presentation he complained of painless urinary retention, bilateral leg weakness and sensory changes. Clinical examination revealed signs consistent with mid-thoracic spinal disease. Magnetic resonance imaging (MRI) revealed a 10cm long segment of mildly expansile T2 hyperintensity within the thoracic spinal cord (Figure 1). His last cycle of bevacizumab was six weeks prior. The differential diagnoses considered at the time were those of transverse myelitis and GBM metastasis of the spinal cord. He was initially managed with high dose dexamethasone, but developed severe bowel stasis and progression of his lower limb neurological deficits.

Vasculitic screen was unremarkable. Cerebrospinal fluid did not reveal malignant cells. Neuromyelitis optica antibodies and oligoclonal bands were not detected. A spinal cord biopsy was performed, which confirmed a high-grade astrocytoma (Figure 2). Following the biopsy there was ongoing deterioration in lower limb strength. Repeat imaging did not reveal any significant local complications related to the biopsy. The patient underwent emergency spinal cord irradiation and then a prolonged period of inpatient rehabilitation. However, lower limb paraplegia did not resolve.

**Discussion**

GBM is a malignant tumor of the brain. Malignant cells can invade nearby blood vessels and white matter tracts leading to tumor cell migration[5]. As with other cancer types, improved local and metastatic control may be changing the natural history of the disease[6]. Thus, unusual sites of metastases are now being recognised. Patients with GBM are living longer, perhaps allowing the development of metastases. Rare case reports have documented spinal metastases presenting symptomatically months after the initial diagnosis[7-10].

A recent systematic review[11] found 37 patients presenting with a variety of symptoms, including radiculopathy, paresis, paraplegia and bowel/bladder dysfunction. The thoracic and lumbar spine are common sites of metastasis. Therapeutic interventions range from surgical debulking or decompression, to radiotherapy and chemotherapy. A median of ten months was found from time of intracranial surgery to spinal metastasis. Prognosis is dismal with death occurring after a median of three months from the detection of spinal metastasis.

Anti-angiogenic therapies may play a role in enhancing glioblastoma invasiveness and decreasing delivery of anti-cytotoxic drugs. High levels of VEGF are seen in necrotic and hypoxic areas[3]. Anti-VEGF antibodies may normalize the tumor vessels and improve symptoms from cerebral oedema by reducing vascular permeability. This leads to restoration of the blood-brain barrier and concerns about reduced accessibility of chemotherapy to tumors in combination regimens[12]. Reduced perfusion and metabolic

shift increases tumor hypoxia. This was demonstrated in bevacizumab treated animals with patient derived GBM xenografts. There were a greater number of invading tumor cells with increased distance from the tumor core and alternative angiogenic pathways were found to be activated[13].

The difficulty of treating glioblastoma is well known. As survival improves, the potential of late metastases will increase. The need to consider spinal metastasis in the differential of suggestive symptoms and neurology is critical for appropriate investigation and early intervention given the associated poor prognosis and morbidity.

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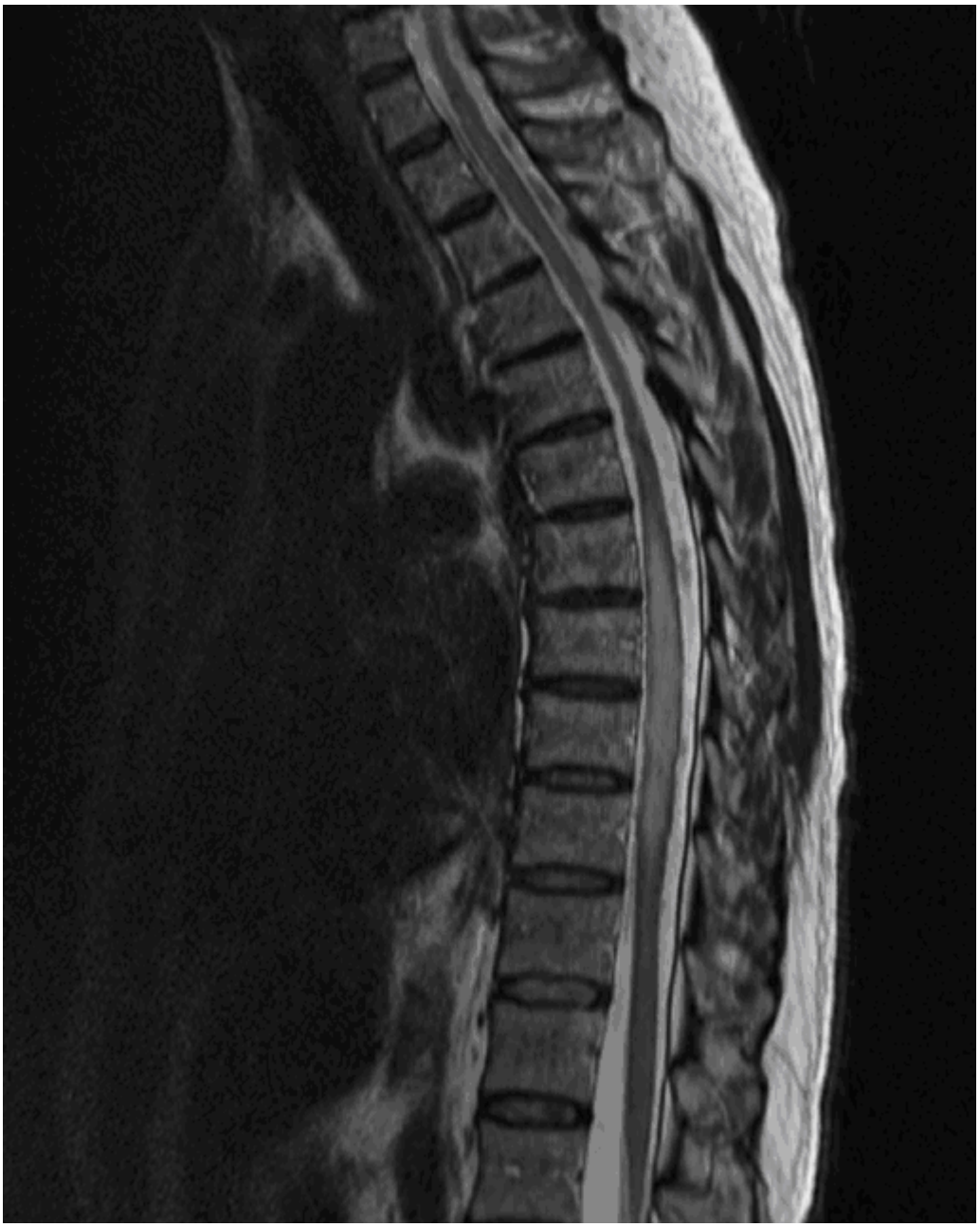
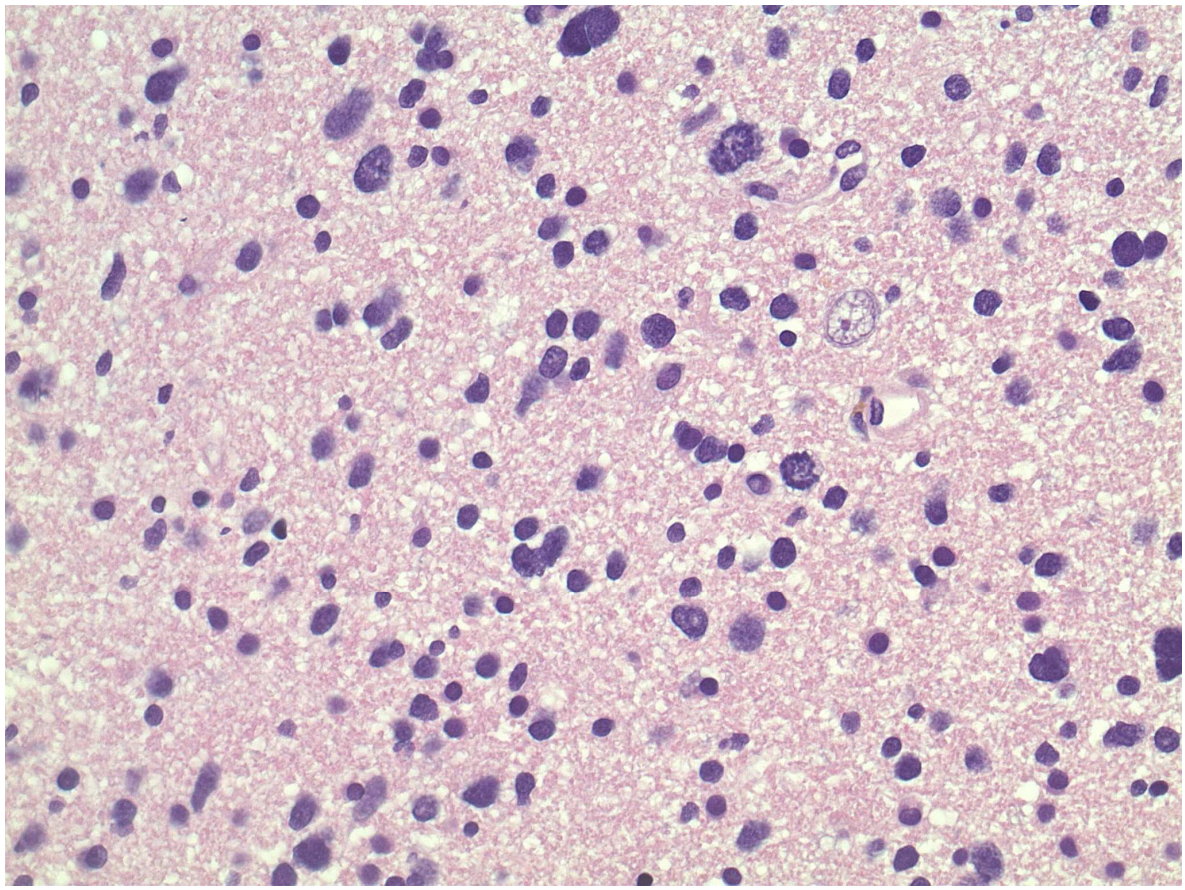
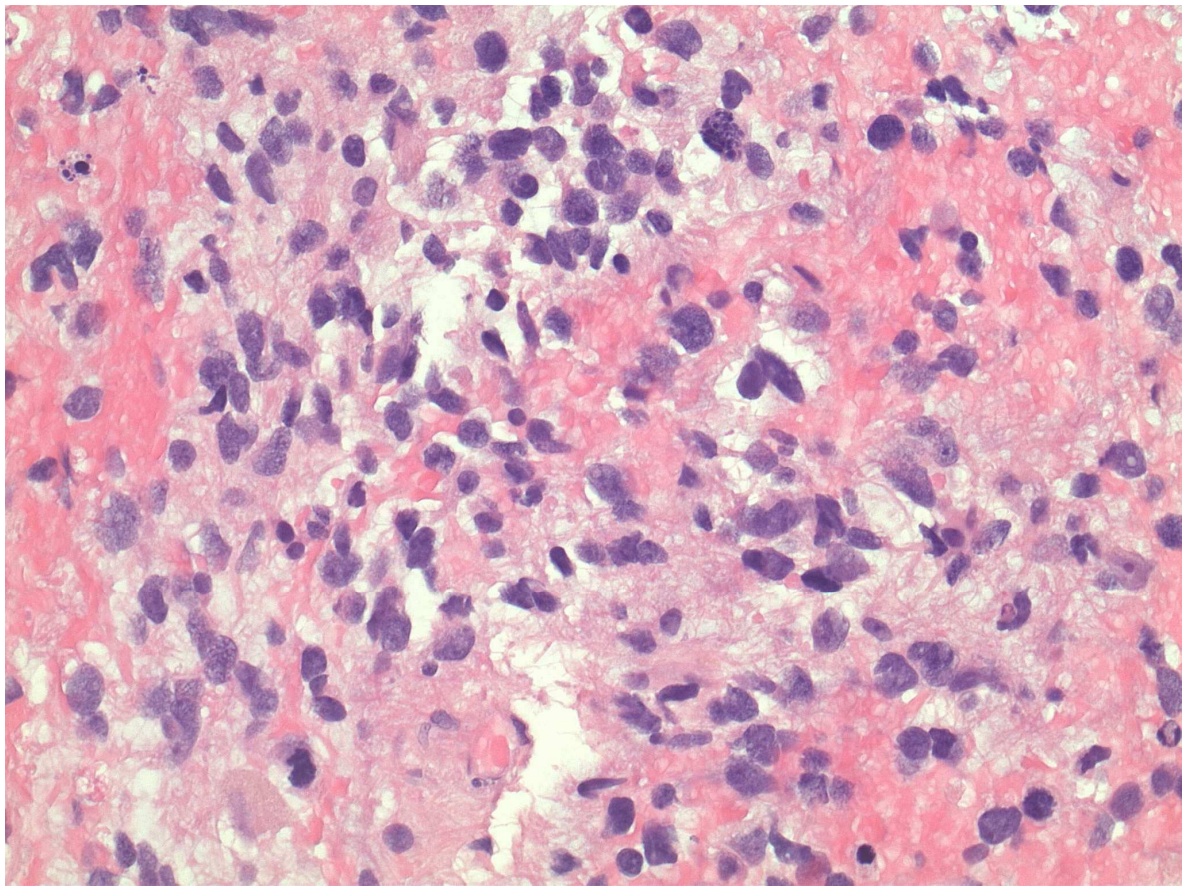
**Figure 1** T2 weighted sagittal MRI sequence showing hyperintensity of the thoracic spinal cord from T6/7 to T10/11, measuring 10cm

**Figure 2** Histopathology of a) left temporal brain tissue demonstrating glioblastoma (original diagnosis) & b) thoracic spinal cord tissue showing high-grade astrocytoma







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