CASE REPORT

Marked functional improvement after combined chemoradiotherapy for cervical spine glioblastoma causing quadriparesis in an adolescent

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SUMMARY

Primary spinal glioblastoma (GBM) is a rare spinal tumour and is considered to have poor prognosis. We describe a case of a 17-year-old adolescent boy with a cervical spine GBM presenting with neck pain and right upper limb weakness. Initial spinal MRI demonstrated a 4.5 cm lesion extending from C2 to C5 suspicious for demyelination. Despite high-dose corticosteroids, his weakness progressed resulting in quadriparesis. Subsequent laminectomy and biopsy confirmed spinal GBM. Shortly after surgery the patient continued to deteriorate and was essentially bedbound. Standard chemoradiotherapy as per the Stupp protocol, together with multimodal rehabilitation, resulted in substantial functional improvement within 6 weeks of initiation. Continued functional improvement was observed for a period of 11 months. Although an Eastern Cooperative Oncology Group (ECOG) performance score of 4 would normally preclude chemoradiotherapy, a prolonged response to treatment and return to independent function were observed.

BACKGROUND

Intramedullary spinal cord tumours occur sporadically and account for less than 5% of intracranial malignancies. Primary spinal cord glioblastoma (GBM), which is a subset of intramedullary spinal cord tumours, is rare and accounts for less than 1% of cases.¹ Given such infrequent presentations, which may initially appear indistinguishable from demyelination, delays in diagnosis of early spinal GBM can occur. Clinical management of primary spinal cord tumours is based on the intracranial literature with limited case series to inform management. To our knowledge, this is the first case of spinal GBM resulting in quadriparesis where substantial and sustained functional recovery has occurred.

CASE PRESENTATION

A 17-year-old boy presented with a 4-week history of right-sided neck pain and upper limb weakness. Initial cervical spine MRI demonstrated an expansile T2 hyperintense lesion, 4.5 cm in length, extending from the lower border of C2 to C4/C5 (figure 1A,B). Demyelination was considered the most likely diagnosis. Despite high-dose glucocorticosteroids, progressive asymmetric quadriparesis was observed with right upper limb weakness of 1/5, gait spasticity and proximal right lower limb power of 2/5. After 3 weeks, repeat MRI

Figure 1 (A) Sagittal turbo spin echo T2-weighted imaging and (B) sagittal spin echo T1-weighted imaging with gadolinium diethylenetriaminepentaacetic acid enhancement and fat saturation MRI cervical spine. There is a swollen 4.5 cm T2 hyperintense segment of the cervical cord extending from the lower border of C2 to the level of C4/C5 disc level with subtle multifocal enhancement seen in the expanded cord at the C4–C5 level.

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Figure 2 (A) Sagittal turbo spin echo T2-weighted imaging and (B) sagittal spin echo T1-weighted imaging with gadolinium diethylenetriaminepentaacetic acid enhancement and fat saturation MRI cervical spine. Progression of the lesion is demonstrated with a 6.5×1.2 cm slightly right centred T2 hyperintense intramedullary mass extending from C2 to C5 with mild irregular ovoid ring contrast enhancement at the C3 level, measuring 2.7 cm in length. Small foci of enhancement were also detected elsewhere within the lesion.

demonstrated progression of the T2 lesion measuring 6.5×1.2 cm with ovoid ring contrast enhancement at the C3 level measuring 2.7 cm in length (figure 2A,B). MRI of the brain excluded intracranial lesions that may have assisted in confirming a demyelinating condition. The patient was subsequently admitted for urgent management and biopsy of the lesion. Given the clinical and imaging deterioration, alternative diagnoses such as tumour were raised.

INVESTIGATIONS

C3–C6 cervical laminectomy was performed to facilitate a biopsy under spinal cord monitoring. As the cord was markedly swollen, a duroplasty was also performed and debulking was not attempted. Histopathology showed a hypercellular tumour composed of small and large pleomorphic cells expressing glial fibrillar acidic protein, p53 and synaptophysin focally. There was palisading necrosis, and prominent endovascular proliferation consistent with grade IV astrocytoma (glioblastoma) (figure 3A,B).

TREATMENT

Postoperatively, the patient deteriorated and was now bedbound with an Eastern Cooperative Oncology Group (ECOG) performance status of 4. His lower limb weakness progressed with significant bilateral involvement. After informed consent was obtained, combination of temozolomide (75 mg/m² daily orally) with conformal radiotherapy (50.4 Gy in 28 fractions) was started on day 4 postoperatively to the cervical spine as per the Stupp protocol.² Multimodal inpatient rehabilitation was instituted during chemoradiotherapy, including tilt table and respiratory muscle training.

Apnoeic episodes were observed in the second postsurgical week, which were not abated when narcotic and other analgesics were withheld. Non-invasive ventilation (NIV) was initiated when erect spirometry demonstrated respiratory muscle impairment

Figure 3 (A) Cellular glioblastoma composed of pleomorphic small and larger cells, including multinucleated forms, having hyperchromatic nuclei. There is coagulative tumour necrosis (lower left and lower right borders) including palisading tumour necrosis (left; H&E, ×400). (B) Pleomorphic glioma cells including multinucleated forms in a background showing prominent microvascular proliferation (H&E, ×400).

Figure 4 Sagittal turbo spin echo T2-weighted imaging MRI cervical spine. Demonstrates the T2 appearances of the lesion at 6 weeks (A) and 5 months following surgery (B). Initially, there is increased heterogeneity of the T2 lesion signal reflecting biopsy and a large surgical collection is seen on the laminectomy bed (C3–C5). At 5 months, there is almost complete resolution of the cord swelling and T2 signal change. (C and D) Sagittal SE T1-weighted imaging with gadolinium diethylenetriaminepentaacetic acid enhancement and fat saturation MRI cervical spine. Demonstrates the enhancement characteristics of the lesion at 6 weeks (C) and 5 months (D) following surgery. Initially, there is a significant increase in the enhancing lesion which may in part reflect biopsy and a large surgical collection is seen on the laminectomy bed (C3–C5). At 5 months, there is notable regression of the enhancement and cord swelling.

with forced expiratory volume in 1 s (FEV₁) 0.85 L and forced vital capacity (FVC) 1.06 L. Long-acting narcotics were slowly reintroduced as respiratory function improved.

Chemoradiotherapy was well tolerated until week 5 when grade 4 thrombocytopaenia occurred (nadir platelet count = $7 \times 10^9/L$), requiring cessation of temozolomide and use of platelet transfusions (Common Terminology Criteria for Adverse Events, V3.0). Other potentially contributing drugs, including cotrimoxazole, were ceased concurrently. He developed febrile neutropaenia

secondary to *Pseudomonas* urinary tract infection, and was treated with intravenous piperacillin–tazobactam (nadir neutrophil count = $0.10 \times 10^9/L$). Bone marrow aspiration confirmed reduced megakaryocyte population and excluded other haematological malignancies. The duration of grade 4 thrombocytopaenia was approximately 5 weeks.

Despite these complications, the patient made significant functional gains and was able to walk with a single point stick 6 weeks following surgery (figure 4A,C). His sustained

improvement in limb power was matched with respiratory muscle function progress ($FEV_1=2.5$ L and $FVC=2.72$ L after 5 weeks) and NIV was ceased. Right-sided weakness improved, but fine motor control remained impaired. He was discharged 10 weeks after treatment initiation. Follow-up imaging demonstrated a substantial reduction in tumour and cord swelling at 5 months, correlating with sustained clinical improvement (figure 4B,D). Right-sided muscle strength improved with biceps and triceps power of 3/5 and he was able to mobilise without aids. No further temozolomide was used in view of the severe, prolonged thrombocytopaenia and ongoing functional improvement.

The patient continued to improve until 11 months after treatment was started, when radiological and clinical progression was observed. Temozolomide (150 mg/m^2 , day 1–5) was reintroduced; however, grade 3 thrombocytopaenia developed and no clinical or radiological benefit was derived. Bevacizumab (15 mg/kg , 3 weekly) was started with ongoing cyclical temozolomide as tolerated haematologically. This combination stabilised his clinical condition with improved mobility and decreased neck pain, which permitted complete weaning of glucocorticoids.

Bevacizumab treatment with low-dose temozolomide was maintained until progression after 8 months, and was complicated by a nasal septal perforation and an extensive right lower limb deep venous thrombosis, which were treated with anticoagulation.

DISCUSSION

Primary spinal cord GBM is rare and sporadic. Reported ages at diagnosis range from 3 to 88 years, with most cases occurring in young adults up to 30 years.^{1–3} Spinal GBM usually presents in the cervicothoracic region.^{1–5} Management with surgical resection and temozolomide-based adjuvant chemoradiotherapy using intracranial GBM protocols has been previously described and was well tolerated in these series.^{4–6} However, establishing margins of intramedullary tumours is technically difficult and was not attempted in our case. Postoperative chemoradiotherapy followed by 6 months of adjuvant temozolomide is the current standard of care for intracranial GBM, improving progression free (5.0 vs 6.9 months) and overall survival (12.1 vs 14.6 months) compared with radiotherapy alone.² In the absence of clinical trials, these results have been extrapolated to spinal GBM.

Prognosis of spinal GBM is generally considered poor, with median survival of 9–10 months reported in patients who received adjuvant chemotherapy.^{1–3} One case reported survival as long as 51 months, but functional benefit was not described.³ Seven of these patients also received adjuvant chemotherapy although the regimen was not reported.³ A recent case has reported survival of 33 months in a 26-year-old patient presenting with cervical spine GBM treated with total surgical resection and adjuvant chemoradiotherapy with temozolomide.⁶ In contrast to our case, functional recovery was not observed with the patient remaining wheelchair bound post therapy. Metastases to the brain, liver and spleen from primary spinal GBM have also been reported.^{1–7}

Our patient did not proceed to adjuvant temozolomide following completion of chemoradiotherapy due to severe thrombocytopaenia, which is a recognised complication occurring in approximately 10–15% of patients treated with this drug.^{2–8} The risk factors that contribute to prolonged thrombocytopaenia are unclear although radiotherapy is believed to contribute given the median onset of 52 days corresponds with completion of cranial radiation.⁶ In our patient, bone marrow

aspirate confirmed reduced megakaryocyte population. However, the site of his iliac crest aspirate was well clear of his cervical spine radiation field. Treatment of a large cervical spine field may have contributed to his reduced bone marrow reserve. Supportive cotrimoxazole and concurrent use of antiepileptic agents may also be implicated but there is a paucity of data that explain this relatively common but idiosyncratic complication.

Given the poor tolerance of reintroduced temozolomide, limiting our ability to treat with adequate dose intensity, the patient was then treated with bevacizumab on progression at 11 months postsurgery. Bevacizumab is a monoclonal antibody against vascular endothelial factor with known activity in intracranial and spinal GBM. While experience with spinal GBM is limited, one series described six cases treated with bevacizumab following treatment failure with temozolomide.⁴ Duration of response was between 3 and 11 months with overall survival of 5–13 months. Stable disease was observed in three patients, with partial responses in two patients. Bevacizumab was well tolerated with no grade 4 adverse events.

To our knowledge, this is the first report of rapidly progressive and profound quadriparesis where multimodal therapy has achieved significant and sustained functional gains. Usual practice precludes use of chemotherapy in patients with poor performance status, severe quadriparesis and respiratory muscle compromise. The decision to proceed with combined chemoradiotherapy in this setting may be considered controversial, but was made after extensive multidisciplinary consultation and deliberation with the patient and his family. The resulting improvement to independent mobility and ongoing post-discharge functional gains vindicate this decision. Given the infrequency of spinal GBM, prospective registration of cases would describe current patterns of care and outcomes in the context of the full range of clinical and treatment settings.

Learning points

- ▶ Primary spinal glioblastoma (GBM) are rare and account for less than 1% of intramedullary tumours.
- ▶ High-grade gliomas are a rare cause of progressive spinal cord dysfunction in a young individual and should be considered in the differential diagnosis of unexplained weakness.
- ▶ Management of primary spinal GBM is based on case series and adaptation of the intracranial literature.
- ▶ Early follow-up imaging may assist in highlighting temporally aggressive lesions of uncertain aetiology.
- ▶ While prognosis of spinal GBM is considered poor, treatment in limited performance status patients can lead to substantial functional improvement, and should be considered in selected cases.

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