

Case Report

Primary intramedullary spinal gliosarcoma: case report and review of the literature

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Abstract: Primary gliosarcoma (GS) in the spinal cord is extremely rare. To our knowledge, there are only two cases reported in the literature. The clinical feature, treatment, and prognosis for this rare entity have been uncertain. In this paper, we present a unique case of histopathologically proven primary intramedullary spinal GS without intracranial involvement. A 46-year-old male presented with a 3-month history of progressively worsening numbness and weakness of his left leg and gait instability. Spinal magnetic resonance imaging revealed an intramedullary lesion at the level T4-7 with irregularly heterogeneous enhancement. Intracranial or other bodies' lesions were absent. The patient underwent a T4-7 laminectomy and subtotal tumor removal was achieved. Histopathological findings confirmed a GS. Postoperatively, the patient received adjuvant radiotherapy combined with concurrent and adjuvant chemotherapy with Temozolomide. However, he had tumor recurrence 5 months after surgery and experienced a progression of paraplegia with rapid enlargement of residual tumor. The patient died of severe pneumonia and respiratory failure 6 months after diagnosis. The clinical features and treatment outcome of this rare entity are discussed along with a review of the relevant literature. Primary GS should be considered in the differential diagnosis of spinal cord tumors. Multidisciplinary treatment including surgical resection and adjuvant radiochemotherapy should be performed as standard protocol due to highly malignant nature, although overall prognosis of this tumor is poor.

Keywords: Gliosarcoma, intramedullary, surgical resection, radiochemotherapy, spinal cord

Introduction

Gliosarcoma (GS) is very rare and highly malignant tumor in the central nervous system, accounting for only 1.8-8% of astrocytic neoplasms [1]. The tumor was firstly described in 1895 as glioblastoma (GBM) with a sarcomatous component and had similar clinical features with those of GBM [2]. Histopathologically, GS is typically composed of biphasic patterns of malignant glial and sarcomatous components, based on the 2007 WHO classification. GS can occur throughout the whole neuraxis and mostly affects the cerebrum, especially the temporal lobes. Primary GS in the spinal cord is extremely rare, and there are only two cases reported in the English literature [3, 4]. Here we present a unique case of histopathologically proven primary intramedullary spinal GS in a 46-year-old male patient, which may contribute to the knowledge of this unusual entity.

Case report

A 46-year-old male patient presented to our outpatient clinic with a 3-month history of progressively worsening numbness and weakness of his left leg and gait instability. He denied any bowel or bladder symptoms. Neurological examination revealed that muscle power was grade 2/5 in his left leg and grade 4/5 in the right leg (classified by the Medical Research Council grading system). Somatic superficial sensation below left T2 level was reduced. Increased deep tendon reflexes and positive Babinski sign were noted in the left lower limb. Laboratory findings were within normal limits and the medical history was unremarkable.

Preoperative magnetic resonance imaging (MRI) of the thoracic spine demonstrated an intramedullary lesion at the T4-7 level, measuring 5 mm×5 mm×56 mm in maximal dimen-

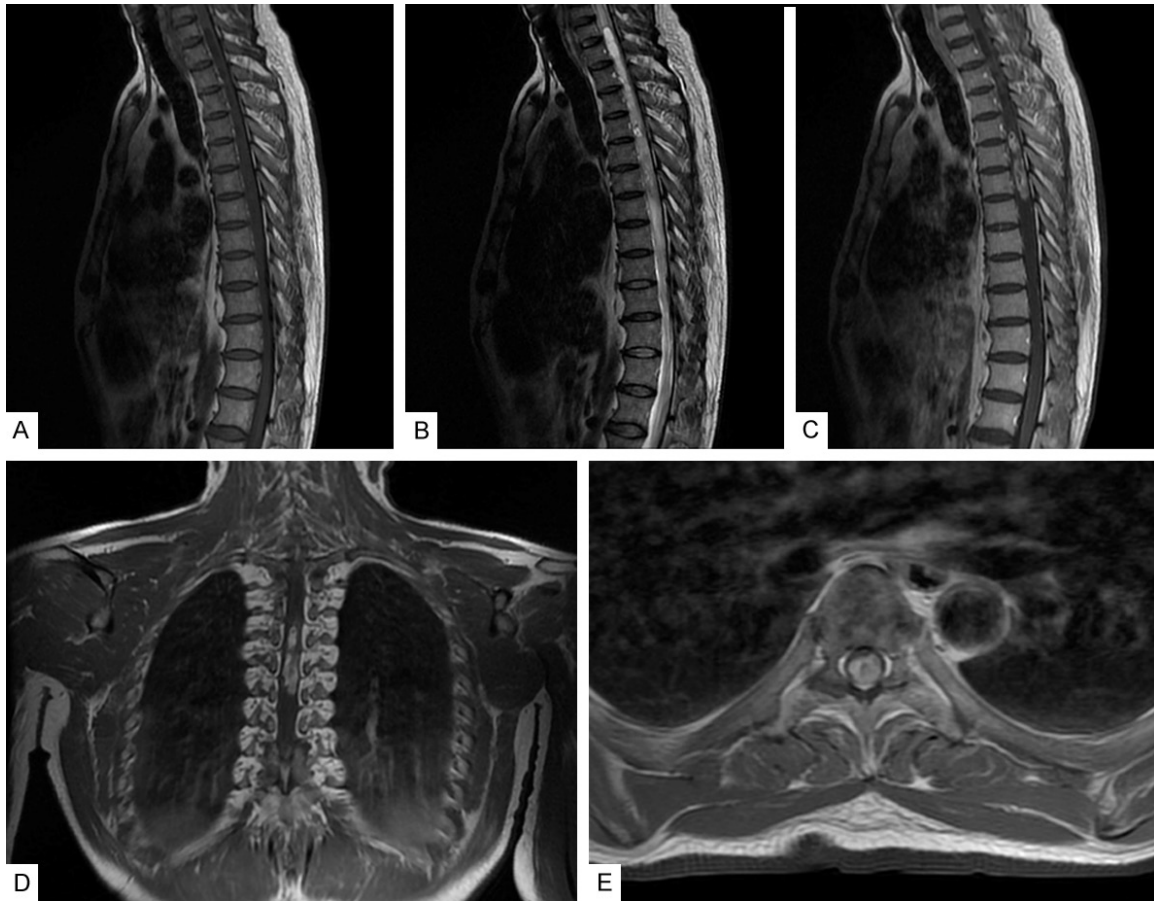


Figure 1. Preoperative magnetic resonance imaging showed an intramedullary lesion at the T4-7 level with mixed iso-/hypointensity on sagittal T1-weighted image (A) and mixed hyperintensity on sagittal T2-weighted image (B). Gadolinium-enhanced sagittal (C), coronal (D), and axial (E) T1-weighted images demonstrated irregularly heterogeneous enhancement. Peritumoral edema and associated syringomyelia were observed.

sions (**Figure 1**). The tumor showed mixed iso-/hypointensity on T1-weighted imaging (WI) and mixed hyperintensity on T2WI. Contrast-enhanced imaging of the mass showed irregularly heterogeneous enhancement after gadolinium administration. Peritumoral edema and associated syringomyelia were noted. Cranial and other spinal region MRI findings were normal. Moreover, bone scanning and abdominal ultrasonography showed no other tumors, which ruled out a metastatic origin for the spinal cord tumor. Based on the radiological features of the tumor, the lesion was preoperatively diagnosed as an ependymoma.

The patient underwent a T4 to T7 laminectomy for tumor resection through the posterior mid-line approach. The dura was intact but highly tense and a longitudinal incision was made on the center of it for cord exploration. The intraop-

erative findings showed that the tumor was red and greyish in color, mixed in texture, and highly vascular. The lesion had ill-defined margins with adjacent neural tissue and spread ventrally to the cord. Due to diffuse tumor infiltration to the cord, gross total resection is difficult based on protection of spinal functions and subtotal tumor removal was finally achieved under spinal evoked-potential monitoring. After surgery, the effect of cord compression was vanished.

On histopathological examination, the tumor was composed of malignant fibrillary and epithelioid glial cells and spindled sarcomatous cells in biphasic patterns with mixed gliomatous and mesenchymal areas (**Figure 2A, 2B**). The immunohistochemical examinations revealed that glial fibrillary acidic protein (GFAP) had strongly positive reactivity in gliomatous areas

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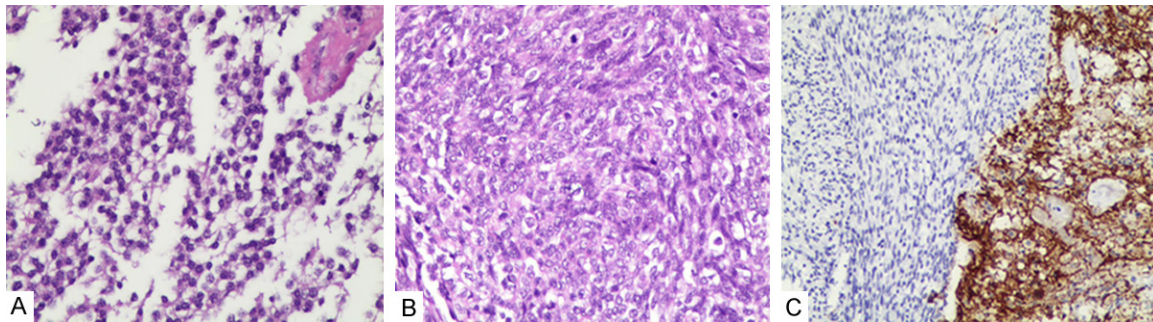


Figure 2. Photomicrograph revealed malignant fibrillary to epithelioid glial cells (A) and spindled sarcomatous cells (B) in biphasic patterns with mixed mesenchymal and gliomatous areas (hematoxylin-eosin staining, original magnification, $\times 200$). The immunohistochemical examinations showed that glial fibrillary acidic protein had strongly positive reactivity in glial differentiated areas but negative reactivity in sarcomatous areas (C) (original magnification, $\times 100$). The findings were consistent with the diagnosis of a gliosarcoma (WHO Grade IV).

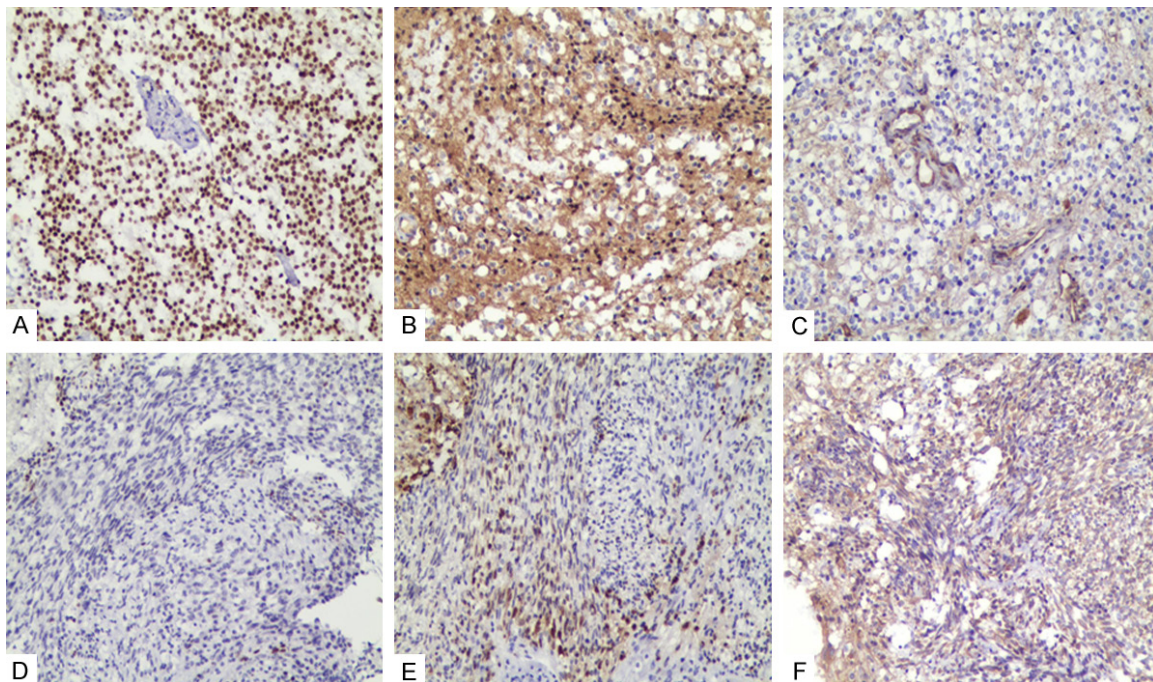


Figure 3. The immunohistochemical examinations demonstrated that in gliomatous areas (A-C), Olig-2 (A) and S-100 (B) showed strong positivity and vimentin (C) showed sparse positivity, while in sarcomatous areas (D-F), Olig-2 (D) and S-100 (E) showed sparse positivity and vimentin (F) showed strong positivity. (original magnification, $\times 100$).

but negative reactivity in sarcomatous areas (Figure 2C). Moreover, Olig-2 and S-100 showed positivity in gliomatous areas but sparse positivity in sarcomatous areas, while vimentin showed positivity in sarcomatous areas but sparse positivity in gliomatous areas (Figure 3). Approximately 40% of cells were positive for Ki-67. All these findings were consistent with the diagnosis of a GS (WHO Grade IV).

Postoperative course was uneventful and sensory deficits were apparently relieved. Postoperative adjuvant radiotherapy combined with concurrent Temozolomide (TMZ) was strongly recommended. The interval between surgery and the start of radiochemotherapy was 18 days. The patient received focal radiotherapy 50.4 gray/28 fractions (5 fractions/week) with concurrent TMZ 75 mg/m²/day. After concurrent treatment, adjuvant chemotherapy was

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Table 1. Summary of previously reported primary spinal gliosarcomas

Author/year	Age (years), sex	Duration of illness	Tumor location	Presentations	Treatment	Outcome
Barbagallo et al., 2002 [3]	73, M	3 weeks	C1-2, IDEM	Neck pain; progressive hemiparesis; sensory reduction; urinary urgency and incontinence	GTR	Dead of postoperative cardiopulmonary complications
Kumar et al., 2016 [4]	54, M	2 months	C1-4, T6, T9, L1, IM+IDEM	Progressive sensory dysfunction of legs and gait instability	PR+RTX/TMZ+Avastin	Dead at 9 months*
Present case	46, M	1 month	T4-7, IM	Numbness and weakness of left leg and gait instability	STR+RTX/TMZ	Dead at 6 months

GTR: gross total removal; IDEM: intradural and extramedullary; IM: intramedullary; M: male; PR: partial removal; RTX: radiotherapy; STR: subtotal removal; TMZ: Temozolomide. *After initial diagnosis.

given with TMZ 150-200 mg/m²/day (day 1-5/4 weeks) for six cycles. The patient tolerated the radiochemotherapy well and occurred no significant complications or side effects. Gradual improvement in strength of the limbs was noted during the follow up. No tumor cell was found in cerebrospinal fluid (CSF) by routine monitoring. Regular follow-up MR imaging of the whole neuraxis was performed and the residual tumor had no regrowth or metastasis at 3 months postoperatively. Unfortunately, the patient had a recurrence 5 months after the operation and experienced a progression of paraplegia with rapid enlargement of residual tumor. The patient died of severe pneumonia and respiratory failure 6 months after surgery.

Discussion

GS accounts for only 0.48% of all intracranial tumors, and its clinical features are similar to those of GBM [5, 6]. The clinical presentations of GS depend on tumor location and size, usually affecting male patients in their fifties to seventies [7, 8]. The neuraxis can be involved at any level with a significant predilection for the supratentorial location and the occurrence of primary intraspinal GS is exceedingly rare. Since Barbagallo et al. described the first case in 2002, only two cases of primary intraspinal GS have been reported in the English literature. **Table 1** summarizes the clinical features of previous cases and our patient. The age of all three patients at presentation is above 45 years, which is like that of intracranial GS. The tumors mainly arise from the cervical or thoracic spinal regions. The symptoms of GS are non-specific and consistent with those of common intraspinal tumors. The clinical presentations include somatic pain, numbness, progressive weakness in the limbs, and sphincter dysfunction. In our presented case, the duration between symptom onset and presentation was 1 month, much shorter than common spinal cord tumors, which reflects highly malignant nature and aggressive growth pattern of the tumor.

MRI is the modality of choice for the diagnosis of spinal cord tumors. Preoperative differential diagnosis for spinal cord tumors is significant when planning surgical strategies and determining the extent of the required resection to avoid overtreatment and unacceptable complications. Most GSs show iso-/hypointense signals in T1WI, hyperintense signals on T2WI, and

heterogeneous enhancement after gadolinium administration [9-11]. However, the radiological features of GS are indistinguishable from those of common spinal cord tumors in the preoperative period due to lack of highly specific appearance. Thus, a definitive preoperative diagnosis of GS was difficult based only on MRI, and a complete histopathological examination was required to differentiate between other spinal cord lesions.

Detailed pathological features of GS have been described in some clinicopathologic studies [12-14]. Histologically, GS is characterized by malignant fibrillary to epithelioid glial cells and spindled sarcomatous cells in biphasic patterns with mixed mesenchymal and gliomatous areas. The glial component of GS mostly consists astrocytes with nuclear atypia and mitotic figures. Necrosis and vascular endothelial proliferation may also be present. GFAP positivity is a significant marker in distinguishing between GS and pure sarcoma. In GS, the glial component exhibits strong staining for GFAP, unlike the GFAP-negative sarcoma-like component. The histological differential diagnosis of GS should include GBM, sarcoma, and ependymoma.

Due to rarity of GS, standard treatment strategy remains ill-defined. The presence of a WHO IV grade tumor should guide clinicians down multidisciplinary treatment, possibly resulting in surgical resection combined with adjuvant radiochemotherapy and close follow-up. Thus, treatment for GS is generally identical to that of GBM, involving surgical resection with concurrent radiation and TMZ chemotherapy. Since GS is histologically malignant, gross total removal using a microsurgical technique based on protection of spinal function should be attempted during surgical exploration. However, due to diffuse aggression to the cord with ill-defined margins, the tumor in the present case had to be subtotally removed for mass effect relief to improve the myelopathic symptoms and avoid severe operative complications. This incomplete removal may lead to increase the risk of recurrence and cause a poor outcome.

The introduction of adjuvant radiation therapy and TMZ therapy has showed a considerable improvement in survival and clinical outcomes of patients with spinal cord GBM [15]. Thus, in this study we performed postoperative early

radiotherapy combined with concurrent and adjuvant chemotherapy with TMZ to avoid the toxicity of spinal cord, although there is no data concerning the effect of radiotherapy or chemotherapy on survival now. Other systemic therapies may be considered for the tumors, but further investigation is required. Because risk of recurrence or metastasis for GS is very high, regular follow-up whole-body imaging works and neuroaxis MRI are necessary. Moreover, because of high rate of leptomeningeal metastasis via CSF spread [16], routine monitoring of CSF cytology is recommended after postoperative pathological diagnosis is confirmed and CSF involvement may determine the prognosis of patients with spinal cord GS. Overall prognosis of spinal cord GS is fatal and the tumor results in death usually due to complications related to progressive spinal cord involvement, respiratory impairment, and metastases.

Conclusions

The present case and literature review suggest that GS is not limited to supratentorial involvement and should be added to the differential diagnosis of primary spinal cord tumors. Considering highly malignant nature of this rare entity, surgical resection combined adjuvant radiochemotherapy is recommended although overall prognosis is still poor. Further studies with larger sample sizes are required to establish well-defined treatment protocols.

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Disclosure of conflict of interest

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