Brain Tumour Primary Intramedullary Spinal High-Grade Glioma: A Case Series with Review of Literature

Aashita¹ Rajiv Sharma¹ Vikas Yadav¹ Muthu Manikandan¹ Ankit Dhameliya¹ Hemendra Mishra¹ Pragyat Thakur² Abhidha Malik¹

¹ Department of Radiation Oncology, VMMC and Safdarjung Hospital, New Delhi, India

² Department of Radiation Oncology, Homi Bhabha Cancer Hospital, Sangrur (Affiliated to HBNI, Mumbai), Maharashtra, India Address for correspondence Aashita, MD, Department of Radiation Oncology, VMMC and Safdarjung Hospital, New Delhi 110029, India (e-mail: aashita77@gmail.com).

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Abstract



Aashita

Keywords

- glioblastoma
- spinal glioblastoma
- spinal astrocytoma
- intramedullary glioma
- high-grade glioma

Background

Tumors of central nervous system (CNS) can occur in brain and spinal cord. Spinal cord tumors (SCT) are almost 15 times uncommon compared with intracranial tumors.¹ Depending on the site of tumor, SCT can be divided into intramedullary, intradural extramedullary, and extradural.¹ Primary intramedullary SCTs are infrequent and constitute 5 to 10% of SCT.² There are no prospective randomized trial on treatment of spinal high-grade glioma (SHGG) as a result of which there are no consensus guidelines available in the literature. Treatment recommendations are usually based on experiences of various case reports and series available in the literature.

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Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Background Primary intramedullary high-grade glioma (HGG) and glioblastoma of spinal cord are uncommon tumors of central nervous system. Treatment recommendations are based on current guidelines of intracranial HGG and glioblastoma multiforme (GBM).

Methods We retrospectively analyzed records of 9,686 patients who reported to our center over past 7 years. Only three cases of primary intramedullary HGG of spinal cord were found.

Results In this article, we have reported three cases of primary intramedullary HGG of spinal cord. A comparison of intracranial and intramedullary spinal HGG and review of literature is presented.

Conclusion Despite aggressive treatment using surgery, radiation, and chemotherapy, the survival rates are dismal. Emerging evidence has shown difference in biological behavior of intracranial and spinal HGG. Genetic studies to understand the biology and prospective studies are needed.

	Patient 1	Patient 2	Patient 3	
Age (y)	12	21	18	
Sex	Female	Female	Female	
Site of tumor	Intramedullary at D7–9	D2-7	Intramedullary D3–5, D8–9, D11–L2	
Symptom duration	Progressive abnormal gait × 2 years, loss of pain, & temperature sensation × 3 months	Backache, weakness in lower limbs \times 3 months, progressive loss of sensory and motor functions	Lower limbs weakness × 3 month, urinary & bowel incontinence × 1 month	
Imaging	Peripherally enhancing intramedullary mass at D7–9 of size $4.9 \times 1.2 \times 1.3$ cm	Intramedullary mass from D2–7. Focal contrast enhancement in caudal equina with leptomenin- geal enhancement	Heterogenous intramedullary D3–5, D8–9, D11–L2	
Histopathology	GBM, GFAP, IDH, P53 positive, EMA negative, ki67 high	GBM, GFAP, p53 positive, EMA negative, ki67 30%	GBM, ki67–8–9%	
Surgery	D7–9 laminectomy and GTE	D2–10 laminectomy and partial resection	D2–6 laminectomy and partial resection	
Radiation	Adjuvant RT—45Gy/25# with concurrent TMZ	Palliative RT—20Gy/5#	Planned	
Chemotherapy	Adjuvant TMZ	-	Planned adjuvant TMZ	
Follow-up	Currently on adjuvant chemotherapy	Patient did not report back after RT	Patient did not report back for adjuvant RT and CT	

Table 1 Patient characteristics and treatment summary

Abbreviations: CT, chemotherapy; EMA, epithelial membrane antigen; GBM, glioblastoma multiforme; GTE, gross tumor excision; IDH, isocitrate dehydrogenase; PCV, procarbazine, lomustine, vincristine; RT, radiation therapy; TMZ, temozolomide.

 Table 2
 Baseline demographics of six patients with spinal highgrade glioma

Sl. no.	Characteris	tics	Number of patients (n = 3)
1	Gender	Male	0
		Female	3
2	Age	Median	17 years (12–21 years)
		Mean	15 years
3	Mean symptom duration		10 months
4	Site	Thoracolumbar	1
		Thoracic	2
5	Histology	Astrocytoma	0
		Glioblastoma	3

Methods

This is a retrospective analysis performed at a tertiary cancer center in India. Records of 9,686 patients from January 2015 to January 2022 were studied. Patient details and histopathology reports of three cases of intramedullary SHGG were recorded and have been summarized in **Tables 1** and **2**.

Cases Description

Case 1

A 12-year-old female with no comorbidities presented with progressive gait abnormality for 2 years with loss of pain and temperature sensations for 3 months. Magnetic resonance imaging (MRI) showed a peripherally enhancing intramedullary mass of size $4.9 \times 1.2 \times 1.3$ cm at D7 to 9 (**Fig. 1**). She underwent D7 to 9 laminectomy and gross tumor excision. Histopathological evaluation (HPE) showed glioblastoma multiforme (GBM) positive for glial fibrillary acidic protein (GFAP), isocitrate dehydrogenase (IDH), p53, and high ki67. She received adjuvant radiation 45 Gy in 25 fractions with concurrent temozolomide. Currently, she is on adjuvant temozolomide and is tolerating well.

Case 2

A 21-year-old female with no comorbidities presented with backache and weakness in lower limb for 3 months with progressive loss of sensory and motor functions. MRI showed an intramedullary mass at D2–7 with focal contrast enhancement at cauda equina and leptomeningeal enhancement. She underwent D2 to 10 laminectomy and partial resection of tumor. HPE showed glioblastoma, GFAP, p53 positive, and 30% ki67. She received palliative radiation 20 Gy in five fractions. She did not follow up after completion of radiation.



Fig. 1 (A and B) Peripherally enhancing centrally necrotic intramedullary mass involving dorsal aspect of D7 to D9 measuring $4.9 \times 1.2 \times 1.3$ cm. (C) Postoperative magnetic resonance imaging (MRI) spine with multiple metallic artifacts in dorsal region with cord hyper intensity at level D5 to 11. (D and E): T1 and T2 images of MRI brain with no evidence of abnormality.

Case 3

An 18-year-old female with no comorbidities presented with bilateral lower limb weakness for 3 months with urinary and bowel incontinence for 1 month. MRI showed heterogeneously enhancing intramedullary lesion at D3 to 5, D8 to 9, and D11 to L2. She underwent D2 to 6 laminectomy and partial resection of tumor. HPE showed glioblastoma with a ki-67 of 8 to 9%. She did not follow up for treatment after biopsy.

Discussion

Epidemiology and Etiopathogenesis

Incidence of primary SCT is rare, comprising 2 to 4% of all CNS tumors.² Intramedullary infiltrating SHGG accounts for 7.5%

of intramedullary glioma.³ SHGG has reported annual incidence of 0.12 per 100,000 persons. Among HGG, spinal glioblastoma is even rarer with an incidence of 0.2 to 1.5%.^{4,5}

There is mounting evidence that intracranial and spinal tumors are genetically and at molecular level distinct despite similar morphology.² Differences between intracranial and SHGG are compared in **Table 3**. As a result, 2016 World Health Organization classification of CNS tumors added separate molecular classification for SCT.⁶ The mean age of presentation of SHGG is 35 years with an almost equal incidence in males and females.² However, in this series, all cases were female with a mean age of 15 years. Etiology of SHGG is unknown; however, radiation exposure may be a risk factor.⁷ H3K27M alteration is

Sl. no.	Factors	Intracranial HGG	Spinal HGG
1	Incidence	60% of CNS tumors	Rare (0.12 per 100,000 persons)
2	Most common site	Cerebrum	Thoracic > cervical spine
3	Mean age	75–84 years	30–35 years
4	Gender	Male > Female	Male = Female
5	Symptoms	Headache, seizure	Pain, motor deficits
6	Workup	CEMRI brain	CEMRI spine + CSF cytology in spinal GBM (CT may show canal widening and scalloping of the vertebral bodies. MRI reveals hypo-T1W and hyper-T2W with irregular enhancement)
7	Surgery	More chance of gross tumor resection and it increases survival	Less chance of gross tumor resection (~10% cases) and controversial role in increasing survival
8	Chemotherapy	Response seen with PCV in 1p-19q co-deletion and with TMZ in MGMT hypermethylation	Less response with TMZ
9	Radiation	60 Gy in 30 fractions or 40 Gy in 15 fractions or 25 Gy in 5 fractions depending on performance status	45 to 54 Gy, 1.8–2 Gy/fraction For tumors below conus medullaris, dose up to 60 Gy
10	H3K27M alteration	Rare (seen in midline glioma)	Higher incidence \sim 50% cases
11	BRAF V600E mutation	Seen in \sim 12% cases	Not seen (except 1 case report
14	TERT promoter mutation	Common (~46%)	Lower incidence (\sim 7%)
15	CDKN2A	Lower incidence	Higher incidence
16	IDH mutation	More common in low grade glioma	Usually negative
17	TP53 mutation	Common	Common (~80–90%)
18	ATRX loss	Common	Lower incidence (~33%)
19	Immunotherapy	Bevacizumab is indicated in recurrent GBM	Bevacizumab improved response with median OS 22.8 months
20	Overall survival	5 years OS <10%	Grade III—25.5 months; Grade IV—12.5 months

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Table 3 Summary and comparison of intracranial and spinal astrocytoma and glioblastoma ^{2, *, *}	,13,13,21 24

Abbreviations: CEMRI, contrast-enhanced magnetic resonance imaging; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; GBM, glioblastoma; HGG, high-grade glioma; IDH, isocitrate dehydrogenase; MGMT - O6, methylguanine-DNA methyltransferase; OS, overall survival; PCV, procarbazine, lomustine, vincristine; T1W, T1-weighted; T2W, T2-weighted; TMZ, temozolomide.

frequently observed in SHGG and is considered a key driver for tumor development.⁸ They are found in the histone H3F3A gene or HIST1H3B genes, which encode the histone H3 variants H3.3 and H3.1, respectively. H3K27M alterations in the N-terminal tail of the histone H3 genes substitute a lysine on the histone H3 tail for a methionine and result in global loss of trimethylation on histones H3 molecules, which leads to potential tumorigenesis.⁹ Also, TP53 gene mutation and loss of α-thalassemia/mental retardation syndrome X-linked (ATRX) affects loading of histone H3.3 in heterochromatic telomeric regions and are associated with H3K27M alteration. TP53 mutation has been shown to be expressed in 80 to 90% spinal cord GBM.² Telomerase reverse transcriptase gene promoter has been found to be useful for prognostication, with poor outcomes reported among patients with IDH wildtype infiltrating gliomas.³

Clinical Presentation and Diagnosis

Pain is the predominant symptom in patients. Patient can present with back pain, radicular pain, or central pain. Other symptoms depend on the site of tumor that may include motor disturbance, sensory deficits, or autonomic dysfunction. Patient may also present with progressive scoliosis and if tumor is located at cervicomedullary junction, it may affect cranial nerves.¹

In cases suspicious for SHGG, spine MRI is used for imaging. Tumors are more commonly located in thoracic and cervical spine region with an average involved length of 4 vertebrae. Thoracic spine was involved in all the cases reported in this series and the patient presented in later stages as 7 vertebral length was involved on average. Usually, it is an infiltrating solid lesion with variable focal enhancement causing fusiform expansion of cord that may be accompanied by cysts and surrounding edema. Tumor appears iso- to hypointense on T1-weighted, hyperintense on T2W with lower apparent diffusion coefficient on diffusion-weighted imaging.^{1,5} A few studies have concluded that MRI findings cannot be used to differentiate between H3K27M alteration and wild-type tumor.⁹ Screening of the entire neuroaxis should be done to rule out primary SHGG as well as to identify drop metastasis. In 20 to 30% cases, cerebrospinal fluid (CSF) metastasis can occur in spinal GBM and therefore, CSF analysis should be done in spinal GBM patients.¹⁰

On HPE, HGG has atypia, high mitotic figures, and endothelial proliferation. Necrosis is found in spinal GBM. Immunohistochemistry (IHC) like glial fibrillary acidic protein (GFAP), ki67, and S-100 is required to differentiate HGG from others. Differential diagnosis includes ependymoma, hemangioblastoma, lymphoma, and metastasis.⁵ In our patients, diagnosis of SHGG was established by clinical presentation, radiological features, and HPE including IHC. Molecular testing is not done routinely in our institute, and hence, information on molecular analysis could not be obtained.

Management

Primary intramedullary spinal cord tumors are extremely rare with occasional case reports and series and thus, no standard treatment protocol has been established.¹¹ Treatment options include surgery, radiation therapy (RT), and systemic therapy.

The goal of surgery is maximal resection with preservation of neural function. Surgical resection could be either gross total resection (GTR) with more than 90% of tumor removal, subtotal resection with 50 to 90% tumor removal, and partial resection with less than 50% tumor removal or open biopsy.¹² Due to the highly infiltrative nature of these tumors, it is difficult to find a good resection plane and hence, GTR rates are low.² However, a few contradicting reports showing no effect on survival with extent of resection are there.^{4,13}

Various approaches that are used for resection are dorsal root entry zone (DREZ) myelotomy, posterior midline myelotomy, myelotomy anterior to DREZ for lateral or ventrolateral tumors with intraoperative monitoring using motor evolved potentials, somatosensory evoked potentials, and electromyography to assist in deciding further resection when planes are not clear.^{2,14} In unresectable tumors, biopsy and duraplasty are done to allow for inevitable uncontrolled growth of tumor.²

Literature on use RT in SHGG is limited. Intent of RT can be radical or palliative. RT is indicated for patients with highgrade histology, incomplete resection and those with progressive disease.¹ For grades III to IV tumors, radiotherapy may be initiated earlier than usual 4 to 6 weeks. Pre- and postoperative MRIs are coregistered to treatment planning computed tomography (CT) images to delineate the target volume including the residual disease and postoperative cavity, as well as the region at risk of microscopic disease spread (but not including the syrinx associated with the tumor).¹⁵

RT dose for spinal cord gliomas is 45 to 50 Gy in conventional fractions at 1.8 Gy per fraction with five fractions delivered over 5 days in a week. However, in tumors below the conus medullaris, higher doses, up to 60 Gy, can be delivered. Dose is limited to 45 to 54 Gy in conventional fractionation due to dose-limiting structure including spinal cord, as there is a risk of radiation-induced myelopathy. Intensity-modulated RT (IMRT), volumetrically modulated arc therapy (VMAT), or proton beam therapy with daily image guidance should be used for conformal treatment of the at-risk spinal disease.¹⁵ However, RT dose can be further increased by use of IMRT and stereotactic body radiation (SBRT) while minimizing the dose to surrounding normal tissue. Pre- and postoperative MRIs are coregistered to treatment planning CT and target volume is delineated to include the residual disease and postoperative cavity along with region at risk of microscopic disease spread.¹⁵ Radiation is usually given by VMAT technique using 6 MV photons to a dose of 45 Gy in 25 fractions to low-risk planning target volume (PTV) followed by a 9 Gy boost to residual disease. For CTV 45, a margin of 1.5cm is given superoinferiorly to gross tumor along with an additional margin of 1cm for PTV 45. For boost dose, 1cm margin to gross tumor is considered and confirmed with cone-beam CT.¹⁰ Recommended SBRT doses are 12.4 to 14.0 Gy in one fraction, 17.0 Gy in two fractions, 20.3 Gy in three fractions, 23.0 Gy in four fractions, and 25.3 Gy in five fractions; however, there are as yet no reported randomized trials that prove the benefit in spinal GBM.¹⁶

For gliomas with CSF positivity, craniospinal irradiation is usually indicated.⁷ Based on the Stupp regime for intracranial HGG, RT is preferred to be given with concurrent temozolomide at dose of 75 mg/m² orally given daily. It is followed by six cycles of adjuvant temozolomide at 150 to 200 mg/m² orally on days 1 to 5, repeated every 4 weeks.¹⁰ Radiation with proton has been tried in low-grade spinal glioma and had the advantage of delivering lower dose to normal tissue and lesser acute toxicity without reducing the results.¹⁷

Temozolomide, an oral alkylating agent, has been used in the treatment of intracranial HGG. However, the survival benefit seen in intracranial HGG should not be extrapolated to SHGG as there are genetic and molecular differences between them. Multiple retrospective studies evaluating temozolomide have shown variable outcomes with inconclusive benefit and with an observed 3 months median time to tumor progression who fail to show response.¹¹

Other chemotherapy agents that have been tried are lomustine, carboplatin, vincristine, procarbazine, lomustine, vincristine regime and "8 in 1" regime. However, none of them appear to be highly effective.¹

Bevacizumab, a vascular endothelial growth factor inhibitor, has antiangiogenic and antiedema effects. Patients have shown prolonged and durable response with median overall survival of 22.8 months. Moreover, results have shown improvement in neurologic function that may be attributed to reduction in the edema around compact location of spinal cord.¹⁸

Use of immunotherapy for SCT has been tried recently in a phase 1 trial of autologous GD2-CAR T cells. It was studied in

children and young adults with nonbulky pontine and spinal cord DMG with H3K27M alteration. Imaging of SHGG patient showed more than 90% reduction in tumor volume at 1 month along with improvement in neurological deficit. As a result of functional recovery, it was highlighted that this diffusely infiltrating tumor disrupts rather than destroys the neurological circuits. However, at present, clinical experience is limited and optimal dose, route, and schedule are yet to be ascertained.¹⁹

Many ongoing trials are using targeted agents against BRAFV600E, BRAF target fusion protein, and H3K27M.² Also, it has been observed that neural stem cells (NSC) have tropism for tumors that can be used to deliver toxic drugs to tumor cells. So, various engineered NSC, that expresses an enzyme that activates an administered prodrug at tumor site resulting in higher concentration at tumor site, have been tried. An NSC line that expressed cytosine deaminase- HB1. F3.CD.C21, which converts the pro-drug 5-fluorocytosine to the cytotoxic 5-fluoruracil, showed a good safety profile and was itself nontumorigenic.² Also, a direct intratumoral injection is not practical for these subsites so intrathecal delivery, biodegradable polymers, and convection enhanced delivery may prove to be useful.²

Prognosis

Prognosis of SHGG is extremely poor.³ Despite the multimodality aggressive treatment, recurrence rates are high. Poor prognostic factors include older age (>40 years), cervical location, inability to achieve GTR, higher grade, necrosis, H3K27M alteration, and p53 mutation.^{4,20} Median survival of spinal GBM is 10 to 20 months depending on treatment modality used and it increases slightly to 25.5 months for grade III astrocytoma.⁴ H3K27M alteration has been shown to be associated with poor prognosis with an average life expectancy of 10 months. The reported 5-year survival is less than 1%.¹⁹

Conclusion

Primary intramedullary HGG and GBM of spinal cord are uncommon tumors of CNS. In this article, we have reported a series of three cases with GBM of spinal cord. Due to rarity of cases, a randomized prospective study to compare treatment strategies has not been feasible. Treatment recommendations are based on current guidelines of intracranial HGG and GBM. Despite aggressive treatment using surgery, radiation and chemotherapy, the survival rates are dismal. Emerging evidence has shown difference in biological behavior of intracranial and SHGG. Newer molecules are under study that may have positive results for SHGG; however, genetic studies to understand the biology and prospective studies are needed.

Ethical Approval

Taken as applicable in our center. The patients consented for treatment and collection of data.

Consent for Publication

Written informed consent to publish was obtained from individual patients.

Authors' Contributions

A was involved in conceptualization, writing—original draft and editing; RS contributed to conceptualization, editing, and review; VY contributed to editing and supervision; MM and AD edited and reviewed the manuscript; HK, PT, and AM supervised and reviewed the study.

Conflict of Interests

None declared.

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