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CASE REPORT

Intensity Modulated Radiotherapy in a Rare Case of Spinal Glioblastoma Multiforme: A Case Report

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ABSTRACT

Introduction- Primary spinal cord glioblastoma multiforme (GBM) is a rare clinical entity with an aggressive course and an invariably dismal prognosis. There are around 200 reported cases of spinal cord GBM in total and approximately 70 cases in the cervical region. Median survival for this disorder is only 12 months. We report a case of a 36 year old female patient with primary spinal cord GBM.

Case Summary- A 36 year old female patient presented with complaints of pain in neck and progressive left limb paresis. MRI Cervical Spine was suggestive of an infiltrating intramedullary lesion. She underwent C2-D1 laminectomy and tumor decompression. Histopathology was suggestive of spinal cord Glioblastoma. Post- operative MRI was suggestive of a possibility of leptomeningeal tumor seeding. Patient was planned for cranio-spinal radiotherapy by IMRT technique along with concurrent chemotherapy with. Temozolomide. Temozolomide was discontinued after the first week due to severe bone marrow suppression. Adjuvant Temozolomide was started after 4 weeks of completion of radiotherapy. But after first cycle she developed febrile neutropenia and thereafter, further chemotherapy was withheld. Patient expired after 13 months from date of diagnosis.

Conclusion- Primary spinal GBM is a clinically rare entity that progresses rapidly with a dismal prognosis and a short survival time despite aggressive management.

Keywords: glioblastoma multiforme, Temozolomide, Spinal cord

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INTRODUCTION

Spinal cord glioblastomas (GBM) are quite rare and account for only 1% to 3% of all primary spinal tumors.[1] These tumors have a high predilection to the cervicothoracic tract. These tumors are associated with a poor prognosis with a median survival of only 12 months. Glioblastoma multiforme (GBM) is one of the most aggressive malignancies and also the most common malignant primary tumor of the brain and central nervous system, accounting for 14.5% of all central nervous system tumors and 48.6% of malignant central nervous system tumors.[2] A poor prognosis of spinal cord GBM may be attributed to various factors such as its high rate of leptomeningeal seeding, disease location, and tumor resectability. Its rarity could be explained by the fact that histologically neuroglial cells outnumber neurons by about 5 to 10 times[3] as the brain has a higher number of neuroglial cells than the spinal cord. GBM is far more commonly seen in the supratentorial compartment than the subtentorial compartment and more commonly in the frontal lobe.[2]

In cases of spinal cord GBM symptom, time greater than 6 months and patient age of 18 years or less predicts for an improved progression-free and cause specific survival.[4] Cervical glioblastomas appear to be the most unfavorable due to increased morbidity.[5] There is no significant difference in the clinical outcome between patients receiving different chemotherapy regimens other than temozolomide (TMZ).

Patients usually present with progressive sensorimotor and autonomic deficits due to multiple tract involvement within the spinal cord.[6]

Histopathological features of spinal cord GBM are identical to intracranial tumors, including cellular pleomorphism, high mitotic activity, necrosis and vascular proliferation.[3,7] They also show focal expression of a glial fibrillary acidic protein (GFAP) and S-100 protein.

Though surgery remains the primary treatment of choice in spinal cord glioblastomas,[7] the extent of surgery is not a reliable predictor of outcome.[1]

The role of radiotherapy is associated with better outcomes. Due to a high risk of intracranial and leptomeningeal spread, few authors have suggested whole brain radiation along with focal spinal irradiation. In contrast, some recommend craniospinal irradiation and administration of intrathecal chemotherapy.

Till date, there are no set standard guidelines for the treatment of spinal cord glioblastomas though surgery

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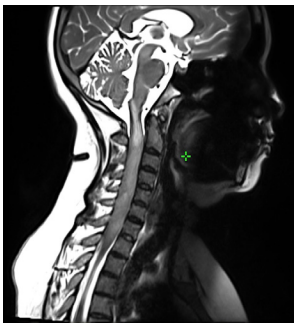


Fig: 1a-Sagittal T2

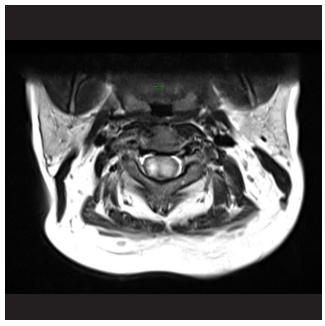


Fig: 1b- Axial T2

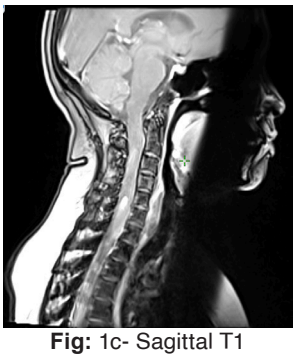


Fig: 1c- Sagittal T1

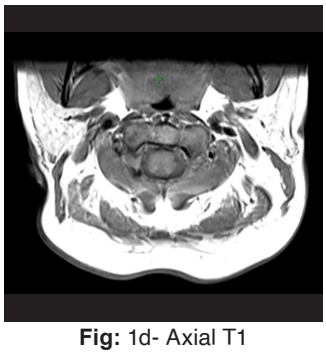


Fig: 1d- Axial T1

Fig: 1a-1d- Gadolinium contrast enhanced MRI showing diffuse infiltrating intramedullary expansile neoplasm involving the cervico-medullary junction, cervical spinal cord and adjacent proximal thoracic spinal cord (from the level of clivus till the superior endplate of D2 vertebrae).

remains the primary treatment of choice in spinal glioblastoma with a median survival of 12 months.[1]

We report a case of a 36 year old female with proven cervical cord Glioblastoma Multiforme (GBM) and are discussing the treatment by radiotherapy aspects and follow-up of the patient.

Case History

A 36 year old female patient presented to the oncology OPD with pre-operative complaints of pain in the neck and progressive left limb paresis since 2 months after which she was confined to bed.

She underwent MRI cervical spine contrast enhanced (MRICSCE) (Fig. 1 (a-d) which was suggestive of a Diffuse infiltrating intramedullary expansile lesion involving the cervico-medullary junction, the cervical spinal cord and the adjacent proximal thoracic spinal cord extending approximately from the level of clivus till the level of the superior endplate of D2 vertebra measuring approximately 11.5 cm cranio-caudal (CC) x 1.8 cm transverse (TR) x 1.2 cm antero-posterior (AP) involving both the half of the spinal cord (left > right) with ill-defined margins, appearing hyperintense to the normal cord parenchyma on long transverse (TR) sequences and iso to hyperintense on T1 weighted images (T1WIs) with heterogeneous patchy mild to moderate post-contrast enhancement. The mentioned lesion showed no significant diffusion restriction or blooming on the

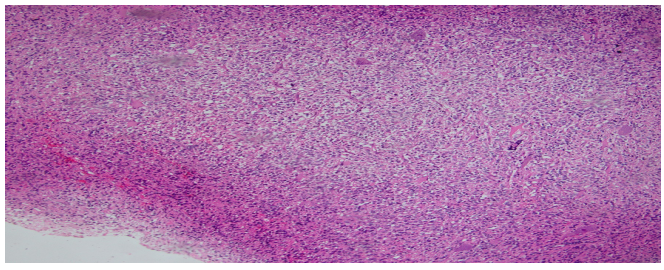


Fig: 2a- Markedly cellular tumor(10X)

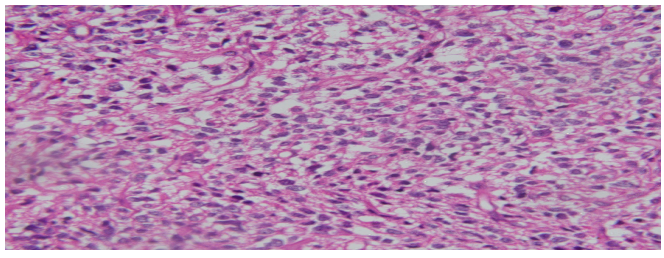


Fig: 2b- Round to pleomorphic cells lying in fibrillary vascular background.(40X)

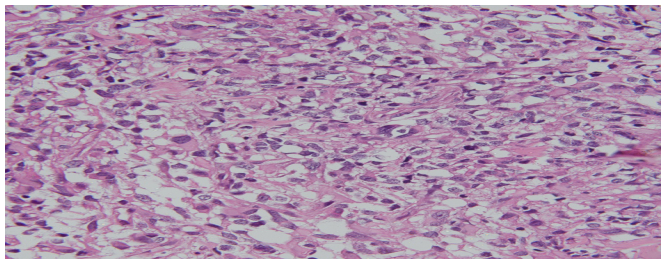


Fig: 2c- Image showing gemistocyte like cells

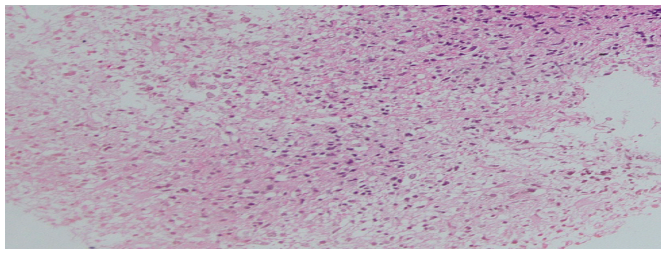


Fig: 2d- Image showing necrotic area

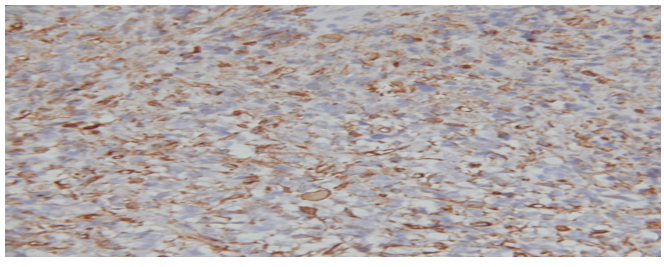


Fig: 2e- Image shows vimentin positivity(40X)

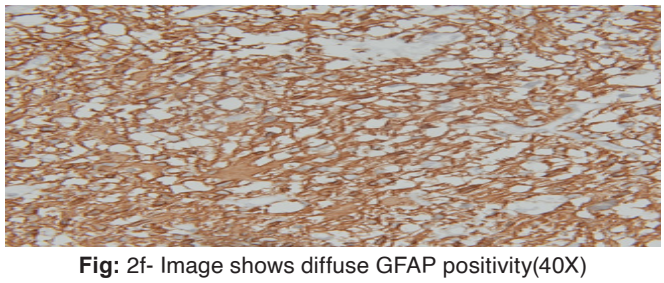


Fig: 2f- Image shows diffuse GFAP positivity(40X)

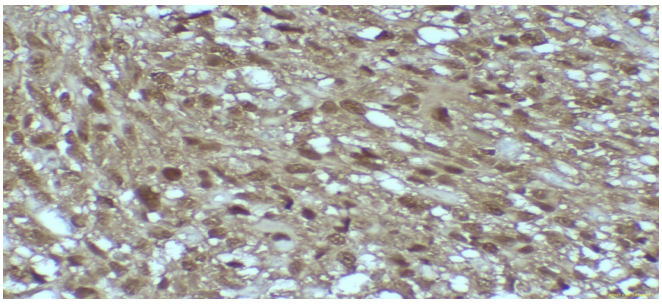


Fig: 2g- Image shows diffuse S-100 positivity (40X)

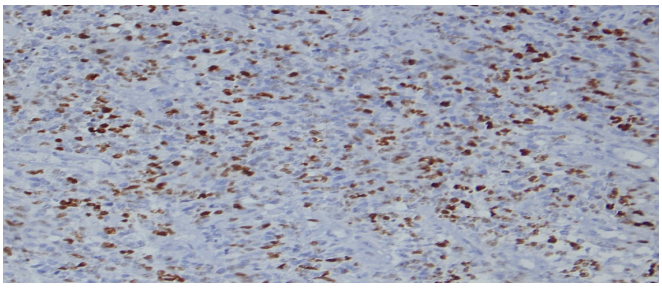


Fig: 2h- Image shows Ki67- > 20% positivity (10X)

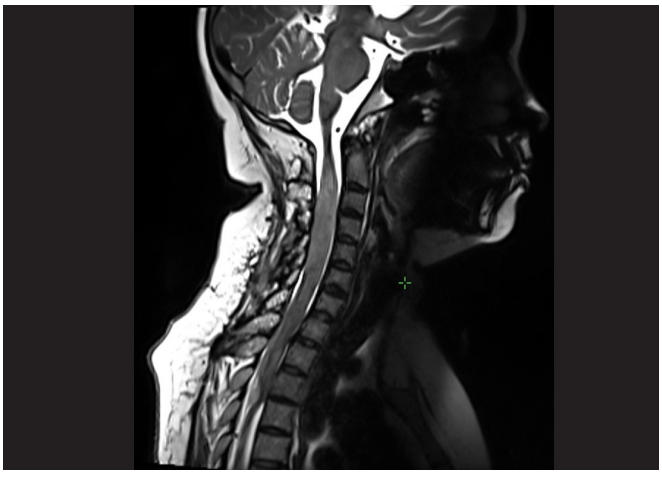


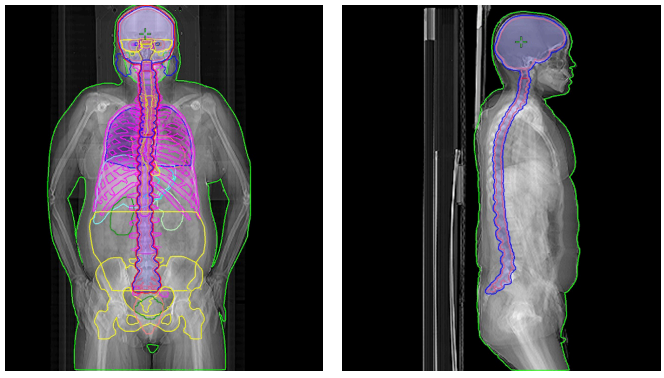
Fig 3: Gadolinium contrast enhanced Post Op MRI showing lesion from the level of clivus till the level of superior endplate of D4 vertebra in Sagittal T2 section

gradient sequence. No signal drop within the lesion was noted on chemical shift imaging.

She underwent C2-D1 laminectomy and tumor decompression. Per-op findings- the tumor was identified on left side surface of C5-C6 levels. Tumor cord interface not identifiable at upper and lower side. Hence, only limited decompression was possible and layered closure was done.

Histopathology was suggestive of glioblastoma (Fig. 2 a-d) as on IHC Vimentin (Fig. 2e) GFAP (Fig. 2f) and S100 (Fig. 2g) were diffusely positive, Ki67 (Fig. 2h) was > 20% positive.

Post-op MRICSCE (Fig. 3) which was done after one month of surgery was suggestive of a Diffuse infiltrating intramedullary expansile lesion involving the cervico-medullary junction, the cervical spinal cord and the adjacent proximal thoracic spinal cord extending approximately from the level of clivus till the level of



a b

Fig 4: Delineation of structures (a) OARs, CTV and PTV volumes, (b) CTV and PTV volumes

superior endplate of D4 vertebra currently measuring approximately 15.0cms CC x 1.8 cms TR x 1.3cms AP involving both the half of the spinal cord (left > right) with ill-defined margins, appearing hyperintense to the normal cord parenchyma on long TR sequences and iso to hyperintense on T1WIs with heterogeneous patchy mild post contrast enhancement. The mentioned lesion showed no significant diffusion restriction or blooming on gradient sequence. Prominent leptomeningeal enhancement was noted along the pons, medulla and cervical spinal cord. Abnormal leptomeningeal enhancement with thickening noted predominantly along the posterior aspect of the visualized thoracic spinal cord approximately from D1 level downward. The findings were suggestive of an overall disease progression as compared to the previous MRI with likely leptomeningeal tumor seeding.

Case was discussed in multidisciplinary tumor board and was planned for radiotherapy along with concurrent TMZ. Radiotherapy was planned with Cranio-spinal irradiation (CSI) technique which was delivered by intensity modulated radiotherapy (IMRT) in 2 phases (Fig. 4a-b).

Dose delivered- Phase I- 36 Gy in 20 fractions @ 1.8 Gy/fraction to whole brain and whole spine upto cauda equina.(Fig. 5a-Fig. 5b)

Phase II-18 Gy in 10 fractions @ 1.8 Gy/fraction from clivus to D5 as boost

A total dose of 54 Gy in 30 fractions @ 1.8 Gy/fraction was delivered to the tumor.

After one week of starting radiotherapy patient had seizures for which she was admitted and conservatively managed with anti-epileptics and diuretics. She underwent imaging of the brain and CSF cytology was also done; both were not contributory to the etiology of seizures. The patient had bone marrow suppression (anemia, leukopenia, thrombocytopenia) for which conservative management was given in the form of blood transfusions, platelet transfusions, G-CSF support, and

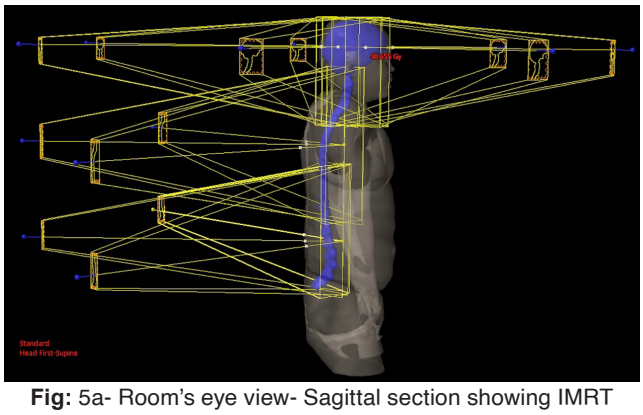


Fig: 5a- Room's eye view- Sagittal section showing IMRT planning field arrangement

Fig: 5b- Dose colour wash

antibiotic coverage. Hence, TMZ could not be given after the first week of radiotherapy.

Radiotherapy was re-started after 10 days and after 4 weeks of radiotherapy patient was symptomatically better in terms of improvement in lower limb weakness. Radiotherapy was completed in December 2020. The patient was advised for whole body physiotherapy.

After one month of completion of radiotherapy, adjuvant chemotherapy with TMZ was planned but delayed as patient developed anemia. After conservative management and blood transfusion, adjuvant chemotherapy was started with TMZ 150-200 mg/m^2(approximately 2 months after completion of radiotherapy).

After 20 days, the patient presented to the OPD with complaints of fever on and off, pain over the gluteal region, and excessive sweating. Her blood counts were deranged(Hb-7.5 gm/dl, TLC-2600/mm^3, neutrophils-83%, lymphocytes-15%,eosinophils-1%, monocytes-1%, basophils-0%, platelets-38000l ac/mm^3) and she was diagnosed with febrile neutropenia. Patient was admitted and managed conservatively with intravenous antibiotics.

Patient did not take TMZ after the first adjuvant cycle as she could not tolerate it and hence, was unwilling to continue the same. She defaulted on her follow-up for 7 months and presented to the OPD with complete loss of power in bilateral lower limbs.

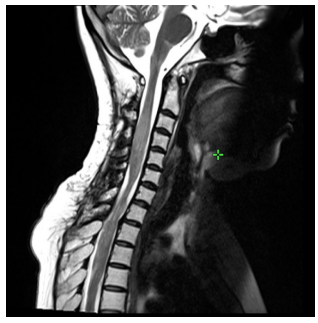


Fig: 6a- Sagittal T2

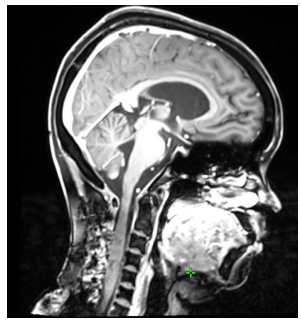


Fig: 6b- Sagittal T1 contrast

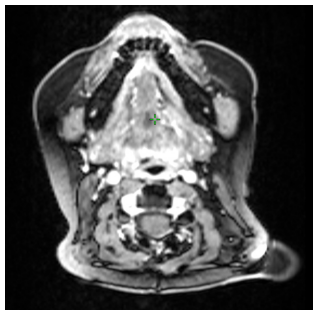


Fig: 6c- Axial T1

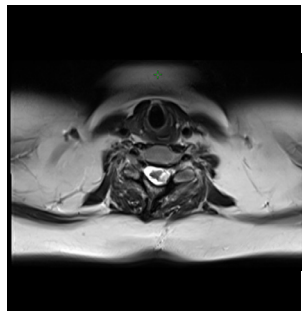


Fig: 6d- axial T2

Fig: 6a- Fig. 6d- Gadolinium contrast enhanced MRI showing mild cervical spinal cord swelling noted from C3/C4 interspace level till C6/C7 interspace level and T1 hypointense lesion involving predominantly left half of the spinal cord.

MRI brain and cervical spine with contrast was done (Fig. 6a-d) which was suggestive of a mild communicating hydrocephalus, non-specific bilateral fronto-parietal white matter ischemic lesions. Mild cervical spinal cord swelling noted from C3/C4 interspace level till C6/C7 interspace level with T2/STIR hyperintense and T1 hypointense lesion involving predominantly left half of the spinal cord measuring approximately 4.5 cm CC x 1.1 cm TR x 1.2 cm AP with no significant diffusion restriction. Faint post-contrast enhancement is noted in the above mentioned lesion. Mild thinning of the cervical spinal cord with heterogeneous signal intensity and no significant post-contrast enhancement noted at C7/D1 vertebral level, likely post-treatment changes. The radiological regression of disease did not correlate with the neurological response.

The patient and attendant were not willing for further adjuvant treatment and were kept on supportive management. Patient expired after 3 months of the last follow-up; with a survival of 13 months (calculated from the date of diagnosis).

DISCUSSION

Spinal cord GBM is a rare entity and is a highly malignant neoplasm with a poor prognosis. Due to the tumor's rarity, there are no set guidelines for treatment though surgery is the primary treatment.

A review article by Timmons et al.[1] reported that primary GBM of the spinal cord is rare and accounts

for only 1% to 3% of all primary spinal tumors. There have been fewer than 200 reported cases of spinal cord GBM in total with a median survival of only 12 months. Another article by Jokovic *et al*.,[8] stated that the primary localization of GBM at cerebellum, brain stem and spinal cord is extremely rare, with a reported annual incidence of 0.12 cases out of 100,000. In the last 15 years, the incidence of Spinal cord GBM was less than 1% in our department out of approximately 150 treated cases of GBM.

In an analysis by Rodrigues *et al*.,[4] they studied different variables and an univariate analysis showed that symptom time greater than 6 months, grade of the tumors, female sex and patient age of 18 years or less predicted for improved progression free and cause specific survival. In the review article by Timmons *et al*.,[1] they inferred that the female sex significantly predicted worse outcomes. Extent of surgery, and total radiation dose were not predictive of outcome. In our case we report a 36 years old female with a symptom duration of 2 months prior to diagnosis and high grade tumor which could be related to poor prognosis.

Timmons *et al*.,[1] inferred that a sizable number of patients with long term disease were found to have afflictions of the thoracic spinal cord. As stated in the article by Jokovic *et al*.,[8] the cervicothoracic region is the most frequent site. According to Raco *et al*.,[5] cervical glioblastomas appear to be the most unfavorable due to increased morbidity associated with the involvement of the higher cervical areas (respiratory insufficiency appears at an earlier stage). In our case, the site of involvement extended approximately from the level of the clivus (cervico-medullary junction) to the level of the superior endplate of D2 vertebra. Though in our case no signs of respiratory insufficiency was seen.

Few authors have reported,[3,7] that the histopathological features of spinal cord GBM are identical to intracranial tumors. We also had similar histopathology and IHC findings with GFAP and S-100 were diffusely positive, Ki67 was > 20% positive.

Due to the rarity of spinal cord GBMs there are no set guidelines for optimal treatment. Surgery remains the primary treatment of choice in spinal glioblastoma same as their intracranial treatment.[7] One of the important prognostic factors for intracranial GBM is maximal safe resection while the same does not hold true for spinal cord GBM. As per the review by Jokovic *et al*.,[(8)] the extent of resection does not appear to be a reliable prognostic factor for overall survival in spinal GBMs and, as reported by Behmanesh[9] and Konar,[10] extensive surgical manipulation can facilitate tumor cell seeding and dissemination. Mallick *et al*.,[7] reported that Cerebrospinal fluid (CSF) involvement and consecutive intracranial seeding determine the prognosis of patients with spinal cord GBM. So the authors recommended that regular monitoring of CSF-cytology and/or spinal magnetic resonance imaging (MRI) appears to be advisable in spinal GBM. In our case also, postoperatively, we could see leptomeningeal seeding which was not present preoperatively, this may have led to the progression of the disease as per radiological findings.

Radiotherapy administration is associated with better outcomes. The radiation protocol requires 50.4 Gy in 28 daily fractions, which is a lower dose than brain radiotherapy (60 Gy).[8] This is due to the spinal cord sensitivity to higher radiation doses, resulting in permanent injuries and neurological deterioration. A traditional radiation dose for spinal cord tumors has been 45 Gy in conventional fractions because of dose limiting structures, including the spinal cord, the cauda equina, and some critical structures such as the lung, esophagus, gastrointestinal tract, and genitourinary tract. However, some institutions used doses as high as 50–54 Gy without significant myelopathy. Garcia *et al*.,[11] and Shaw *et al*.,[12] found significantly improved survival from reduced local recurrence by doses higher than 40 or 50 Gy, respectively. More recently, Kahn *et al*.,[13] reported the good outcomes of modern RT techniques (IMRT or proton therapy), prescribing a median of 51 Gy safely for 32 primary spinal cord gliomas. Adjuvant radiotherapy (54 Gy in 30 fractions) along with concurrent TMZ was given in our case. Radiotherapy was planned by IMRT technique. Radiotherapy was delivered to the whole brain and the whole craniospinal axis.

The role of chemotherapy (CT) is not well-established. There are a wide spectrum of treatment regimens available with variable responses. In various studies TMZ has shown favorable outcomes in concurrent and adjuvant settings. A better outcome with the addition of TMZ may be attributed to the fact that it is a potent radiosensitizer and that the spinal cord's tolerance for radiation is less than that of the brain. While some recommend craniospinal irradiation and administration of intrathecal chemotherapy. Hernandez-Duran *et al*.,[6] concluded that TMZ does increase survival in primary spinal GBM patients, and they did advocate for it, though it did not reach statistical significance between patients with primary spinal GBM treated with TMZ versus those not treated with TMZ. Hence, the role of TMZ is controversial in cases of spinal cord GBM. Shen *et al*.,[14] reported that Bevacizumab (BEV) is another potential chemotherapy drug of interest. An article by Choi et al.,[15] showed that radiation-related toxicities in the spinal cord are more concerning than at other sites. Thus, at the first radiation treatment, we should carefully determine the most appropriate field and dose. However, since hematologic and neurologic toxicity due to CSI remains a major concern, careful radiation delivery is necessary. In our case, after administering a tentatively higher dose of 54 Gy we observed that the patient developed radiation-induced toxicities in the form of lower limb weakness. We also started concurrent TMZ and adjuvant TMZ but

patient could not tolerate it due to severe bone marrow suppression for the complete duration of radiotherapy and later on.

Delgado *et al.*,[16] reviewed the National Cancer Database of 103496 patients diagnosed with primary brain GBM versus 190 patients diagnosed with primary spinal cord GBM between the years of 2004 and 2014 and showed that primary spinal cord GBM had a greater mean survival of 11.2 months compared with cranial GBM median survival age of 9.2 months. Among these 190 spinal GBM, 18 to 65 years age group reported having a longer survival time of 13.2 months, compared with younger than 18 years old and older than 65 years old groups with 11.9 months and 3.9 months, respectively. In our case a survival of 13 months was observed which was inspite of the unfavorable prognosis seen in cervical area involvement, break in radiotherapy treatment and non-compliance of TMZ.

The lack of significant survival improvements with current treatments has paved the way for investigations on the role of immunotherapy.[17] The genomic landscape of high-grade spinal astrocytomas is now understood to be different from intracranial neoplasms and may include mutations in H3K27M, TP53, and TERT promoters. However, immunotherapy research in primary spinal GBM remains limited due to the small number of specific antigens identified, neurotoxicity of drugs to the spinal cord, scarcity of cases, and difficulty obtaining sufficient tissue for immunologic studies.[18] In our case patient refused further treatment due to which the option of immunotherapy could not be explored.

CONCLUSION

Spinal glioblastoma is rare and carries a poor prognosis. The role of surgery is limited and the escalation of radiotherapy dose also has a limited role. The addition of chemotherapy may play an important role if utilized with strict supportive management.

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