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Case Report

Cervicomedullary glioblastoma: A report of two cases with review of literature

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ABSTRACT

Background: Cervicomedullary glioblastoma is an extremely rare clinical entity and the principles of its management are not well understood.

Case Description: We report two cases of cervicomedullary glioblastoma in young patients aged 12 and 30 years with contrasting clinical presentation and outcomes. The 12-year-old child had rapid onset bulbar symptoms, with frank infiltration of the medulla due to which the patient succumbed within 4 weeks of surgery. The 30-year-old adult had a relatively slow disease onset and progression and made a good neurological recovery without disease progression at 16 months after surgery. To the best of our knowledge, we also report only the second adult patient in the literature with a dorsally exophytic cervicomedullary glioblastoma. Difficulties in diagnosis and management are discussed with a review of the pertinent literature.

Conclusion: The overall outcome depends on the rapid progression and severity of preoperative symptoms and the degree of tumor infiltration noted in imaging and during surgery.

Keywords: Cervicomedullary, Exophytic, Glioblastoma, Intramedullary, Spinal cord

INTRODUCTION

Intra-axial cervicomedullary tumors (CMTs) are a heterogeneous group of tumors. CMT is usually a low-grade tumor with only a small fraction being malignant.[15] They have a slow growth rate, are considered histologically "benign," and have an indolent clinical presentation along with progressive and slow onset neurological symptoms.[7,16,17] CMT is typically described more commonly in the pediatric age group;[7,16] however, occasional case series have also described a higher incidence in young adults.[13] As per the Central Brain Tumor Registry of the United States, glioblastomas constitute only 2.2% of pediatric spinal tumors.[14] However, this registry did not stratify glioblastoma as per their location in the spinal cord nor was glioblastoma in the adult population described.[14] High-grade CMT is extremely rare. We report two cases of high-grade CMT and review the pertinent literature. To the best of our knowledge, primary dorsally exophytic cervicomedullary intramedullary glioblastoma in our Case 1 has been reported only once in the literature.

CASE DESCRIPTION

Case 1

A 30-year-old female presented with numbness and heaviness left upper limb associated with a weak grip left hand for 6 months. She also complained of pain in the neck on and off for 1 year. On examination, she had weakness of the left shoulder with a weak left-hand grip. Her left shoulder power was 4/5 while her left-hand grip was approximately 80% of her contralateral normal hand without any other neurological deficits. Magnetic resonance imaging (MRI) of the cervical spine revealed an elongated, bulky, and expansile mass lesion extending from the superior margin of the medulla with a dorsally exophytic component, and caudally was up to C6 vertebral level [Figure 1]. The lesion was hypointense on T1-weighted (T1W) images and predominantly hyperintense on T2-weighted (T2W) images. In the axial images, asymmetric involvement was noted; the left hemicord was more affected than the right [Figure 2]. Mild T2 hyperintensity suggestive of vasogenic edema was seen along the inferior aspect of the lesion, reaching up to the C7–T1 disc level and minimally in the medulla. The spinal subarachnoid space was effaced. Based on these findings, the possibility of a high-grade glial neoplasm was suspected. Suboccipital craniotomy, C1 to C6 laminoplasty, and gross total resection of the tumor were done and the whole tissue was sent for histopathological examination. Intraoperative neuromonitoring using a combination of motor-evoked potentials (MEPs), somatosensory-evoked potentials (SSEPs), and lower cranial nerve monitoring was used during surgery. Loss of SSEP in the left upper limb was noted presurgery but the MEPs in all limbs and SSEP in the other three limbs were undisturbed during the surgery. The patient had an uneventful postoperative recovery. Postoperative MRI done 2 days after surgery showed complete excision of the lesion along with postoperative edema and changes in the tumor bed [Figure 3]. The histopathological report however suggested a glioblastoma. Further studies showed that the tumor retained ATRX protein and was GFAP and p 53 positive, IDH1 R132H negative, and H3K27M mutation absent. MIB 1 index was 5–7% in the highest proliferating areas. Thus, the integrated diagnosis of this patient was glioblastoma, IDH wildtype, and WHO Grade 4. The patient had a complete neurological recovery, after the completion of radiotherapy and temozolomide at her last follow-up 24 months following her surgery without any recurrence. She

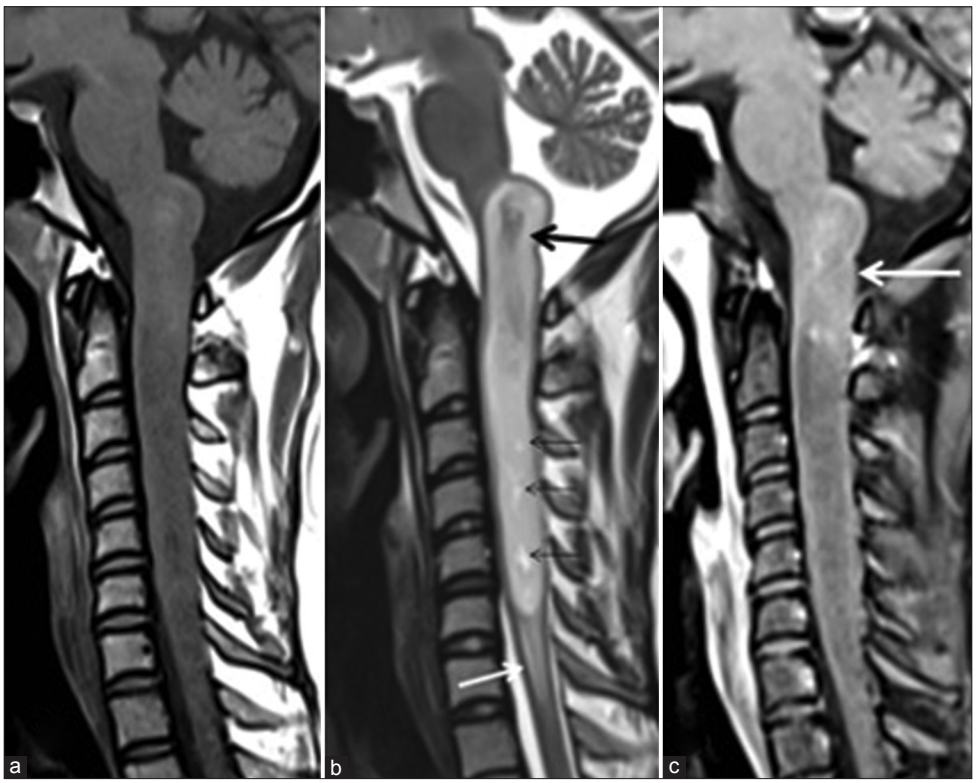

Figure 1: Case 1. Sagittal T1-weighted (a), T2-weighted (b), and post contrast (c) images of the cervical spine show presence of a bulky, expansile, and elongated mass in the medulla and spinal cord upto the C6 vertebral level. Intrinsic T2 hypointensity in the cranial portion (black arrow), tiny cystic foci (thin black arrows), and hyperintense edema (white arrow) are seen in (b). Minimal patchy enhancement is seen in (c) (white arrow).

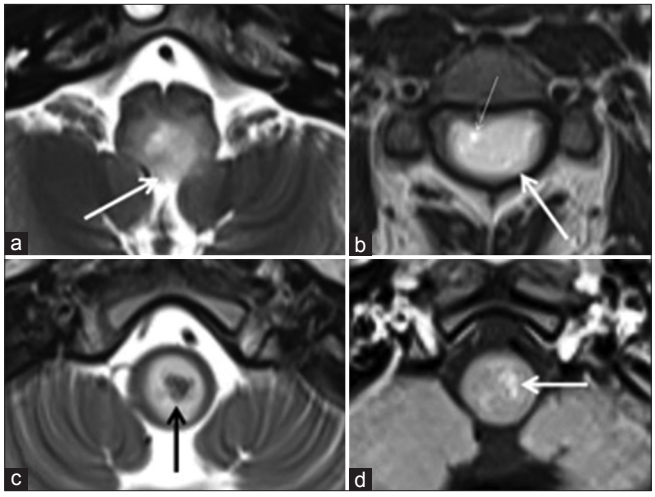

Figure 2: Case 1. Axial T2-weighted (a-c) and post contrast T1-weighted (d) images reveal dorsal exophytic extension in (a) (white arrow), asymmetric involvement, more in the left hemicord (long white arrow), and cystic focus (thin white arrow) in (b), intrinsic T2 hypointensity in (c) (black arrow) and minimal enhancement in (d) (white arrow).

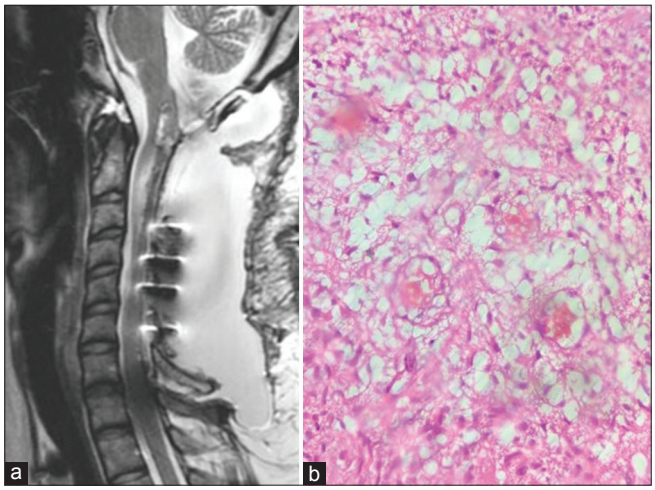

Figure 3: Case 1. (a) Postoperative T2-weighted sagittal image of the cervical spine shows complete excision of the mass. (b) Histopathology showing foci of microvascular proliferation suggestive of glioblastoma (Hematoxylin and Eosin ×40 magnification).

was independent in activities of daily living and had resumed her previous work as a banker.

Case 2

A 12-year female presented with a complaint of acute onset weakness of the right upper and lower limb for 10 days associated with difficulty swallowing liquids and solids. It started with proximal weakness in the right upper limb and then progressed distally up to the hands affecting the grip and also the right lower limb. Power in the right upper limb proximally was 0/5, while the power in the right upper limb distally was 2/5. Her power in the right lower limb was 3/5 with grossly reduced sensations on the right side. Her bowel and bladder functions were intact; however, her gag reflex and cough reflex were weak.

MR imaging showed an expansile intramedullary lesion extending from the cervicomedullary junction to the C5 vertebral body appearing heterogeneously hyperintense on the T2W image and isointense on the T1W image [Figure 4]. It reveals peripheral heterogeneous enhancement. T2 hyperintense cord edema was seen at the caudal end. No evidence of hemorrhage or peritumoral cyst. These findings were suggestive of cervicomedullary high-grade lesions.

Based on imaging findings, suboccipital craniotomy and C1-C6 laminoplasty were done. Tumor infiltration was noted in the right cervical hemicord and medulla. About 90–95% of the tumor could be excised with residual left at the areas of clear infiltration which was confirmed with a postoperative MRI [Figure 5]. Multimodal intraoperative neuromonitoring was used during surgery. During the postoperative course, the patient showed some minimal recovery, in the right upper limb distal power and improved phonation and gag. Three weeks following surgery, patient had a seizure episode along with an altered sensorium. Brain computed tomography showed signs of hydrocephalus for which emergency Ommaya reservoir insertion was done. Two days later, it was converted to a ventriculoperitoneal shunt. The patient's sensorium improved partially and she started mobilizing with support and was discharged 2 weeks after surgery. Unfortunately, the patient expired 2 weeks after discharge while awaiting radiotherapy, most likely due to direct medullary infiltration. Pathologic examination of the specimen was consistent with glioblastoma and revealed sections of cellular glial tumor composed of sheets of irregular oval-shaped cells. Foci of perivascular aggregation of tumor cells were seen but no definite foci of perivascular ependymal rosettes were identified. Mitotic activity, foci of microvascular proliferation, and occasional foci of necrosis were seen. On immunohistochemistry, the tumor showed retained ATRX, MSH2, MSH6, PMS2, and MLH1 proteins (mismatch repair proficient); the tumor was positive for GFAP and was focally positive for p53 protein; while negative for EMA, IDH1 R132H, and MIB-1 labeling index is approximately 12–15%. H3K27M mutational status could not be examined for this patient due to the rapid clinical deterioration. Thus, the integrated diagnosis of this patient was diffuse pediatric-type high-grade glioma, IDH wildtype, and WHO Grade 4.

DISCUSSION

In this paper, we describe two patients with cervicomedullary glioblastoma with contrasting clinical presentation

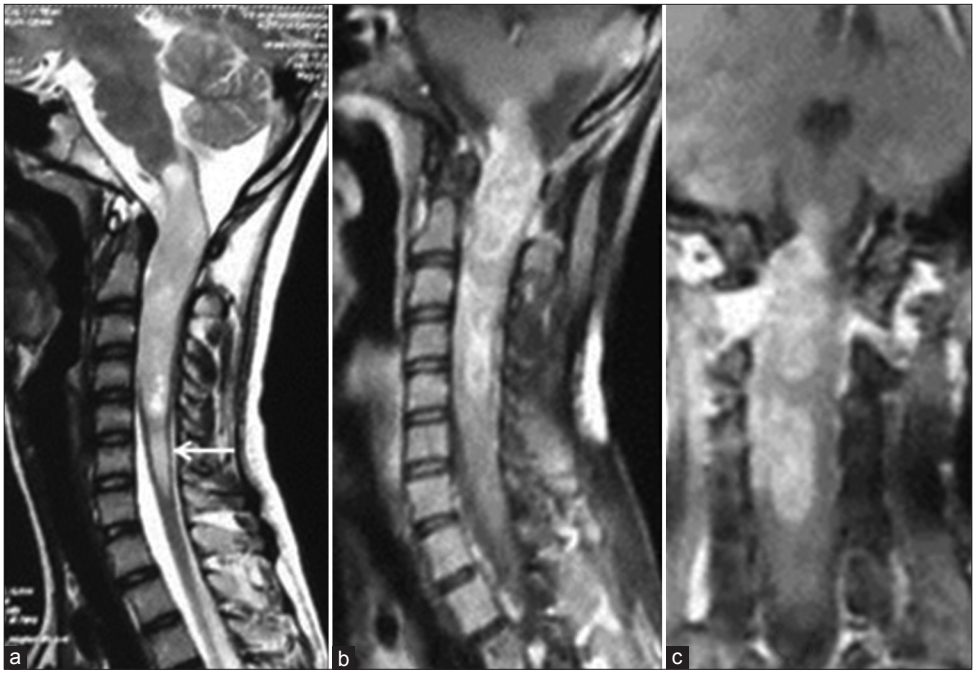

Figure 4: Case 2. Sagittal T2-weighted (a) and post contrast sagittal (b) and coronal (c) images of the cervical spine show a bulky, expansile, and heterogeneously enhancing mass in the lower medulla and spinal cord upto C5 vertebral level. T2 hyperintense edema (white arrow) is shown in (a).

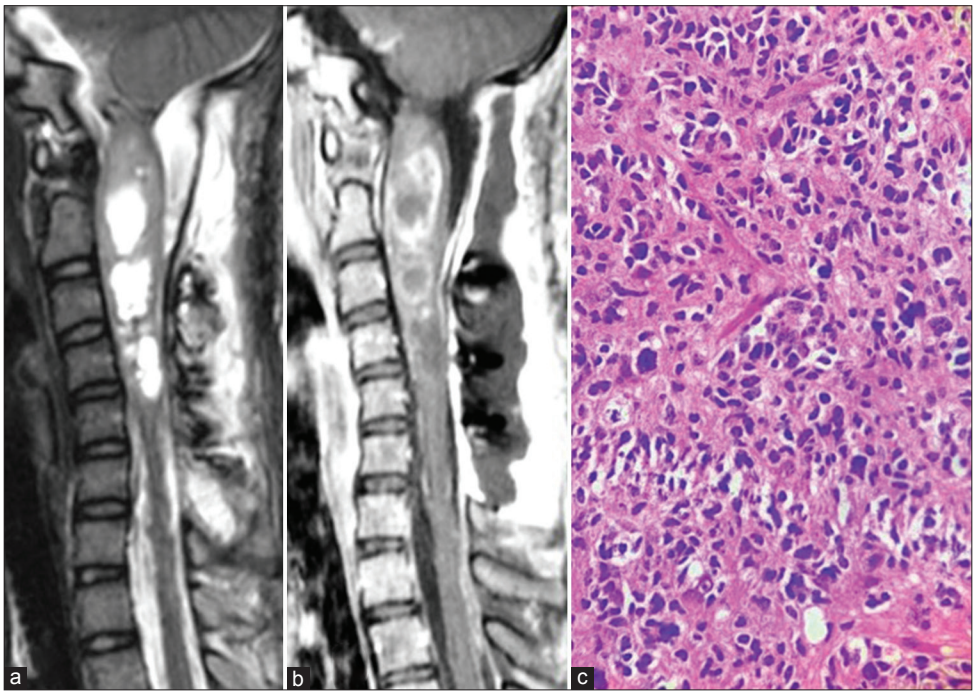

Figure 5: Case 2. Sagittal T2-weighted (a) and post contrast T1-weighted (b) images of the cervical spine reveal marked excision of the mass lesion with postoperative changes. (c) Histopathology showing neurofibrillary background and pleomorphic cells suggestive of glioblastoma (Hematoxylin and Eosin, ×40 magnification).

and outcomes. The adult patient with a slower disease progression, without tumour infiltration into the medulla or cord was amenable for complete tumor resection and thus lead to a good neurological outcome. In contrast, the

pediatric patient had a rapid onset of symptoms, with tumor infiltration into the medulla and cord, which allowed only a subtotal excision. This patient succumbed to her disease within 4 weeks of surgery.

Epstein classified brain stem tumors as diffuse, focal, and cervicomedullary.[6]

A study of 20 patients by Epstein and Wisoff suggested that cervicomedullary neoplasms were often "benign" and amenable to surgery.[6] Nair *et al*. observed that the mean age of presentation in CMT intra-axial tumors was 22.97 years.[13] In a series of 32 patients in their study, males were 65.6% while females were 34.4%. Pediatric patients (below 18 years) were about 40% while 60% were adults.[13] Despite 60% of the reported cases being adults, none of their patients had a high-grade astrocytoma.[13] The vast majority of the cases in their series were pilocytic astrocytoma (about 69%).[13] Only 4/39 patients in a series of cervicomedullary tumors were high grade.[19] Weiner *et al*. reported that the preoperative symptoms of more than 15 weeks are usually associated with better survival.[19] This observation is also corroborated by our findings.

Samartzis *et al*. observed that astrocytomas have an association with NF-1 and are found mainly in males.[15] Adults mainly exhibit high-grade lesions, whereas low-grade lesions are associated with the younger population. Both of our cases were not associated with NF. Although the above-mentioned literature mentions spinal tumors and brain stem lesions separately, the literature specifically dealing with cervicomedullary tumors is sparse.

Landi *et al*. in their analysis of intramedullary tumors of cervicomedullary regions observed cervicomedullary tumors are low-grade tumors affecting mainly the pediatric population.[9] They also observed that primary clinical presentation can be broadly divided into two categories, that is, lower cranial nerves dysfunction and medullary impairment. While Case 1 did not show any involvement of lower cranial nerves, Case 2 had some swallowing difficulty with a bilateral weak gag. Clinical examination and absence of SSEP preoperatively were suggestive of medullary involvement in both cases. Thus, as per our findings, high-grade tumors do not obey the broad categorization described by Landi *et al*., which holds for low-grade tumors only.[9] Large radiological extension of the lesion with a grossly intact patient clinically probably indicates a slower course of the disease in Case 1 while acute onset with rapid neurological worsening was seen in Case 2 suggestive of highly malignant and infiltrative behavior of the tumor. This particular case (Case 1) also makes at least a partial exception to the observation that malignant astrocytomas are intramedullary tumors where a correlation is not seen between early surgical intervention and patient survival or preservation.[9]

Histological type and grade are the most important determinants of prognosis in intramedullary spinal tumors.[11,17] However, it is unclear if this fact can be directly extrapolated to high-grade CMT. To the best of our knowledge, we report the second adult patient in the literature with dorsally exophytic cervicomedullary glioblastoma.[18] Interestingly, the previous case report with dorsally exophytic cervicomedullary glioblastoma was also described in adults, similar to Case 1 of the current paper. Conventionally, dorsal exophytic CMT is low grade and the exophytic tumor growth is due to the resistance of the decussating pyramidal tracts and dorsal columns in the brainstem to the growing neoplasm.[1,5] The characteristic low-grade features and good prognosis of a dorsally exophytic CMT have led to the hypothesis of this tumor is a variant of dysembryoplastic neuroepithelial tumor.[4,19] Case 1 is rare and unique because it is an adult glioblastoma in the cervicomedullary region.

Radical surgical excision of CMT, in general, is the preferred treatment modality.[2] Weiner *et al*. however noted that 3/4 of patients with high-grade CMT showed disease progression, despite achieving complete resection in two of those patients.[19] However, in the case of attachment to the brainstem or lower cranial nerves, a decompression rather than total excision would be a better option to prevent morbidity with monitoring of the lower cranial nerves, MEPs, SSEPs, and cardiovascular parameters.[3,13] Typically, the role of radical surgery in high-grade tumors is unclear.[10] These findings are similar to our observation in Case 2. In addition, the survival benefits of multimodality therapy in pediatric patients with intramedullary high-grade glioma have not been seen.[10] High rates of mortality may be due to the local infiltration and diffuse leptomeningeal disease due to high tumor grade, CSF spread, and infiltrative nature of tumor.[10] The optimal combination of treatment which includes surgery, radiation, chemotherapy, and targeted therapy is still unknown.[10,17,19] Konar *et al*. in a review of pediatric spinal cord glioblastoma analyzed 53 children and showed that gross total tumor resection followed by radiotherapy conferred the best survival benefit; however, there were no cases of cervicomedullary tumors in their review.[8] Merchant *et al.* recommend only biopsy followed by radiation for high grade tumours[12] while reserving radical surgical excision for anaplastic astrocytomas.[17] Unfortunately due to the rarity of cervicomedullary glioblastoma, there is a scarce literature to help in the standardization of treatment of this entity. In our opinion, maximal safe resection under multimodal electrophysiological guidance may be a reasonable surgical goal in cervicomedullary glioblastoma.

The prognosis of these patients, however, is poor in spite of surgery and radiation therapy. This may be due to limitations in the current techniques to accurately determine the true extent of the dissemination of the disease. Based on the

contrasting overall outcome of our two cases, it is reasonable to hypothesize that the rapidity, severity of the symptom onset, and the degree of tumor infiltration are important determinants of overall outcome in cervicomedullary glioblastoma.

CONCLUSION

Cervicomedullary glioblastoma in young patients is an extremely rare entity. The overall outcome depends on the rapid progression and severity of preoperative symptoms and the degree of tumor infiltration noted in imaging and during surgery.

Declaration of patient consent

Patients' consent not required as patients' identities were not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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