Glioblastoma multiforme (GBM) is the most aggressive intracranial tumor and diffusely infiltrates the surrounding brain tissue. Despite their malignant nature, extraneural metastases from glioblastomas are rare with an estimated incidence of <2%. We present a case of a 9-year-old boy with exophytic brainstem GBM who developed cervical node metastases. He had undergone gross total excision of GBM in January 2017. Histopathological examination confirmed the diagnosis of glioblastoma multiforme. The patient underwent chemotherapy and radiotherapy as per hospital protocol. He developed hydrocephalus after 3 months, which required ventriculoperitoneal shunt. Two more months later, he developed drowsiness and was found to have shunt dysfunction causing hydrocephalus and multiple enlarged cervical lymph nodes. Cerebrospinal fluid diversion and neck node biopsy were performed for the patient but he died. The histopathological examination of the neck node biopsy revealed metastases from glioblastoma. We report this case to create awareness regarding possibility of extraneural metastases even in pediatric brainstem glioblastoma.

**Keywords:** Extraneural, glioblastoma multiforme, lymph node, metastases, pediatric

**INTRODUCTION**

Glioblastoma multiforme (GBM) is the most common and the most malignant primary brain tumor in adults, accounting for 12%–15% of all intracranial neoplasms and represents approximately 8%–12% of all pediatric central nervous system tumors. Unlike tumors elsewhere, metastases from intracranial malignancies are rare because there are unique barriers in the brain that prevent their hematogenous and lymphatic spread, such as the dura mater and the thickened basement membrane of the blood vessels. The first report of extraneural spread from GBM was published in 1928. Lymph nodes were the second most common site for metastases after lungs and pleura, and cervical lymph nodes were most common sites for metastases among lymph nodes. We report a pediatric case with brainstem GBM who had extraneural spread in the form of cervical lymph node metastases a few months after surgery.

**CASE REPORT**

A 9-year-old boy presented to us with complaints of facial asymmetry for 2 months and difficulty in swallowing for 3 days. On evaluation with magnetic resonance imaging (MRI), he was found to have heterogeneously enhancing mixed-intensity lesion in the left cerebellopontine angle causing compression on the ipsilateral cerebellum and fourth ventricle. A preliminary diagnosis of exophytic brainstem glioma was made and he was taken up for surgery. He underwent left retrosigmoid craniotomy and gross total excision of tumor. The histopathology was reported as glioblastoma, H3K27M mutant, WHO grade IV. He underwent radiotherapy and chemotherapy as per hospital protocol. He developed hydrocephalus after 3 months, which required ventriculoperitoneal shunt. Two more months later, he developed drowsiness and was found to have shunt dysfunction causing hydrocephalus and multiple enlarged cervical lymph nodes. Cerebrospinal fluid diversion and neck node biopsy were performed for the patient but he died. The histopathological examination of the neck node biopsy revealed metastases from glioblastoma. We report this case to create awareness regarding possibility of extraneural metastases even in pediatric brainstem glioblastoma.

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How to cite this article: Ilangovan VS, Kumar VRR, Sankaran V, Bapu KRS, Kapilavayi S. Aggressive brainstem glioblastoma in a 9-year-old child with neck node metastases: A case report and review of literature. J Pediatr Neurosci 2018;13:234-6.
hospital protocol. Three months later, he presented to us with headache and vomiting; MRI of the brain showed small residual tumor and hydrocephalus. He underwent ventriculoperitoneal shunt and improved clinically. Two months later, he presented with drowsiness to the emergency department and on examination was found to have multiple enlarged cervical lymph nodes. Computed-tomography of the brain showed dilated ventricles with shunt tube in situ. A diagnosis of shunt malfunction was made. Intraoperatively abdominal wound site had a pus collection and cerebrospinal fluid (CSF) flowing through the shunt was cloudy so shunt tube was removed and external ventricular drain (EVD) placed. Excision biopsy of cervical lymph node was performed and the excised node was sent for histopathological examination. The child clinically improved and EVD was removed after 4 days but subsequent neurological deterioration necessitated placement of EVD again the next day. He did not improve neurologically and was declared dead on the next day. Subsequent histopathology of neck node showed metastatic GBM positive for glial fibrillary acidic protein (GFAP).

**Discussion**

GBM is the most common primary brain tumor in adults, accounting for 12%–15% of all intracranial neoplasms. In children, they account for about 6.5% of all intracranial neoplasms. Brainstem gliomas account for approximately 25% of all posterior fossa tumors and are most common in children between 7 and 9 years of age. There is no recognized gender or racial predilection. In children, brainstem gliomas constitute about 10% of brain tumors.

From the view point of extraneural metastases, GBM is the most common extraneurally metastasizing tumor in adults and medulloblastoma the most common in children. It is important to note that despite their highly locally invasive nature, extraneural metastases from GBMs are very rare with a reported frequency ranging between 0.4% and 2.0%. Most of the current literature on extraneural metastases from GBM is limited to single-case reports or small case series.

Among the well-documented cases of extraneural metastases from GBM, the most common sites of extraneural metastases from GBM are lungs and pleura, liver, mediastinal and cervical lymph nodes, and bone or bone marrow. An earlier study described the most frequent sites of extraneural metastases as 60% in lungs and pleura, 51% lymph nodes, 31% bones, and 22% in liver. Lymph node metastases were most commonly situated in the cervical region (62%), often ipsilateral to the site of craniotomy but sometimes bilateral. Skeletal metastases most frequently involved the vertebral spine (73%), followed by the ribs, sternum, skull, and acetabulum.

Several theories on why GBM is rarely associated with extracranial metastasis have been proposed. Due to the aggressive biology of these tumors, patients dying before there is sufficient time for distant metastasis to develop is one possible reason. The second suggestion is based on the concept of capillary basement membrane barrier effect which plays an important role as a physical barrier against migration of the glioma cells into the bloodstream. As a result, most cases of metastasis are considered to occur following craniotomy or intraventricular shunt placement, during which time tumor cells gain access to the bloodstream through defects in the meningeal and parenchymal blood vessels. Stereotactic biopsies may also cause disease spread through similar mechanism. Functional lymphatic vasculature has been identified in the meninges by some authors, which may explain why the cervical lymph nodes are among the most common sites of extraneural metastases from GBM.

Extraneural metastasis is likely to be much more frequent than clinically reported because majority of the patients die early due to the disease and because screening for extraneural metastases is not routine practice. Further, micrometastases in lungs from donors with GBM causing metastatic GBM in recipients of bilateral lung transplantation have been reported, highlighting that there may be unrecognized GBM micrometastases at the time of death.

A combination of clinical history and histopathology can diagnose extraneural metastases from GBM. Fine-needle aspiration cytology is a simple and reliable diagnostic method if such lesions are suspected from the history. In addition to routine cytological examination and light microscopy of a biopsy specimen, immunohistochemistry pattern of GBM at nodal site can reveal GFAP, S-100 protein, and vimentin positivity.

Patients with extraneural metastasis from glioblastoma have a poorer prognosis and hence aggressive treatment is generally not warranted; however, if extraneural metastasis from GBM occurs in patients without intracranial relapse, aggressive therapy for the metastases could prolong survival. Bone metastases are usually treated using palliative radiotherapy, whereas lymph node and liver metastases sometimes respond to chemotherapy. Patients with lung metastasis have the worst prognosis.
Median time to recognition of metastases is around 8.5 months for both intracranial and extraneural metastases and median survival from detection of metastasis to death is around 1.5 months.[9] There has been a demonstrable increase in the median survival after detection of metastases from GBM per decade in the decades between 1940 and 2000. Patients treated with surgery, radiation, chemotherapy, and CSF shunting exhibit the longest average survival interval from metastasis to death. A recent population-based study correlated survival in pediatric high-grade brainstem gliomas positively with lower-grade tumor histology, radiation therapy only in the first 9 months after diagnosis, and surgical resection.[10]

**Conclusion**

Brainstem GBM in the pediatric age group is a rare tumor with poor prognosis in general. Extraneural metastases from such tumors are rarely described in literature. Possibility of extraneural spread from pediatric brainstem GBM is to be considered in the setting of proven GBM with enlarged neck nodes. Early detection and timely intervention may help prolong survival in cases with controlled primary disease as evidenced by the gradual but definite increase in survival over the past few decades.

**Acknowledgement**

I hereby acknowledge that all authors have participated equally in the preparation of this manuscript.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Saad AG, Sachs J, Turner CD, Proctor M, Marcus KJ, Wang L, et al. Extracranial metastases of glioblastoma in a child: Case report and review of the literature. J Pediatr Hematol Oncol 2007;29:190-4.

2. Taran SJ, Taran R, Batra M, Ladia DD, Bhandari V. Survival with concurrent temozolomide and radiotherapy in pediatric brainstem glioma with relation to the tumor volume. J Pediatr Neurosci 2015;10:341-5.

3. Pietschmann S, van Buuren AO, Kerber MJ, Baumert BG, Kortmann RD, Müller K. An individual patient data meta analysis on characteristics, treatments and outcomes of glioblastoma/gliosarcoma patients with metastases outside of the central nervous system. PLoS One 2015;10:e0121592.

4. Wallace CJ, Forsyth PA, Edwards DR. Lymph node metastases from glioblastoma multiforme. AJNR Am J Neuroradiol 1996;17:1929-31.

5. Pasquier B, Pasquier D, N’Golet A, Panh MH, Couderc P. Extraneural metastases of astrocytomas and glioblastomas: Clinicopathological study of two cases and review of literature. Cancer 1980;45:112-25.

6. Ray A, Manjila S, Hdeib AM, Radhakrishnan A, Nock CJ, Cohen ML. Extracranial metastasis of glioblastoma: Three illustrative cases and current review of the molecular pathology and management strategies. Mol Clin Oncol 2015;3:479-86.

7. Ates LE, Bayindir C, Bilgic B, Karasu A. Glioblastoma with lymph node metastases. Neuropathology 2003;23:146-9.

8. Xu M, Wang Y, Xu J, Yao Y, Yu WX, Zhong P. Extensive therapies for extraneural metastases from glioblastoma, as confirmed with the oncoscan assay. World Neurosurg 2016;90:698.e7-e11.

9. Lun M, Lok E, Gautam S, Wu E, Wong ET. The natural history of extracranial metastasis from glioblastoma multiforme. J Neurooncol 2011;105:261-73.

10. Lam S, Lin Y, Auffinger B, Melkonian S. Analysis of survival in pediatric high-grade brainstem gliomas: A population-based study. J Pediatr Neurosci 2015;10:199-206. doi: 10.4103/1817-1745.165656.