

CASE REPORT

Mixed malignant glioblastoma and schwannoma in spinal cord with metachronous ependymoma: A case report

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Abstract

Here, we report a very rare case of mixed spinal tumor comprising of malignant glioblastoma and schwannoma, who was initially treated with tumor resection and adjuvant chemoradiation, but relapsed three years later with grade 3 ependymoma.

KEYWORDS

ependymoma, glioblastoma, schwannoma, spinal tumor

1 | INTRODUCTION

We here report the unusual case of a 60-year-old woman with an intramedullary mixed malignant tumor comprising of glioblastoma and schwannoma, who underwent resection and adjuvant chemoradiation and relapsed with grade 3 ependymoma after one year. After secondary resection, she received PCV chemotherapy and has remained disease-free after 3 years.

Intramedullary spinal cord tumors (IMSCT) are responsible for a rare but remarkable cause of neurological morbidity and mortality.

Primary intramedullary spinal glioblastoma multiform (GBM) is a very rare IMSCT that accounts for only 1%-5% of all GBMs and only 1.5% of all spinal cord tumors.¹

Young males are more commonly affected by this disease, and the most frequently involved sites are cervical and thoracic spinal regions.²

Due to the low incidence of primary spinal cord GBM, reports are necessarily limited to single-case studies and small-number case series. It is, therefore, not surprising that

little is known about the clinical characteristics and treatment protocols of this debilitating malignancy.³

Spinal intramedullary GBM frequently affects the cervical and thoracic regions of the spinal cord.² Back pain which may be diffuse or radicular is the most common presenting symptom. Also, numbness and weakness of the extremities are the other frequent presenting symptoms.⁴

Currently, the standard treatment for newly diagnosed GBM consists of surgical resection to the extent feasible, followed by concurrent chemoradiotherapy with temozolomide (TMZ) and adjuvant temozolomide chemotherapy.⁵

Glioblastomas containing a methylated O-methylguanine-DNA methyltransferase (MGMT) promoter are associated with significantly greater long-term benefit from temozolomide and alkylating chemotherapy drugs than patients with an unmethylated MGMT promoter. Methylation of the MGMT promoter is correlated with improved response to radiotherapy as well.^{6,7}

In conventionally fractionated radiation therapy, the tolerance dose for the spinal cord has been reported to be 50 Gy

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for cord lengths of 5 and 10 cm, and 47 Gy for cord length of 20cm, given a probability of myelopathy of less than 5% within 5 years. Therefore, a maximum dose of up to 45–50 Gy to the spinal cord is tolerable.⁸

With all these measures, the outcome of these cases is exceptionally poor with an average survival of 10.4 months from diagnosis (range: 1–36 months).⁹

2 | CASE REPORT

A 60-year-old woman was referred to our center, with a history of 2-month low back pain and progressive lower limbs paresthesia and paresis, especially on the left side, which caused numbness and weakness. In neurological examination, cranial nerves were intact. Her motor examination showed normal strength with the exception of the left lower extremity, which was 3/5 at the flexor and extensor muscles. Sensory examination was indicative of decreased detection of tactile and painful stimuli in the lower extremities. No neurologic abnormalities of the upper extremities were detected. The patient's medical history did not reveal any notable events.

Magnetic resonance evaluation of the patient's brain was normal, but in spinal imaging, a large intramedullary tumor was detected extending from T10 down to T12 with homogeneous enhancement of the tumor area (Figure 1).

The patient underwent surgery 3 weeks later. Frozen section confirmed GBM, and microsurgical subtotal excision was performed with intraoperative electrophysiological

monitoring. Motor-evoked potentials were stable and showed no change throughout the excision of the tumor mass and at termination of the operation. After surgery, the patient's clinical status was unchanged.

Histopathological study showed a neoplastic tissue composed of atypical proliferation of neoplastic cells with round to ovoid and elongated somewhat vesicular nuclei arranged in interlacing bundles. The neoplastic cells were stellate in some areas showing intervening focal areas of palisading necrosis. The vascular and endothelial proliferation was pronounced with glomeruloid tuft formations. Distributed within the specimen, there were more populated areas with tumor cells having ovoid to elongated nuclei arranged densely somewhat in bundles and tendency to vaguely nuclear palisading. Immunohistochemistry (IHC) staining was positive for GFAP in loose astrocytic area and for S100 in more populated spindle cell components. IHC for p53 showed positivity in scattered individual cells; however, there was no reaction for EMA throughout the section. Following the IHC results, a diagnosis was made as a mixed malignant schwannoma and glioblastoma by an expert pathologist with more than 20 years of experience in central nervous system malignancies.

Because of the unusual tumor pathology, the specimen was sent for review and more cytogenetic examination was done. For cytogenetic analysis, DNA was extracted by formalin-fixed paraffin-embedded (FFPE) QIAGEN kit (QIAamp® DNA FFPE DNA Kit) and the quality/quantity of the DNA was estimated in Nano-drop spectrophotometer. A segment of DNA containing isocitrate dehydrogenase 1 (IDH1) exon 2 and IDH2 exon 4 was amplified using allele-specific polymerase chain reaction (PCR) primers and pyrosequencing data at codons 132, 140, and 172, respectively, and was interpreted by a pathologist. The test result showed wild type for IDH1 (c.394–396 [R132H and variants]) and wild type for IDH2 (c.514–516 [R172K and R140Q and variants]).

Also, the O-methylguanine-DNA methyltransferase (MGMT) promoter methylation status was measured by pyrosequencing technology for 4 CpG islands within the methylated promoter region of the MGMT encoding sequence. No CpG methylated islands were detected in evaluation (fewer than 10 percent methylation in all 4 CpG sites).

Based on Stupp's protocol¹⁰ and considering the spinal cord tolerance to radiation, concurrent chemoradiation was given for the patient: three-dimensional conformal radiotherapy with 1.8 Gy dose per fraction of 6 MV photons up to a total dose of 50.4 Gy delivered in 28 fractions. Concurrent oral chemotherapy with temozolomide was prescribed by 75 mg/m²/day.

Based on our institutional experience, patients with negative MGMT show a quick local recurrence, so we recommend these patients to choose PCV regimen as adjuvant chemotherapy instead (Procarbazine 100mg/m² PO days 1 through 10,



FIGURE 1 Postcontrast T1-weighted MRI in sagittal view. A large intramedullary contrast-enhanced lesion is noted through T10 to T12 spinal segments



FIGURE 2 T1-weighted MRI in sagittal view. A hypointense/iso-intense lesion is seen from T11 to L2. Note the low-signal hypointensity at the upper pole of the lesion (T11) due to hemosiderin deposition in ependymoma (Cap sign)¹⁹

Lomustine (CCNU) 100mg/m² PO day 1, Vincristine 1.5mg/m² IV day 1 every 6 weeks; 6 courses).^{11,12} But, this patient and her family decided to stick to the standard protocol with adjuvant temozolomide (150-200 mg/m²/day for 5 days every 4 weeks; 6-12 courses).

Unfortunately, after 5 courses of adjuvant chemotherapy with temozolomide (13 months after initial symptom development), the patient presented with lower extremities' progressive paresthesia. New whole axis MRI confirmed a new intramedullary lesion through T11 to L2 spinal segments (Figure 2). Patient was referred to surgeon for reoperation and maximal safe resection was done. Surprisingly, this time pathology report was consistent with ependymoma grade 3, with perivascular pseudorosettes and true ependymal rosettes. These results were confirmed by pathologic reevaluation and IHC examination.

Due to the short time from previous radiotherapy (less than one year), reirradiation was not feasible. For this reason, the patient received chemotherapy with PCV regimen as adjuvant treatment. Fortunately, after 6 courses of this salvage treatment, tumor is still stable on imaging.

3 | DISCUSSION

To date, less than 200 cases of primary spinal glioblastoma multiform have been reported in the literature.^{2,13,14} Besides the current case report, only one other case has been reported

to have simultaneous intracranial glioblastoma and spinal schwannoma.¹⁵ Moreover, synchronicity of these two malignancies in the same anatomical location has not been reported previously.

The other unusual feature of the presented case is the different pathologies in the first and second surgeries; especially that both samples were histopathologically re-evaluated with IHC staining. The first pathology reported a mixed malignant schwannoma and glioblastoma, which was treated with surgical subtotal resection, adjuvant concurrent chemoradiation, and subsequent chemotherapy. Five courses into the adjuvant chemotherapy, the patient developed progressive symptoms consistent with new imaging findings and assuming local recurrence she underwent surgery to find out a lesion with an unexpected histopathologic report; ependymoma.

Ependymomas are the most common (50%-60%) intramedullary spinal cord tumors (IMSCT), which occur mostly in adults.¹⁶ In contrast to intramedullary ependymomas, spinal GBM has a poor prognosis because of the more aggressive and more infiltrative nature of this tumor.^{17,18} The fact that the patient is still alive 3 years from the first diagnosis in spite of the generally poor prognosis for spinal cord GBMs, is quite remarkable.

Pathologic diagnosis of ependymoma on the site of previous tumor with mixed features of GBM and schwannoma is a matter that we cannot explain definitively, but radiation-induced secondary malignancy could also be another elaboration to this unusual finding.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Mostafa Farzin and Mohamadreza Hajiabadi: were the physicians in charge of patient treatment and contributed to data gathering, wrote the initial draft, and edited the manuscript. Mohammad Rahmani and Kasra Kolahdouzan: contributed to acquisition of data, writing, editing, and finalizing the manuscript.

ETHICS STATEMENT

The presented information in this manuscript was collected with the patient's informed consent and according to the ethical guidelines.

DATA AVAILABILITY STATEMENT

Access to any data regarding this article will be made possible through contact with the corresponding author on reasonable request.

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REFERENCES

1. Mallick S, Madan R, Julka PK. Primary spinal glioblastoma treated with adjuvant radiation and temozolomide: Report of two cases. *J Cancer Res Ther.* 2015;11(3):654.
2. Timmons JJ, Zhang K, Fong J, et al. Literature review of spinal cord glioblastoma. *Am J Clin Oncol.* 2018;41(12):1281-1287.
3. Shen CX, Wu JF, Zhao W, Cai ZW, Cai RZ, Chen CM. Primary spinal glioblastoma multiforme: a case report and review of the literature. *Medicine (Baltimore).* 2017;96(16):e6634.
4. Jallo GI, Freed D, Epstein F. Intramedullary spinal cord tumors in children. *Childs Nerv Syst.* 2003;19(9):641-649.
5. Kim BS, Seol HJ, Nam DH, et al. Concurrent chemoradiotherapy with temozolomide followed by adjuvant temozolomide for newly diagnosed glioblastoma patients: a retrospective multicenter observation study in Korea. *Cancer Res Treat.* 2017;49(1):193-203.
6. Rivera AL, Pelloski CE, Gilbert MR, et al. MGMT promoter methylation is predictive of response to radiotherapy and prognostic in the absence of adjuvant alkylating chemotherapy for glioblastoma. *Neuro Oncol.* 2010;12(2):116-121.
7. Thomas RP, Recht L, Nagpal S. Advances in the management of glioblastoma: the role of temozolomide and MGMT testing. *Clin Pharmacol.* 2013;5:1-9.
8. Lee SH, Lee KC, Choi J, et al. Clinical applicability of biologically effective dose calculation for spinal cord in fractionated spine stereotactic body radiation therapy. *Radiol Oncol.* 2015;49(2):185-191.
9. Linsenmann T, Westermaier T, Vince GH, et al. Primary spinal glioblastoma multiforme with secondary manifestation as a cerebral "angioglioma." Literature review and case report. *J Neurol Surg Rep.* 2015;76(1):e128-e134.
10. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987-996.
11. Medical Research Council Brain Tumor Working Party. Randomized trial of procarbazine, lomustine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a Medical Research Council trial. *J Clin Oncol.* 2001;19(2):509-518.
12. Sandberg-Wollheim M, Malmstrom P, Stromblad LG, et al. A randomized study of chemotherapy with procarbazine, vincristine, and lomustine with and without radiation therapy for astrocytoma grades 3 and/or 4. *Cancer.* 1991;68(1):22-29.
13. Medhkour A, Chan M. Extremely rare glioblastoma multiforme of the conus medullaris with holocord and brain stem metastases, leading to cranial nerve deficit and respiratory failure: a case report and review of the literature. *Surg Neurol.* 2005;63(6):576-582; discussion 82-3.
14. Morais N, Mascarenhas L, Soares-Fernandes JP, Silva A, Magalhaes Z, Costa JA. Primary spinal glioblastoma: a case report and review of the literature. *Oncol Lett.* 2013;5(3):992-996.
15. Shi H, Wright CH, Rivera T, Wright J. Simultaneous diagnosis of glioblastoma, cervical schwannoma, adrenal masses and growth hormone-secreting adenoma in a previously healthy patient. *BMJ Case Rep.* 2019;12(8):e229675.
16. Chamberlain MC, Tredway TL. Adult primary intradural spinal cord tumors: a review. *Curr Neurol Neurosci Rep.* 2011;11(3):320-328.
17. Raco A, Esposito V, Lenzi J, Piccirilli M, Delfini R, Cantore G. Long-term follow-up of intramedullary spinal cord tumors: a series of 202 cases. *Neurosurgery.* 2005;56(5):972-981; discussion -81.
18. Tobin MK, Geraghty JR, Engelhard HH, Linninger AA, Mehta AI. Intramedullary spinal cord tumors: a review of current and future treatment strategies. *Neurosurg Focus.* 2015;39(2):E14.
19. Kobayashi K, Ando K, Kato F, et al. MRI characteristics of spinal ependymoma in WHO grade II. *Spine.* 2018;43(9):E525-E530.

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