



Case Report

Primary Spinal Glioblastoma Multiforme: A Case Report and Review of The Literature

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Summary

Introduction: Primary spinal glioblastoma multiforme is a very rare disease with high morbidity and mortality rates. No definite treatment algorithm can be constituted, but multimodal treatment regimens have been administered. Aim of the treatment is to excise the mass nearly completely, and then application of radiotherapy and chemotherapy in a short period.

Methods: Publications were identified by browsing search engines such as PubMed and MEDLINE for English-language articles since 1989 using a list of keywords; as well as identifying references from review articles. The following keywords were used for searching databases: primary, spinal, glioblastoma multiforme.

Results: Intramedullary mass was detected at the levels of C2-T8 in the spinal magnetic resonance imaging (MRI) examination performed in our 4-year old male patient, who applied to us with complaints of weakness in lower extremities and gaita-urine incontinence. Sepsis was developed in postoperative period of the patient, whose mass was gross-totally resected by using microsurgery method. After the patient was started to have radiotherapy, he was extubated with improvements in the clinical state and neurological picture. He has been followed up at the hospital in the three-month monitorization after the treatment. Literature data suggested that all three therapy modalities can be used for sGBM, sequentially or concurrently, it has a poor survival, most of the patients die due to disease and the duration of symptoms are very short.

Conclusion: Because the disease is very rare, prospective studies cannot be performed in this patient population.

Key words: Primary, spinal, glioblastoma multiforme

Primer Spinal Glioblastoma Multiforme: Bir Vaka Sunumu ve Literatür Derlemesi

Özet

Giriş: Primer spinal glioblastoma multiforme yüksek morbidite ve mortalite hızına sahip çok nadir görülen bir hastalıktır. Kesin bir tedavi algoritması yoktur ancak multimodal tedavi rejimleri uygulanmaktadır. Tedavinin amacı kitlenin tama yakın çıkarılması, sonrasında radyoterapi ve kemoterapinin kısa sürede uygulanmasıdır.

Metod: 1989'dan itibaren İngilizce yazılmış makaleler, anahtar kelimelerin kullanılması ve derleme makalelerinden referansların ayrıştırılması yoluyla PubMed ve MEDLINE gibi arama

motorları taranarak ayrıştırılmıştır. Kullanılan anahtar kelimeler primer, spinal ve glioblastoma multiformedir.

Sonuçlar: Alt ekstremitelerde güçsüzlük ve gayta-üriner inkontinans ile başvuran 4 yaşındaki bir erkek hastada spinal manyetik rezonans görüntülemeye (MRI) C2-T8 seviyesinde intramedüller kitle saptandı. Mikrocerrahi metodla kitlesi tama yakın çıkarılan hastada postoperatif dönemde sepsis gelişti. Radyoterapi başlanmasından kısa bir süre sonra klinik durumunda ve nörolojik tablosunda düzelme olan hasta ekstübe edildi. Tedavi sonrası hastanede 3 ay daha izlenmiştir. Literatür bulguları sGBM tedavisinde sekansiyel veya eş zamanlı olarak her üç modalitenin de kullanılabileceğini, kötü prognoza sahip olduğunu, hastaların çoğunluğunun hastalığa bağlı olarak öldüğünü ve semptomların süresinin çok kısa olduğunu göstermektedir.

Tartışma: Hastalık nadir görüldüğü için, bu grup hasta popülasyonunda prospektif çalışmalar yapılamamaktadır.

Anahtar Kelimeler: Primer, spinal, glioblastoma multiforme

INTRODUCTION

In adults, spinal glioblastoma multiforme (sGBM) constitutes only 4-8% of primary intramedullary tumors. However, sGBM forms 1% of all intramedullary tumors encountered during childhood⁽²⁶⁾. These tumors are generally developed from transformation of low grade neuroepithelial tumors. Winograd et al. reported a case, which was with low grade at the baseline, and then transformed into the high grade glioblastoma⁽⁴⁵⁾. Intramedullary glioblastoma is quite an aggressively progressive disease, which should be operated as soon as it is diagnosed, and after that emergent initiation of radiotherapy and chemotherapy are required. Median survival rates are around only 14 months^(17,40). Because pediatric sGBM is very rarely encountered, a few number of cases have been reported for treatment options (surgery, radiotherapy, and chemotherapy), and no treatment algorithm can be constituted. Patient age at the diagnosis, tumor localization, and neurological deficit state are very important for the survival^(23,30).

CASE PRESENTATION

A 4-year old male patient applied to our institution because of sudden onset weakness in his lower extremities and gaita-urine incontinence. In his physical

examination; progressive weakness and paraparesis were detected in his both lower extremities. Hemogram, peripheral blood smear, biochemical tests and chest radiography were within normal limits. There were cafe au lait spots on his skin. No pathologic signs were detected in his ophthalmological and neurological examinations, which were performed to differentially diagnose neurofibromatosis disease. In his family history, his parents had a consanguineous marriage. In preoperative contrasted cranial and spinal MRI examinations performed in November 2012, a lesion was observed in heterogeneous inner structure with isointense signaling in T1A and high in T2A, especially marked in the sagittal cross-sections, from C8 to thoracal 8 (Th8) levels in the axial and sagittal planes. After I.V. contrast substance injection, a lesion which was prominent at C7-Th8 levels, with intense surrounding but irregular borders, with 14 mm of thickness and 130 mm long in the craniocaudal alignment, and with irregular contrast enhancement, was observed. The lesion was filling the medullary canal completely. Spinal cord borders could not be definitely identified at that region. The preliminary diagnosis was intramedullary mass. There was a syringohydromyelitis cavity in the central portion of distal thoracal cord (Figure 1, 2). No pathological sign was detected in

cerebral MRI and abdominal CT of the patient.

OPERATION

Patient was lied down in the prone position, and skin incision was performed between T1 and T10. After bilateral paravertebral muscle dissection, laminectomy was performed between T1 and T10. Durameter was opened, the intramedullary located lesion which was expanding the spinal cord, very vascular and with heterogeneous characteristics, was excised gross-totally by the microsurgery method. Then duraplasty was performed.

POSTOPERATIVE SIGNS

In the postoperative thoracal MRI, thinning in the spinal cord at T3-T8 level, irregularities, and signaling hemorrhage foci were observed (early postoperative changes). When it was examined by contrasted thoracal MRI, previous total laminectomy was observed at T3-T8 level. There were postoperative changes in the posterior paravertebral soft tissues. Thoracal vertebral corpus height, cortex and medulla spinalis characteristics, other

intervertebral discs, facet joints, and flaval ligaments appeared normal (Figure 3).

PATHOLOGY

In the cross-sections, vascular endothelial proliferation, and GFAP (+) atypical glial cells including palisading necrosis were observed. While KI 67 proliferation index was above 70%, P53 result was diffuse nuclear 3 positive. Histomorphological and immunohistochemical signs were reported as primarily consistent with WHO grade IV glioblastoma.

Postoperative radiotherapy

Patient was planned for the adjuvant radiotherapy. In Phase I, external RT was performed all over the medulla spinalis with 3420cGy from 19x180cGy by using PA 6MV- X ray, and all over the head (in two areas like R lateral/L lateral) with 3420cGy from 19x180cGy by using PA 6MV- X ray; in Phase II the route of therapy was arranged so that it would pass below the base of skull and T9 vertebra with 1980cGy from 11x180cGy by using PA 6MV- X ray. The total dose was 5400cGy.

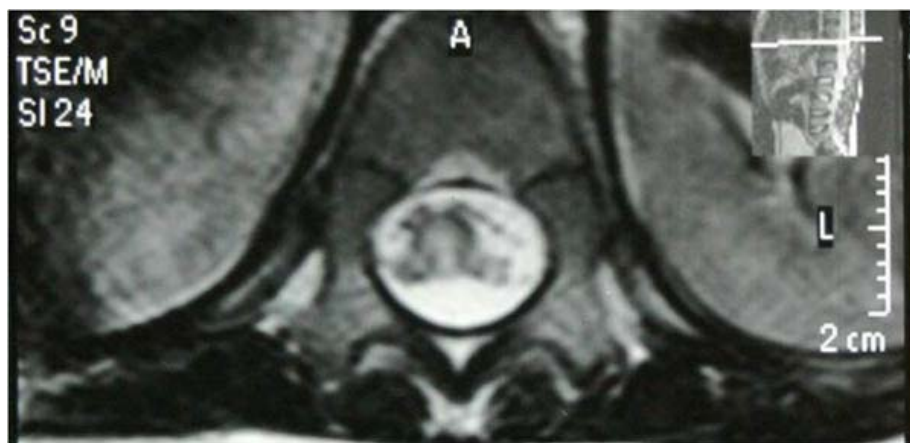


Figure 1: Intramedullary mass in the axial cross-section of MRI.



Figure 2: Intramedullary mass in the sagittal cross-section of MRI.



Figure 3: Postoperative MRI.

DISCUSSION

High grade sGBM is a very rarely encountered tumor⁽³⁴⁾. In its treatment, adjuvant radiotherapy should be performed postoperatively in the leptomeningeal space. Despite gross total resection, overall survival is only around 30 months. Ononiwu et al. reported disease free survival rate in patients, who were aged between 10 months and 1 year, with gross-total resection and laminectomy, and received adjuvant RT as 16 months⁽³¹⁾. Because tolerance dose of the spinal cord was 50 Gy, different RT doses were applied (38-66 Gy)⁽⁴³⁾. In recent studies, it has been reported that RT dose at and over 35 Gy was more beneficial for the survival than lower doses of RT or no RT at all⁽²⁷⁾. High grade spinal tumors, especially sGBM is quite important for leptomeningeal spread. Despite aggressive therapy, leptomeningeal spread has been reported as 58% in some series, whereas 47% in others^(3,7,8,21). This rate has been shown in only 5-10% of cases with brain diagnosis in the neuroaxis dissemination^(13,16). Craniospinal radiotherapy should be performed in patients with leptomeningeal dissemination. However, prophylactic craniospinal RT should also be performed in cases without leptomeningeal dissemination.

There is no evidence indicating that chemotherapy has elongated the survival rate in patients diagnosed with high grade spinal astrocytomas⁽³⁵⁾. There is one related study, which was performed by the Children's Cancer Study Group. When a group, which received chemoradiotherapy (lomustine, vincristine and prednisone containing), was compared with the group, which received only RT 5-year event-free survival was defined as 46% vs. 18%, respectively⁽³⁸⁾. On Day 1 of the chemotherapy, 8 drugs were given to children with anaplastic astrocytoma and glioblastoma, who were below 2 years of age. Progression free survival rates were

detected as 44% in astrocytoma and 0% in glioblastoma patients⁽¹⁴⁾. In another study, which was conducted just after it, it was shown that there was no difference in high grade astrocytoma patients between giving 8 drugs on the first day of chemotherapy and giving 2 cycles of lomustine, prednisone, and vincristine postoperatively before RT⁽¹³⁾. In the recent years, it has been reported that beneficial impacts are observed in concomitant radiotherapy with temozolomide after the gross or nearly gross excision of high grade astrocytoma in adults. However, studies performed on children did definitely not support beneficial impacts of concomitant radiotherapy with temozolomide⁽⁹⁾. In another study, it was shown that high dose chemotherapeutic agents (thiotepa and etoposide) decreased the survival in 16 high grade astrocytoma patients by hematological toxicity they caused⁽¹¹⁾.

In this case report, we have reviewed all pediatric and adult spinal glioblastoma cases, which were reported in the literature and the ones we could reach in full-text (Table). As it is seen in the table, symptoms appear in a short time period in spinal GBM cases; localization may be changeable; immunohistochemical examinations and MIB1-KI67 supports the diagnosis; patients are treated generally by total or subtotal or near total or gross-total surgery methods; and adjuvant radiotherapy and chemotherapy are not featured among the treatment options. Among the chemotherapy options, temozolomide has been leading as it has been in glioblastoma cases in the recent years; and bevacizumab, irinotecan based treatments are being administered in recurrences. Death occurs generally due to the disease itself or treatment toxicity. Unfortunately, survival is short, and is generally around 12-18 months. However, because the disease is very rare, prospective studies cannot be performed in this patient population.

Table 1. Clinopathologic features of patients with spinal glioblastoma multiforme. (DOD: dead of disease; DOT: dead of toxicity; NA: not applicable; w: week; m: month; DOS: duration of symptoms; IHC: immunohistochemistry; CT: chemotherapy; RT: radiotherapy; CSI: craniospinal irradiation; WBI: whole brain irradiation; PD: progressive disease; SD: stabil disease)

No	Year	Ref	Age	Sex	DOS	Localization	IHC	MIB1-Ki67	Surgery	CT	RT	Follow-up	Outcome
1	2013	28	19	M	4 w	T6-T11	GFAP, S100	high	Subtotal	tem	45 Gy	21 m	DOD
2	2012	33	15	F	4 m	C6-T7		22%	Subtotal	yes	yes	6 m	
3	2012	33	35	M	1 m	T11-L1	GFAP,p53	25%	Near total	yes	yes	15 m	
4	2012	12	27	F		Torakolomber	PDGFRa						
5	2011	15	17	F	2 m	T11-L1	GFAP,p53	20%					
6	2011	15	36	M	6 m	C2-T2	GFAP, EGFR	18%					
7	2011	15	50	M	1 m	T4-T6	GFAP,p53	12%					
8	2011	15	65	M	1 m	T1-T3	GFAP,p53, EGFR	20%					
9	2011	15	21	M	40 d	C2-C7	GFAP,p53	15%					
10	2011	15	20	F	2 w	conus cauda	GFAP,p53	15%					
11	2011	44	34	M	6 m	conus medullaris	GFAP	2-20%	Subtotal	tem	yes	18 m	
12	2010	22	14	F	6 m	C6-T5	GFAP, P53	30%	Total	tem	50 Gy	14 m	DOD
13	2010	22	8	F	3 w	C3-T4		20%	Subtotal	tem	yes	14 m	DOD
14	2011	4	22	M		cervical			Biopsy	tem, bev	54 Gy	5 m	DOD
15	2011	4	25	M		cervicothoracic			Subtotal	tem, bev	54 Gy	8 m	DOD
16	2011	4	28	F		thoracic			Subtotal	tem, bev	54 Gy	13 m	DOD
17	2011	4	38	M		thoracic			Subtotal	tem, bev	54 Gy	10 m	DOD
18	2011	4	45	M		thoracic			Biopsy	tem, bev	54 Gy	11 m	DOD
19	2011	4	53	M		thoracolumbar			Biopsy	tem, bev	54 Gy	5 m	DOD
20	2010	43	18	F		C7-T7			Gross total	NA	55 Gy	10 m	NA
21	2010	43	14	M		C7-T2			Subtotal	NA	CSI 38.5 Gy	4 m	NA
22	2010	43	10	F		C3-T7			Biopsy	NA	48 Gy	14 m	NA
23	2010	43	17	M		C1-C5			Subtotal	NA	54 Gy	4 m	NA
24	2010	43	13	F		C1-T1			Biopsy	NA	54 Gy	1 m	NA
25	2010	43	15	F		T10-T11			Subtotal	NA	CSI 39.6, focal 51.3	1 m	NA
26	2010	43	9	F		T2-T7			Subtotal	NA	CSI 36, focal 54	10 m	SD
27	2009	37	21	M	6 w	C1-C7			Subtotal		spinal and WBI	3 m	DOD
28	2009	6	46	M	2 m	T12-L2		>10%	Subtotal	tem	yes	6 m	PD
29	2006	46	17	F		thoracic		19%	Yes				

30	2005	25	39	M		conus medullaris		Yes		46 Gy		
31	2005	24	20	M	1 m	T12-L1	GFAP	Subtotal	no	yes	11 m	DOD
32	1999	26	18	F		C7-T7		Gross total	no	55 Gy	14 m	DOD
33	1999	26	14	M		C7-T2		Subtotal	yes	CSI 38 Gy	13 m	DOD
34	1999	26	10	F		C3-T7		Biopsy	yes	48 Gy	24 m	DOD
35	2000	40	31	F		T10-T11	p53	Subtotal	NA	NA	13 m	DOD
36	1995	5	22	M	2 w	cervical	high				11 w	DOD
37	1985	41	20	M		T5-T8		Subtotal	NA	NA	5 m	DOD
38	1998	1	4	M		holocord		Subtotal	yes	no	37 m	DOT
39	1998	1	13	F		cervical		Total	yes	54 Gy	15 m	DOD
40	1998	1	15	M		cervical		Subtotal	yes	no	8 m	DOT
41	1989	8	16	F	10 m	T12-L1		Subtotal	NA	yes	6 m	DOD
42	1989	8	14	M	9 m	T12-L1		Subtotal	NA	yes	4 m	DOD
43	1996	10	<3			NA		Subtotal	yes	yes	23 m	Alive
44	2001	20	12	F	12 m	C1-C7		Subtotal	NA	NA	NA	Alive
45	1997	34	0.7	M		C5-L1		Total	NA	40 Gy	144 m	Alive (12 years)
46	1997	34	17.9	M		T9-L1		Subtotal	NA	no	3 m	DOD
47	2003	36	19	F		NA		NA	NA	NA	9 m	DOD
48	2003	36	18	F		C7-T7		Total	NA	yes	21 m	DOD
49	2003	36	3	M		T7		Biopsy	yes	yes	13 m	DOD
50	2003	36	14	M		C2-C7		Subtotal	yes	yes	9 m	DOD
51	2003	36	19	M		C4-C6		Subtotal	NA	yes	12 m	DOD
52	2003	36	29	M		T12		Biopsy	NA	NA	10 m	DOD
53	2003	36	23	M		conus medullaris		Subtotal	NA	NA	8 m	DOD
54	2003	36	27	M		T12-L2		Total	no	yes	16 m	DOD
55	2003	36	59	F		T3-T5		Subtotal	no	yes	5 m	DOD
56	2003	36	46	F		C5-T5		Biopsy	no	no	5 m	DOD
57	2003	36	25	M		L1		Subtotal	yes	yes	36 m	DOD
58	2003	36	34	F		C6-T3		Subtotal	yes	yes	9 m	DOD
59	2003	36	88	M		T5		Subtotal	NA	NA	5 m	DOD
60	2003	36	75	M		T12-L2		Subtotal	NA	NA	2 m	DOD
61	2003	36	73	M		C3-C6		Subtotal	NA	NA	1 m	DOD
62	2005	39	14	M	24 m	T12-L1	25%	Total	NA	NA	9 m	NA
63	1946	29	16	M		conus medullaris				yes	16 m	DOD
64	1976	42	12	F		conus medullaris		yes	NA	NA	11 m	DOD

65	1978	2	45	M		T12			yes	NA	yes	13 m	DOD
66	1993	18	50	M		T11-L2			yes	NA	40 Gy	NA	NA
67	2011	19	16	F		T12-L1			Biopsy	bev, cp,nim, iri	CSI 30.6, boost 14.4	12 m	DOD
68	2011	19	48	M		T11-L2			Biopsy	tem, cp, nim	45 Gy+30 Gy	16 m	DOD
69	2013	32	59	M	5 y	T1	p53	high	Gross total	no	27 Gy	8 m	DOD
70	2013	32	22	F		C5-T2			Subtotal	tem	36 Gy	14 m	DOD
71	2013	32	54	F	2 m	C3-C4			Gross total	no	no	10 w	DOD

CONCLUSION

The spinal site is a rare site of GBM with poor survival despite multimodality therapy. The future novel agents, like integrin inhibitors, dendritic cell based vaccines, valproic acid, telomerase inhibitors, gamma secretion inhibitors and antiangiogenic agents may be new hopes for treatment of high grade glioma cases. Childhood sGBM cases, which are very rarely encountered, require a multidisciplinary approach. Concomitant chemoradiotherapy has been recommended after total or near total aggressive microsurgical excision. The identification of specific genetic alterations of spinal GBMs could help in therapy, and it is important for the prognosis. Improvements in targeted studies to define genotypical abnormalities in pediatric embryonal tumors and high risk embryos provide hopes for the future.

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