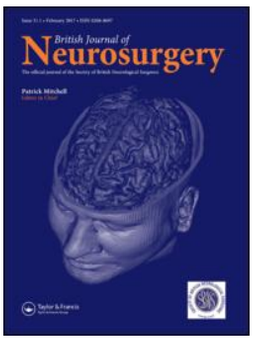

British Journal of Neurosurgery

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ibjn20

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To cite this article: Okan Turk , Nuriye Guzin Ozdemir , Ibrahim Burak Atci , Hakan Yilmaz , Feray Gunver , Veysel Antar & Adem Yilmaz (2020): A rare case of cervical metastatis of glioblastoma after cranial tumor resection: case report and review of literature, British Journal of Neurosurgery, DOI: 10.1080/02688697.2020.1814994

To link to this article: https://doi.org/10.1080/02688697.2020.1814994

BRITISH JOURNAL OF NEUROSURGERY
https://doi.org/10.1080/02688697.2020.1814994

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REVIEW ARTICLE

A rare case of cervical metastatis of glioblastoma after cranial tumor resection: case report and review of literature

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common and the most malignant primary intracranial tumor in adults. GBM extraneural metastases occur in only approximately 0.2–0.4% of patients. We present a case of a cervical metastasis of glioblastoma after cranial tumor resection. In concord with case presentation, we reviewed the metastatic location and metastasis time of the gliablastomas seen in the literature.

ARTICLE HISTORY
Received 21 February 2018
Revised 29 April 2020
Accepted 21 August 2020

KEYWORDS
Cervical; extraneural; glioblastoma multiforme; metastases

Introduction

Glioblastoma is the most malignant intracranial tumor. It infiltrates the brain without invading blood vessels. It rarely metastasizes out of the central nervous system.[1–6] The incidence of intracranial metastasis to spinal region is 2–4%, however reported autopsy series are higher as a rate of 25%.[7,8] Pleura, lung, bone, liver, lymph nodes were the most common sites.[1,2,9]

Case

A 31-year-old woman was admitted to our clinic with complaints of headache and seizures, after which she was diagnosed as having a left frontal low grade tumor on her magnetic resonance imaging (MRI) (Figure 1). She was operated and pathology report was reported as low grade glial tumor. Four years later she was found to be right hemiparetic (grade 3/5) after admission with a complaint of headache. Evaluation of her preoperative MRI showed that anterior region of the tumor was cystic necrotic, and posterior part was solid (Figures 2 and 3). She was reoperated and the pathology report was high grade glial tumor, glioblastoma. Immunohistochemical analysis relieved that Ki-67 proliferation index of the cystic areas was 15%, whereas of the solid part was 80%. The patient was treated using three-dimensional radiotherapy (6,000 cGy, 200 cGy, 30 fraction) combined with temozolomide.

On follow-up after a year, she was found to have a severe right upper extremity pain not responding to medication and later progressing to a motor deficit. The relevant dermatome was C7-8.

On cervical MRI, a C-7 mass, invading to anterior, posterior corpus and paraspinal region with foraminal and extraforaminal extension was observed. Surgical decompression was planned. Hemilaminectomy at the level, tumor resection, foraminotomy and unilateral facetectomy was done. Dura was not totally cleared of adherence, however foraminal and partial dural decompression was achieved. Frozen section showed malignancy. Decompression was achieved by 40% of the tumor removal, since the tumor was adherent to the surrounding structures (Figures 4 and 5). Instrumentation was not considered since the lesion was unilateral and foraminotomy and facetectomy was accomplished unilaterally; and instability was not observed on preoperative images. The patient's survival rate was also evaluated.

Pathological report was glioblastoma metastasis with PNET-like areas. Ki-67 proliferation index was 90%. The pathology of the metastatic site has shown the identical characteristics of the solid part of the primary pathology (Figures 6–8).

On post-operative examination she had no motor defisit and her complaints were relieved. Fifteen days after, she had again severe pain in her neck and arm. Cervical MRI showed the residual tumor was triplicated, and she was referred to oncology department for radiotherapy.

The patient died 20 months after the diagnosis of glioblastoma.

Discussion

Glioblastoma is the most common primary tumor of the cerebral hemispheres in adults accounting for 17.1% of all central nervous system (CNS) tumors. It's the mostly seen malignant neoplasm spreading by direct extension and infiltration into the adjacent brain through the white matter tract. The prognosis is poor. Survival rate is less than 12% two years after the first diagnosis.[9] Current literature reports a 2-year survival rate of 16.9%, and as high as 27% with the combination of radiation therapy and temozolomide.[10,11]

The local invasion and recurrence rate is high, whereas the metastasis out of the CNS is very rare and indicates a poor clinical outcome.[1,4,9] Glioblastomas comprise two thirds of the neuroepithelial tumors that metastasize extraneurally, though.[6]

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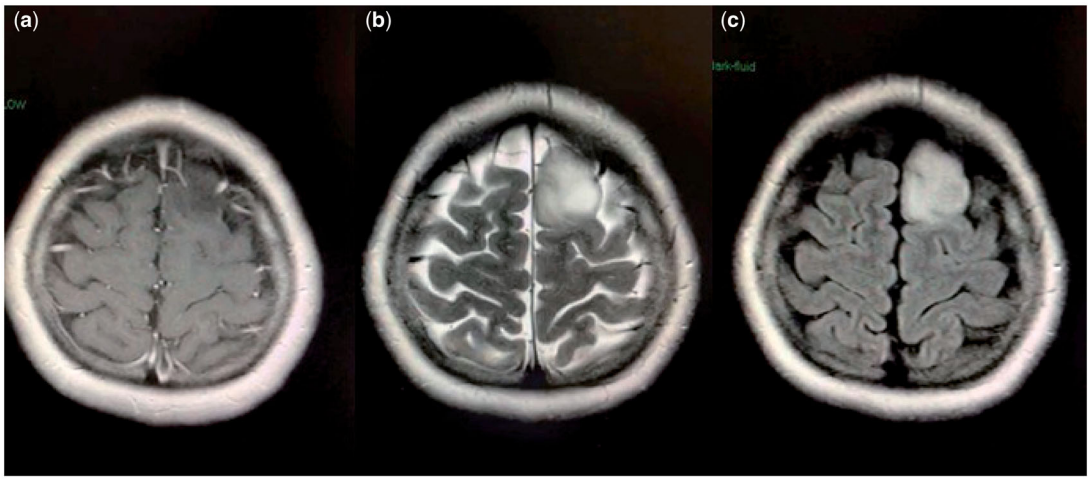

Figure 1. (a, b, c) Preoperative axial flair (a), T2W (b) and contrasted T1W (c) MRI shows left frontal contrast enhancing lesion.

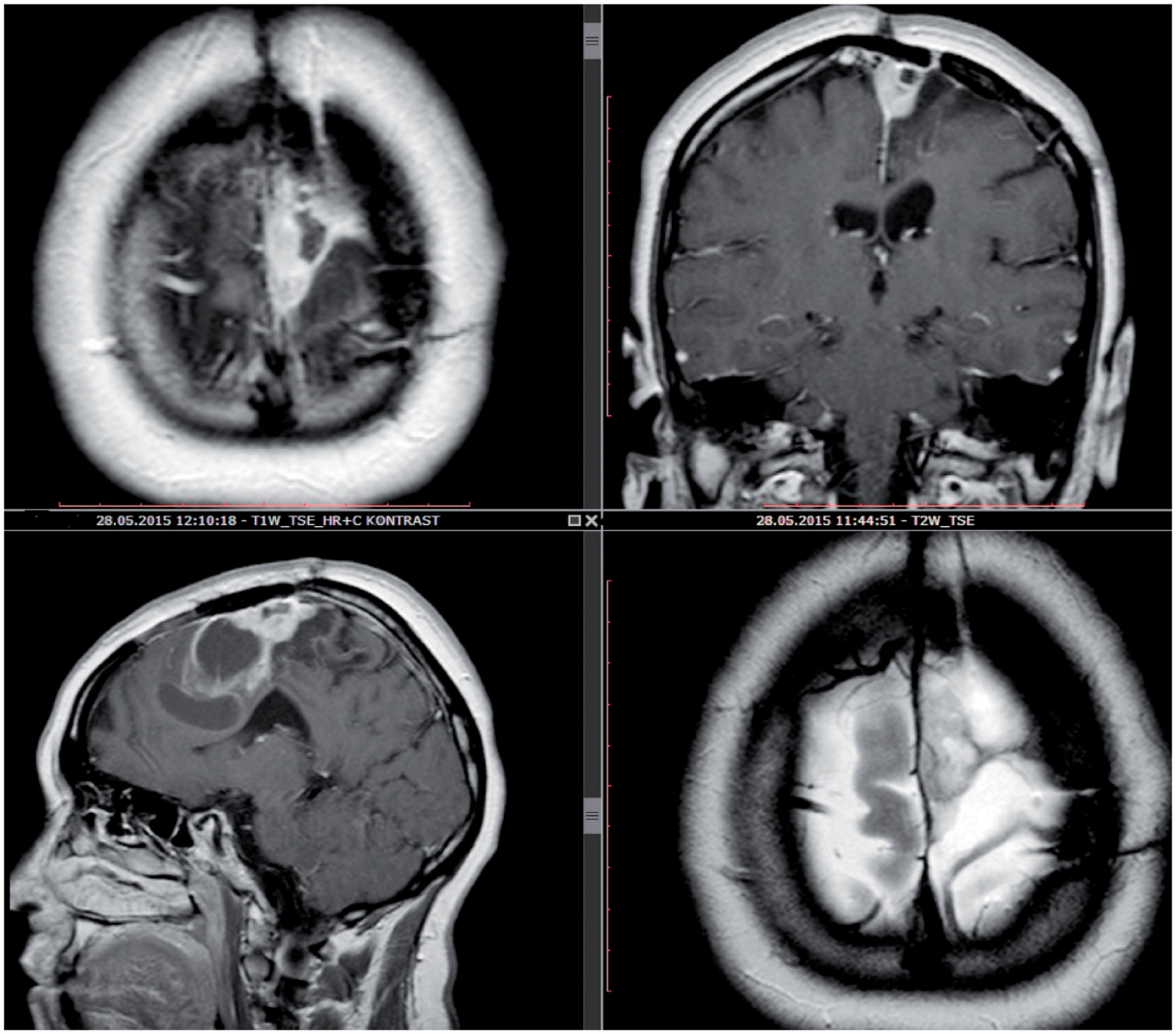

Figure 2. Pre-operative MRI before the third intracranial tumor resection showing both the cystic anterior and posterior solid parts of the recurrent tumor.

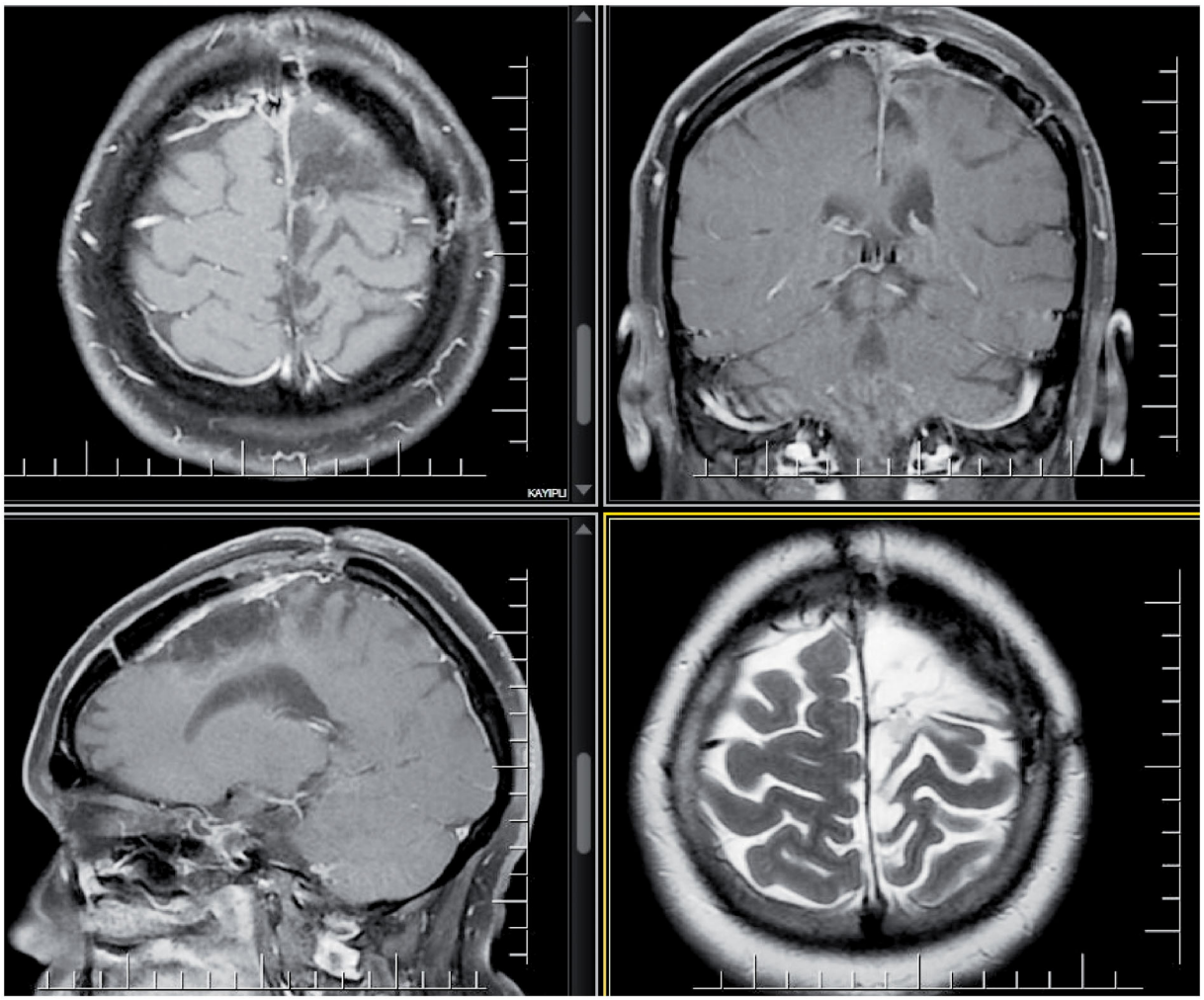

Figure 3. Post-operative MRI after the third operation.

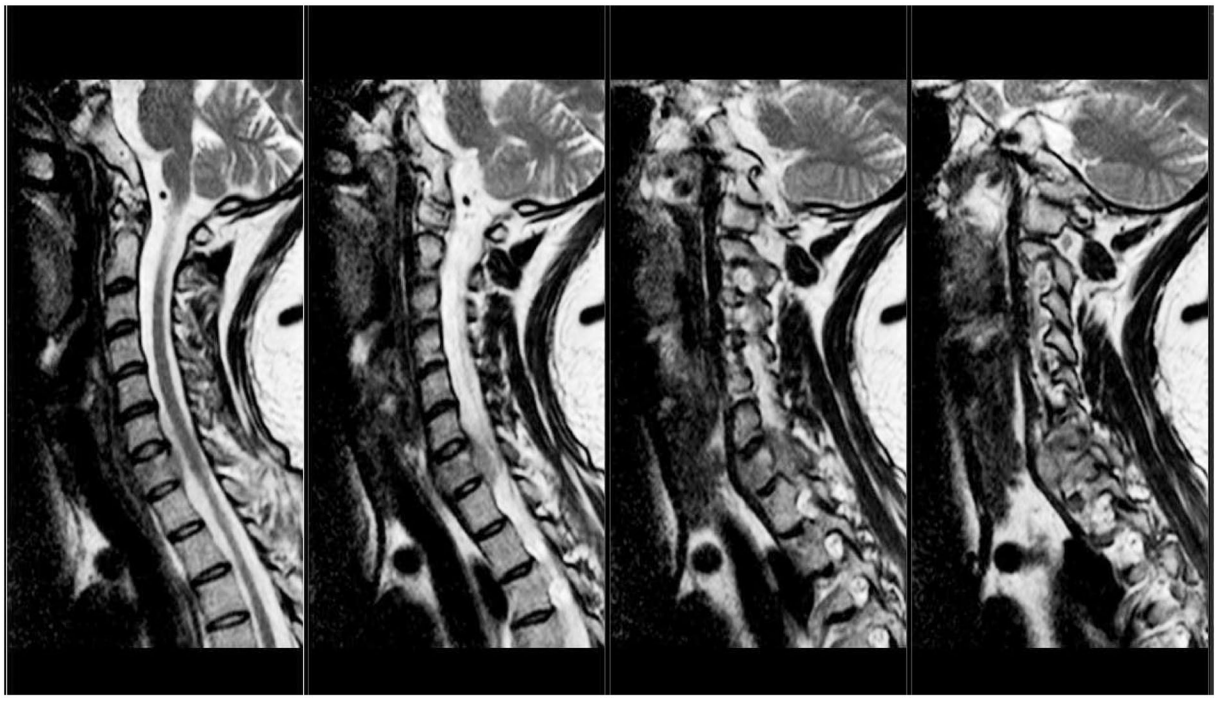

Figure 4. Pre-operative cervical MRI showing the metastatic tumor at C-7 level.

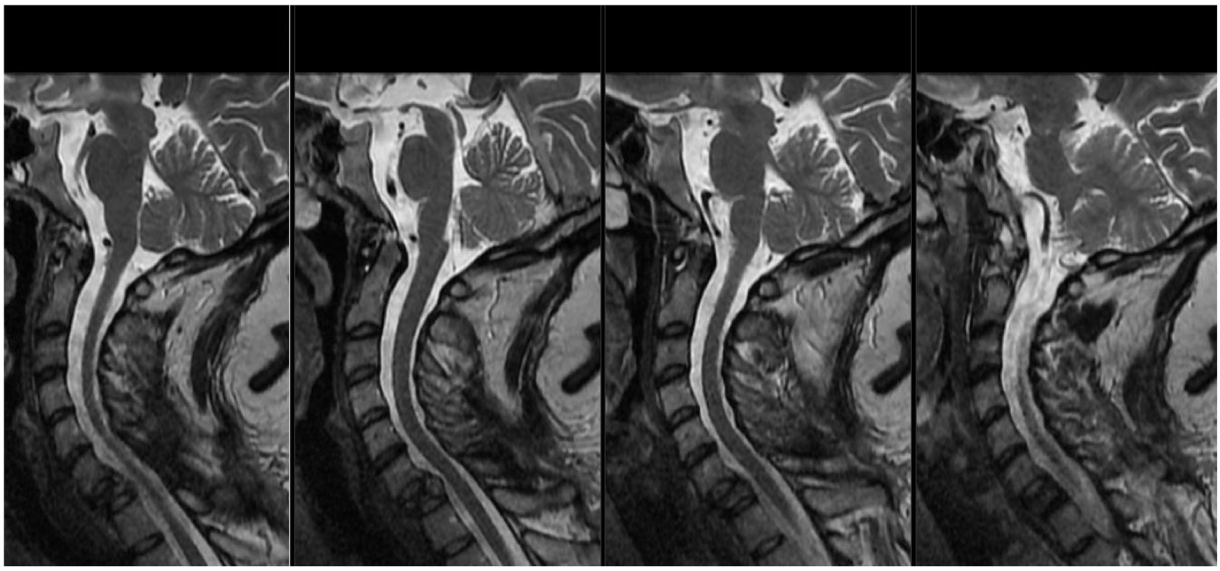

Figure 5. Post-operative cervical MRI after the metastatic cervical tumor resection.

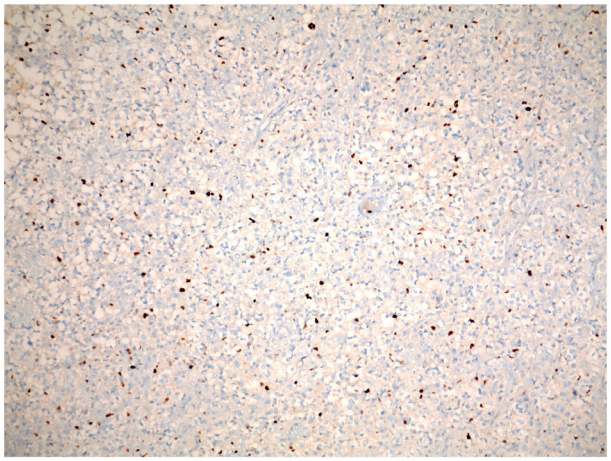

Figure 6. Immunohistochemical staining with Ki67 is observed in Glioblastomas like Primitive Neuroectodermal Tumor (PNET) in frontal lobe tumor (Ki67 X100).

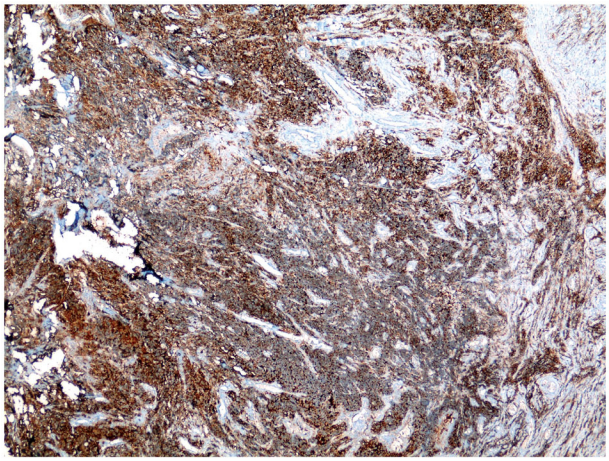

Figure 8. Immunohistochemical staining with sinaptofizin is observed in the cervical vertebra-localized tumor (Sinaptofizin X40).

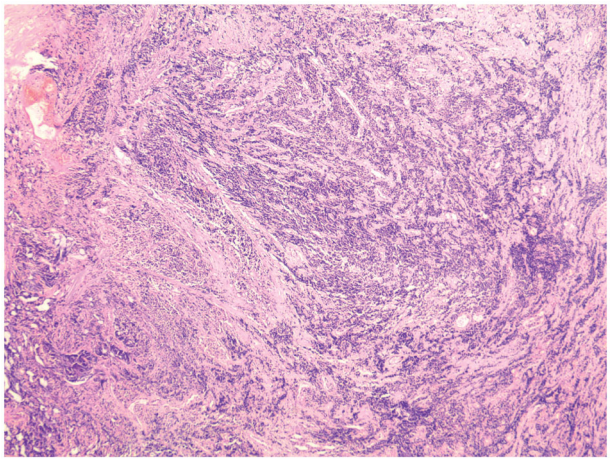

Figure 7. Primitive Neuroectodermal Tumor (PNET) like areas are observed in the cervical vertebra-localized tumor (HEX40).

The mean age of the patients with extraneural metastasis was reported as 40, whereas the average age of the first diagnosis of glioblastoma is 54 years.[8]

The short survival time for the patients may prevent detecting the metastases. Also, protective blood brain barrier with capillary basement membrane may play a role in preventing metastasis.[1,7] Lack of extracellular matrix components as collagen and fibronectin may be another factor.[1,7] The other reasons are reported as sparcity of the connections between the subarachnoid space and extracranial lymphatic vessels, non-communication of intracranial perivascular spaces with extracranial fluid space and thin property of the walls of intracerebral veins. The absence of lymphatic vessels in the CNS may prevent extraneural metastasis as well.[6,7,9,12,13]

The incidence of extraneural metastases has reported to be increased from 0.2–0.44, 0.5% to 2%.[1,6,7,9,14,15] The mean survival time of a patient with glioblastoma has prolonged from 6 months to 2 years and prolonged survival is considered as a factor in the increased rate of extraneural metastasis.[5,16,17]

A total of 128 cases of extra CNS metastases were reviewed by Piccirilli et al. The mean overall survival of extraneural metastasis was reported as 17 months.[16] Improved radiology techniques have also allowed the increased survival.[9]

Table 1. The Review of the gbm metastasis.

Case no	Author	Age, sex	Site	Survival from primitif GBM	Lifetime after metastasis
1	Xu	58, M	bone, lymph node	54 month	5 month
2	Undabeitia	20, F	lung, bone,	8 month	3 month
3	Kim W	39, M	vertebra bone, peritoneum,pleura	10 month	3 month
4	Razmagolova	64, F	lung	Early period	
5	Mujtaba	20, M	lymph node	19 month	
6	Blume	35, M	lung, bone, lymph node	> 43 month	10 month
7	Seo	46, M	lymph node	>66 month	5 month
8	Ulitin		lymph node		
9	Templeton	58, M	lung, bone	11 month	6 month
10	Templeton	47, F	pleura	>24 month	
11	Astner	54, M	liver, bone	36 month	33 month
12	Chelly	26, M	bone	>18 month	
13	Mentrikoski	58, F	skin	>16 month	
14	Ray	29, F	lung	35 month	
15	Ray	29, M	skin	14 month	
16	Taskapilioglu	30, F	parotid, lymph node	16 month	6 month
17	Romero-Rojas	26, M	parotid,lymph node,bone	24 month	17 month
18	Snopkowska-Wiaderna	38, K	lymph node	19 month	9 month
19	Pham	61, F	Cervical vertebrae	>13 month	
20	Zhen	25, M	lymph node,bone	>9 month	
21	Senetta	48, F	skin		
22	Senetta	53, F	skin	>9 month	
23	Kraft	58, M	parotid	17 month	2 month
24	Saad	13, F	skin, liver,lung	10 month	
25	Johansen	59, F	lung	8 month	
26	Johansen	60, M	liver	10 month	
27	Anghileri	30, M	lung, lymph node	78 month	4 month
28	Anghileri	43, M	skin	25 month	1 month
29	Guo	19, F	cervical subcutaneous	>14 month	>6 month
30	Bouillot-Eimer	60, F	subcutaneous	>8 month	
31	Kup	70, F	oral cavity	>12 month	> 1 month
32	Kumar	11, M	subcutaneous	>14 month	>2 month
33	Khattab	51, M	lung, lymph node, bone	46 month	6 month
34	Forsyth	59, F	skin	10 month	4 month
35	Takanen	F	bone	>8 month	
36	Nauen	57, M	pleura		
37	Miliaras	63, M	scapular subcutaneous	10 month	3 month
38	Chelly		Bone,liver,pancreas	>18 month	
39	Mujic	39, M	pleura	26 month	1 month
40	Astner	54, M	liver,bone	36 month	>12 month
41	Frank	36, M	lung,subcutaneous	15 month	12 month
42	Yokosuka	21, M	peritoneum, pleura, lymph node	10 year	13 month
43	Ozturk	58, M	skin	20 month	7 month
44	Torres	63, F	skin	>14 month	>6 month
45	Rashid	21, M	bone, lymph node	18 month	
46	Pace	26, F	bone,leptomeningeal	>11 month	
47	Wassati	60, M	lymph node	10 month	4 month
48	Yilmaz	50, M	skin	29 month	13 month
49	Lei	35, M	bone	?	10 month
50	Sharma	54, F	bone,leptomeningeal	24 month	
51	Alan	35, M	skin	21 month	3 month
52	Moukhlissi	65, M	bone	14 month	8 month
53	Vugnier	70, M	vertebra torasik	>6 month	

Interstitial radiotherapy is another etiological factor in the increased incidence of extraneural metastatic glioma.[18]

The site of glioblastoma growth influences the extraneural spread of the disease.[19] The modification of the histological and genetic features of primary glioblastoma may be also related the increased rate of extraneural metastasis.[13]

When metastasis is observed, it may be by the lymphatic cerebrospinal fluid drainage into the extraneural tissue; by hematogenous way of venous invasion via the leptomeningeal sinuses or the intracerebral vein; direct invasion through the dura and bone; or tumor cell migration by the way of ventriculoperitoneal shunts.[1,20]

Hematogenous and/or lymphogenous spread after infiltration of the skull and extracranial soft tissues is the most common route. These patients uusually have undergone prior craniotomy, and the brain anatomy has been altered, leading to tumor infiltration of extracranial soft tissue, blood and lymphatic vessels.[13]

In the presented case we also think that the primary tumor metastasis is by the hematogenous route. There were two components of the intracranial tumor; the anterior cystic part and the posterior solid part adherent to sagittal sinüs. The anterior solid part of the tumor adherent to the sagittal sinus and the cervical metastatic tumor had the same pathology with PNET like regions, and both had high ki-67 proliferation index. Cervical metastasis was considered to be from this adherent solid component via hematogenous way.

Lung, bone and spleen metastases may be by hematogenous way. Batson plexus is thought to play role in case of vertebral involvement. The Batson plexus supplies the inferior vena cava, lumbar and sacral vertebrae and gives way to lung, liver, lumbar

and sacral vertebrae metastases. Connections between the meningeal venous and craniocervical venous system with the internal vertebral venous plexus explains the hematogenous spread to the axis metastasis.[13]

Intracranial operations may lead to dissemination of glioblastoma tumor cells by increasing the disruption of the blood brain barrier. Spillage may be by a contact of the tumor cells with extracerebral blood and lymphatic vessels. The risk may be decreased by changing surgical gloves and instruments after intradural tumor removal, irrigating the tumor cavity and with water tight closure of the dura.[8,9,21]

CSF dissemination occurs in 15–25% cases of supratentorial glioblastoma, 60% of infratentorial glioblastoma.[22]

The most common metastatic sites were pleura, lungs, bone, lymph nodes and liver.[1,4] Heart, adrenal glands, kidneys, diaphragm, mediastinum, pancreas, the thyroid gland, the peritoneum, orbita, muscles, neck, skull, scalp, cutaneous tissue, cervical nodes, bone marrow, sternum, spine, vertebra, trochanter minor, thigh were also reported.[1–3,5,6,9,10,12,13,15–18,20,23,24] Lung was the most common metastatic site, followed by bone at which vertebrae was affected most frequently as seen in our patient.[13] The rate of cervical lymph node metastasis was reported as 62%. Repeated craniotomies were accused by leading access to lymphatics by dural or scalp extension through the surgical defect.[6] When skeleton is involved, vertebral bodies are the most common site.[13]

Head and neck metastasis from glioblastoma is usually seen in patients with previous and repeated surgery and can be debilitating.[5,6,25] A patient with intraspinal extradural metastasis was also reported.[13] The most common sites for spinal metastasis are the lower thoracic, upper lumbar, and lumbosacral regions; the nerve roots of the cauda equina, the root sleeves and thecal sac being the most common sites. Intramedullary metastasis was very rare.[22]

Positron emission tomography scan (PET) may be helpful in revealing multiple metastases.[2] Fiberoptic bronchoscopy is helpful in the diagnosis of the extraneural metastasis of intracranial glioblastoma to the lung.[23]

The presence of extraneural metastasis criteria was; the histological diagnosis of the metastatic lesion as CNS tumor, the presence of the primary neoplasm as CNS tumor, the absence of any other primary tumor as the metastatic primary focus, the identification of the primary and metastatic lesion with same histological diagnosis.[1,3,6,12,17,20,26]

The extraneural metastasis may be related to p53 gene mutations and differential clone section.[9] The overexpression of insulin growth factor is thought to play a role in tumor progression, a decrease of DNA-PK genetic expression is considered to be involved in the malignant transformation of the glioma. Distant dissemination is thought to be the consequence of direct infiltration of tumor cells into extracranial blood vessels. Sarcomatous component of the glioblastoma is reported to be related with the tendency to metastasize. Adjuvant radiotherapy and chemotherapy may cause these sarcomatous changes.[13]

Differential diagnosis of the extraneural metastasis from small cell carcinoma, poorly differentiated carcinoma, embryonal rhabdomyosarcoma and neuroblastoma should be made.[6]

The risk factors was reported as young age, prolonged survival time, repeated recurrence, high grade of tumor histology, sarcomatous component and the operation itself.[7] It's reported that 96% of the patients with extraneural metastases had an intracranial operation before.[7,8]

Extraneural metastases have been reported to ocur between 8 to 24 months after the initial diagnosis and were evaluated as the advancement of the disease.[9]

İntracranial relapse was not observed in most of the cases of extraneural metastasis of glioblastoma as observed in our case. Prognosis of glioblastoma metastatic lesion may be very poor, although no recurrence is observed in the primary site.[7] Metastasis has been reported to precede regrowth of the primary glioblastoma, however this data did not change the fact that the death was as a result of cerebral glioblastoma regrowth into deeper structures.[13]

Extraneural metastasis may be treated by either radiotreapy, radiosurgery or chemotherapy which will prolong the survival.[20] Poor outcome has been reported in elderly patients, however an aggressive treatment for those with a Karnofsky performance >60 was recommended.[13]

The review table of the gbm metastasis was given (Table 1).

Conclusion

The glioblastoma can metastasize to extraneural tissue, although rare. Spinal metastasis should be kept in mind as a differential diagnosis. Hematogenous spread by the infiltration of the dural sinuses should be considered as a metastatic route. Since the survival rate of glioblastomas has been increased with adjuvant therapy, the possibility of extraneural metastasis should be considered and these patients should be more frequently surveyed. Appropriate systemic evaluation with holospinal MRI and CT of thorax and abdomen is necessary, so that the therapeutical management can be performed earlier and accordingly.

Informed consent

Written informed consent for submission of the paper was obtained from the patient.

Disclosure statement

We have no conflict of interest.

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