Primary Spinal Glioblastoma Multiforme with Secondary Manifestation as a Cerebral "Angioglioma." Literature Review and Case Report

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Abstract

Primary intramedullary spinal glioblastoma multiforme (sGBM) with a secondary cerebral manifestation is a very rare entity with a poor outcome. Case studies show a mean average of survival of 10 months after diagnosis. These tumors tend to develop at a young age. A combination with an arteriovenous malformation in the same location has never been published before. Vascular malformations in association with cerebral glioblastomas have only been reported in five cases so far. Proangiogenic factors are assumed to be involved in the appearance of both entities. We present a case study and a review of the literature.

Keywords
- spinal glioblastoma
- cerebral angioglioma
- arteriovenous malformation

Introduction

Primary intramedullary spinal glioblastoma multiforme (sGBM) is a rare disease entity and accounts for only 1 to 5% of all GBMs and only 1.5% of all spinal cord tumors. It develops from the spinal cord or as a secondary metastasis from the brain. It tends to have a predilection in the cervical region in primary cases and more often occurs in younger patients (< 30 years of age). Despite the best treatment with surgery and adjuvant therapy, overall survival barely exceeds 6 to 16 months.[1–9] Twenty cases of primary sGBM with secondary cerebral manifestation have been reported since 1938.[2,4,10–22]

Vascular malformations associated with gliomas are also extremely rare and include venous malformations, cavernous angiomas, or arteriovenous malformations (AVMs). AVM in combination with a cerebral GBM in the same location has been reported in only five cases so far.[23–26]

Methods

Databases Ovid Medline and PubMed were searched using a combination of thesaurus terms and relevant text words: *intramedullary GBM, primary spinal GBM, spinal GBM with secondary manifestation, spinal glioblastoma and secondary cerebral manifestation, spinal GBM cerebral metastases, glioblastoma and vascular malformation,* and *angioglioma.* Previously reported cases were reviewed and discussed in the light of our own observations. Mean age, gender distribution, and location of the GBM were calculated and analyzed based on the data we collected.

Case Report

A 35-year-old German male patient was transferred to our institution with a short history of progressive left-sided hemihypesthesia downward from the chest to the toes without motor deficits and gait disturbance.

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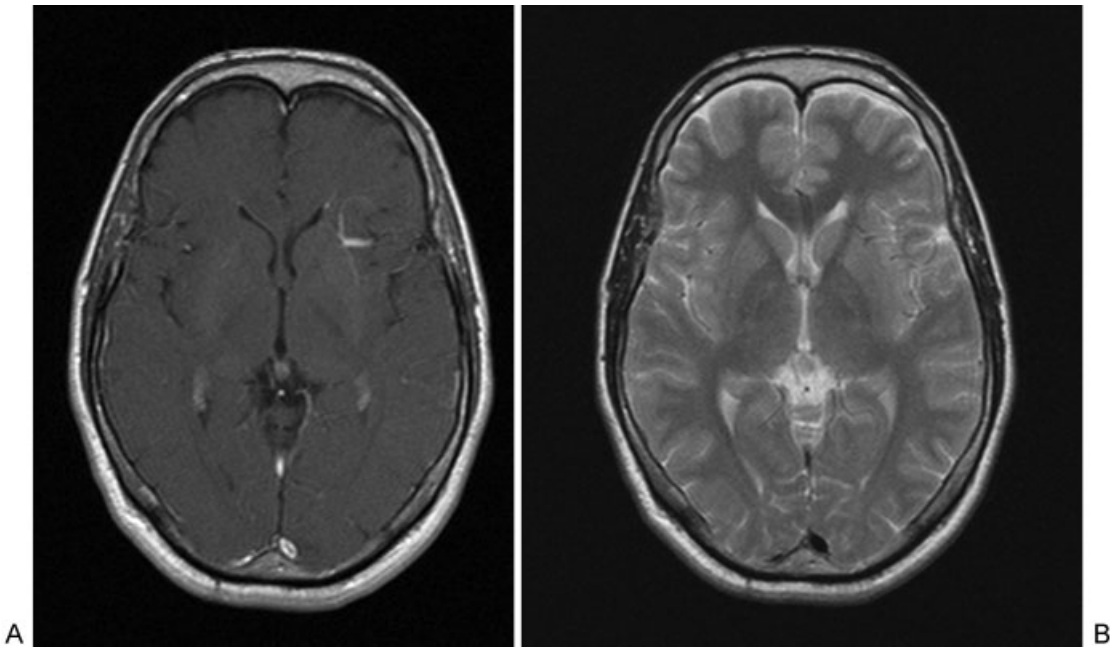

Fig. 1 (A) Axial T1-weighted magnetic resonance image enhanced with gadopentetate dimeglumine. (B) Axial T2 image demonstrating a venous malformation in the left frontal lobe. There was no further evidence for a cranial manifestation of a tumor or a cerebral hemorrhage.

The first diagnostic steps included cranial magnetic resonance imaging (MRI) showing a venous malformation in the left frontal lobe. There was no further evidence of a cranial manifestation of a tumor or a cerebral hemorrhage (►**Fig. 1**).

The initial spinal MRI depicted alterations of the morphology and signal intensity of the spinal cord from T2 to T3 and a slight gadolinium (Gd) enhancement in this area (►**Fig. 2**).

We performed laminotomy and laminoplasty between T2 and T3, and partial tumor removal under motor-evoked potential monitoring. The histopathologic study confirmed the diagnosis of GBM with typical histologic findings of pleomorphism, atypical cells, vascular proliferation, and a high expression of glial fibrillary acidic protein. There was also a high Ki-67 proliferation index of ~20%. Postoperatively, the patient showed right-sided hemihypesthesia distal dermatome T5, marked gait disturbances, reduced proprioception, and less superficial sensation mainly left sided. The patient received spinal radiotherapy between T4 and T5 (60 Gy) and six cycles of chemotherapy with temozolomide (TMZ).

Sixteen months after surgery, MRI showed stable disease without evidence of further tumor growth or a new spinal manifestation. Nineteen months after the operation, the patient was hospitalized due to a massive headache and progressive

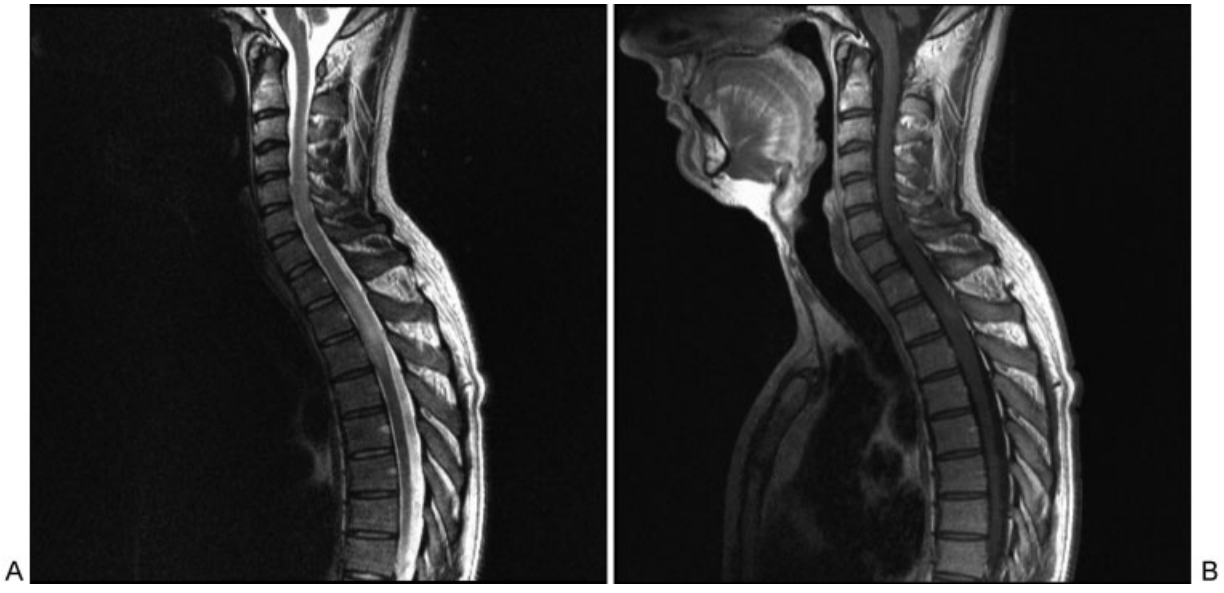

Fig. 2 (A) Sagittal T2-weighted and (B) sagittal T1-weighted plus gadopentetate dimeglumine magnetic resonance images demonstrating alterations of the morphology and signal intensity of the spinal cord from T2 to T3 and a slight gadolinium enhancement in this area.

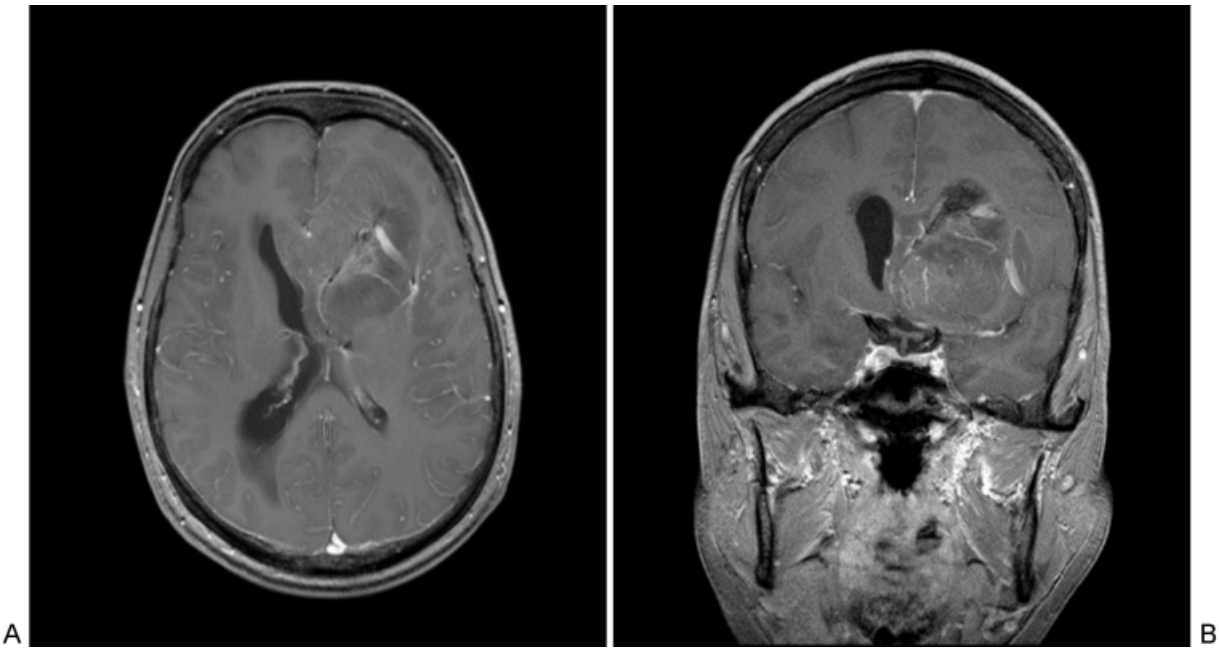

Fig. 3 (A) Axial and (B) coronal T1-weighted magnetic resonance images enhanced with gadopentetate dimeglumine demonstrating an intracranial tumor in the left frontal lobe with spread to the opposite hemisphere crossing the corpus callosum and still including radiologic signs for a venous malformation.

fatigue. MRI revealed an intracranial tumor in the left frontal lobe with Gd enhancement and spread to the opposite hemisphere crossing the corpus callosum, still including radiologic signs for a venous malformation (►**Fig. 3**). Microsurgical biopsy and intraoperative ultrasonic guidance (►**Fig. 4**) revealed a cerebral GBM World Health Organization grade IV with close association with an AVM (►**Fig. 5**). The patient died a few days after the biopsy due to malignant brain edema.

Discussion

Primary Spinal Glioblastoma with Cranial Manifestation

The incidence of sGBM drop metastases secondary to cerebral GBM is extremely rare (0.4–1.1%), whereas 25% of all sGBMs are drop metastases.[8] The reverse process is extraordinarily rare.[4,27]

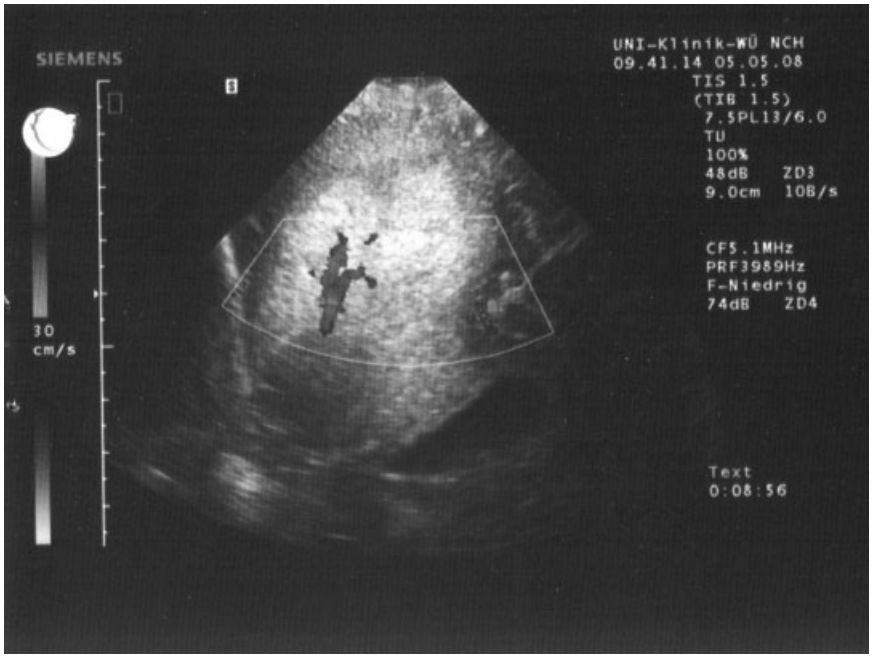

Fig. 4 Intraoperative ultrasound demonstrating a tumor with close contact to an arteriovenous malformation.

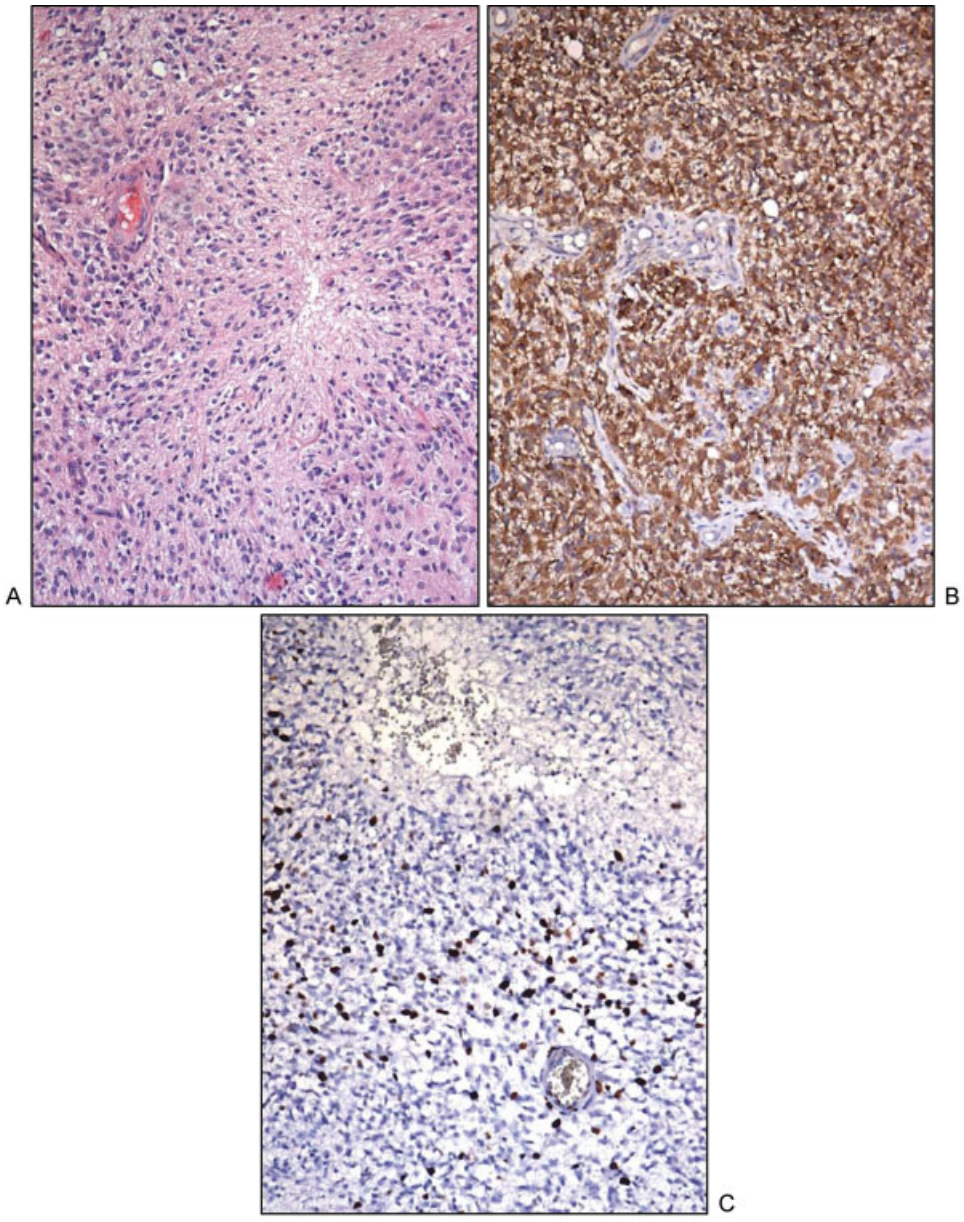

Fig. 5 (A–C) The histopathologic examination revealed a predominant glial (astrocytic) differentiated tumor, with increased cellularity, cellular pleomorphism, microvascular proliferation, and necrosis, corresponding to a glioblastoma World Health Organization grade IV. (A) Hematoxylin and eosin (×100). (B) Strong reactivity for glial fibrillary acidic protein (×100). (C) Area with high MIB-1 labeling index (×100).

We performed a review of the literature and, to the best of our knowledge, only 21 cases of primary sGBM with secondary cerebral manifestation have been previously reported since 1938 including this case.

The outcome of these cases was exceptionally poor with a mean average survival of 10.4 months from diagnosis (range: 1–36 months).[4,22] These tumors have a tendency to develop at a young age (mean: 23.9 years) with a slight male predominance (52%) and location in the thoracic spine (38%). Overall, 19% were located either in the conus or cervical spine.[4,9,21,27] The remaining cases were described as holocordal or diffuse spreading within the spinal column (►**Table 1**).

Spinal cord astrocytoma frequently involves the cervical spine. Although cervical spine astrocytomas are common, metastases to the brain mostly occur from the thoracic spinal cord.[10,28] Most of the patients received combined radiotherapy after surgical treatment (47%). Adjuvant chemotherapies have been described only in three cases since the early 1990s.

Patients with malignant spinal cord astrocytomas may develop disseminated disease mostly via the leptomeningeal route.[4,5] Treatment strategies include tumor debulking and high-dose postoperative radiation that may exceed the radiation tolerance of the spinal cord.[29] Most authors suggest focal spine radiotherapy and chemotherapy with TMZ. Others recommend a more aggressive course of whole-brain irradiation in addition to focal spine irradiation, even if there is no evidence of intracranial dissemination.[8] MRI is considered the gold standard imaging modality to diagnose intramedullary tumors, and Gd-enhanced MRI of the entire neuraxis is

Table 1 Literature review of 21 patients with spinal glioblastoma and secondary cerebral manifestation

Case no.	Study	Age	Sex	Localization	Metastases	Treatment	Survival Time, mo
1	Eden[13]	19	M	Spinal cord	Cerebral leptomeninges	Surg	7
2	O'Connell[17]	16	M	T7–T12	Ventricle, subarachnoid space	Biopsy, Rad	4
3	Russel and Rubenstein[9]	11	F	Cervical	Subarachnoid space, ventricles	Surg	6
4	Tashiro et al[21]	12	F	Conus	Cerebellum, hypothalamus, brainstem, thalamus	Surg	11
5	Andrews et al[2]	45	M	T12	Septal region, right ventricle	Surg, Rad	13
6	Hely 1985[30]	38	F	Dorsal cord	Subarachnoid space, ventricles, hypothalamus, brainstem, thalamus	Surg, Rad	9
7	Takara et al[20]	20	M	T5–T8	Basal cisterns	Surg, Rad	5
8	Johnson and Schwarz[27]	9	F	Dorsal cord to conus	Subarachnoid space, ventricles	Surg, Rad	14
9	Cohen et al[4]	16	F	Conus	Septum pellucidum	Surg	6
10	Cohen et al[4]	14	M	Conus	Intracranial sites	Surg	4
11	Cohen et al[4]	9	M	Cervical	Brainstem	Surg	1
12	Asano et al[10]	23	F	T11–L1	Bilateral lateral ventricles	Surg, Rad	12
13	Yamazaki et al[22]	35	F	T9–L1	Cerebral	Surg, Rad, Chem	36
14	Kawanishi et al[14]	50	M	T11–T12	Cerebellum, cingulated gyrus, Sylvian fissure	Surg, Rad	25
15	Chida et al[11]	22	M	Diffuse	Subarachnoid space along brainstem and cerebellum	None	3
16	Cursiefen et al[12]	16	M	C5–T1	Bilateral supratentorial	Surg, Rad, Chem	5
17	Strik et al[19]	31	F	T11	Multiple intracranial and meningeal	Surg, Rad	13
18	Medhkour and Chan[15]	20	M	T12–L1	Pontomedullary junction, cerebellum, suprasellar cistern, left lateral ventricle	2 Surg, Rad	11
19	Mori et al[16]	10	F	Holocordal	Pituitary stalk, cervicomedullary junction	Chem	14
20	Ozigiray et al[18]	54	F	C3–C4	Cranial meningeal, pontine medullary junction, cerebellum, suprasellar cistern, left lateral ventricle	Surg, Rad (ceased)	2
21	Present case	33	M	T3–T4	Left frontal lobe	2 Surg, Rad, Chem	19

Abbreviations: C, cervical spine; Chem, chemotherapy; F, female; M, male; Rad, radiation; Surg, surgery; T, thoracic spine.

Table 2 Literature review and data of six patients with vascular malformations in association with cerebral glioblastomas in the same location

Case No.	Study	Age	Sex	Localization	Treatment	Survival time, mo
1	Hubbell et al[33]	70	M	Right parietal	Surg	< 1
2	Zuccarello et al[35]	50	M	Left temporal	Surg, Rad	5
3	Ziyal et al[34]	58	M	Right temporoparietal	Surg	NR
4	Cemil et al[24]	58	M	Right temporoparietal	Surg	NR
5	Aucourt et al[23]	65	m	Left frontotemporal	Surg, Rad, Chem	NR
6	Present case	35	m	Left frontal	Surg, Rad, Chem	19

Abbreviations: Chem, chemotherapy; NR, not reported; Rad, radiation; Surg, surgery.

advocated to rule out cranial metastasis, evaluate treatment efficiency, and detect local relapse.[16,31,32]

Arteriovenous Malformation in Combination with Cerebral Glioblastoma

None of these 20 cases showed a cerebral AVM within the same location in addition to the cranial manifestation. Generally, vascular malformations in association with cerebral glioblastomas in the same location have only been reported in five cases so far[3,24,33–35] (►**Table 2**).

These entities have a tendency to develop in older patients (average: 56 years of age) with a very clear male predominance (100%). The relation of affected hemispheres (right to left) was 50%. All the patients underwent surgical treatment. Precise information about the survival time was only given in three cases and was poor as previously described.

Vascular malformations associated with gliomas are very rare in general and include venous malformations, cavernous angiomas, or AVMs.[25] It is supposed that the hyper-angiogenic environment of high-grade tumors induces abnormal arteriovenous connections.[36] Some authors suggested a new term for these entities and named them *angiogliomas*, historically first mentioned by Councilman who described a highly vascularized cerebellar tumor that is now regarded as the cellular variant of hemangioblastoma.[37,38] However, only a very few brain neoplasms develop large arteriovenous connections as mentioned. Enhanced angiogenesis, thickened basement membranes, and highly proliferative endothelial cells mediated by proangiogenic factors such as vascular endothelial growth factor (VEGF) overexpressed by the tumor is essential to diagnose high-grade gliomas.[39] VEGF secreted by tumor cells binds to endothelial cells expressing VEGF receptors with subsequent activation of neoangiogenesis.[40] VEGF is expressed in both entities, GBM and AVM, and may be the link for the simultaneous occurrence.[39] Thus adjuvant therapies with antiangiogenic factors may be preferred in this special situation of a combined occurrence of both entities.

Conclusion

A sGBM with secondary malformation is a very rare entity in mostly younger patients and has a poor outcome. Surgery, focal spine radiotherapy, and adjuvant chemotherapy with TMX are recommended for treatment. MRI of the neuraxis is considered the gold standard for controlling treatment efficiency and detecting cranial metastasis and local relapse.

Cerebral AVMs in association with GBM represent a very rare entity with very few reports in the literature. Proangiogenic factors appear to be involved in the appearance of both entities in the same location.

A combination of a primary sGBM with secondary cerebral manifestation in association with a cerebral AVM in the same location is reported here for the first time.

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