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Case Report

Gliosarcoma Occurrence After Surgical Clipping of Aneurysm – Coincidence or Causal Relationship?

Cerrahi Anevrizma Kliplemesi Sonrasında Gliosarkom Oluşması - Tesadüf mü Nedensel İlişki mi?

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ABSTRACT

Gliosarcoma is relatively rare brain tumor of glial and sarcomatous origin. The occurrence of this highly malignant brain tumor in the vicinity of the clipped aneurysm has not been reported in the literature. The authors report a case of 37-year-old man who developed sudden onset severe headache. Angiogram displayed a saccular aneurysm located on the bifurcation of left internal carotid artery, and a fusiform aneurysm on the M-1 segment of the left middle cerebral artery. The patient underwent successful surgical clipping of the aneurysms. Three years later, a mass lesion in the vicinity of the clipped aneurysm was detected on magnetic resonance imaging; gliosarcoma was pathologically confirmed after complete tumor extirpation. Despite postoperative radiotherapy and temozolomide chemotherapy, reoccurrence and subarachnoid metastasis unavoidably emerged. Brain injury, co-existence of two pathologies, metal ions released from aneurysm clips, and radiation might have led to tumorigenesis.

KEYWORDS: Aneurysm, Brain injury, Gliosarcoma, Metal ion, Radiation

ÖZ

Gliosarkom, beynin glial ve sarkomatöz kökenli nispeten nadir bir tümörüdür. Bu yüksek ölçüde malign beyin tümörünün kliplenmiş anevrizma çevresinde oluşması literatürde bildirilmemiştir. Yazarlar ani şiddetli başağrısı gelişen 37 yaşında bir erkeği rapor etmektedirler. Anjiyogramda sol internal karotid arter bifurkasyonunda sakküler bir anevrizma ve sol orta serebral arterin M-1 segmentinde fusiform bir anevrizma saptandı. Anevrizmaların başarılı bir şekilde kliplenmesi yapıldı. Üç yıl sonra manyetik rezonans görüntülemede kliplenmiş anevrizma bölgesinde bir kitle lezyonu saptandı; tam tümör ekstirpasyonundan sonra patolojik olarak gliosarkom doğrulandı. Postoperatif radyoterapi ve temozolomid kemoterapisine rağmen nüks ve subaraknoid metastaz ortaya çıktı. Beyin hasarı, iki patolojinin birlikte olması, anevrizma kliplerinden salınan metal iyonlar ve radyasyon tümörigeneze neden olmuş olabilir.

ANAHTAR SÖZCÜKLER: Anevrizma, Beyin hasarı, Gliosarkom, Metal iyonu, Radyasyon

INTRODUCTION

The contemporary therapeutic modalities for treatment of aneuyrsmal SAH include surgical clipping and endovascular obliteration. The surgical procedure occasionally leads to complications such as cerebromalacia, vessel occlusion and changes in cerebral blood flow. The occurrence of tumor in vicinity of the clipped aneurysm is rare. The estimated incidence of co-existent intracranial tumors and aneurysms is 0.5% and of all intracranial tumors 27% are glioma (5,10). We report a case of gliosarcoma diagnosed three years after aneurysmal clipping.

CASE REPORT

Admission for Cerebral Aneurysm Rupture

A 37-year-old man developed sudden onset severe headache, dizziness and vomiting while swimming, in August 2005. After 10 days conservative treatment in local hospital, the patient was transferred to our hospital. He had past history of SAH that was treated conservatively in 2000. Neurological examination revealed somnolence, mild right hemiparesis and mild aphasia. Magnetic resonance imaging (MRI) showed intracranial hematoma and an area of hypointensity with heterogeneous margin in the left basal ganglia and mildly dilated ventricle (Figure 1A). A four-vessel intra-arterial digital angiogram displayed a saccular aneurysm located on the bifurcation of left internal carotid artery, and a fusiform aneurysm on the M-1 segment of the left middle cerebral artery (Figure 1C). The young age of the patient and the location of aneurysm at distal internal carotid artery guided the decision of surgical clipping of aneurysm employing a craniotomy via left pterional approach. Both the aneurysms were separately clipped with Yasargil clips. Digital Substraction Angiography (DSA) demonstrated disappearance of the aneurysms and well enhanced primary ICA as well as its branches (Figure 1D). The pathological finding of the surrounding tissue was reported as gliosis. Postoperative course was marked by transient right hemiparesis that resolved after 2 months

of rehabilitation therapy. At 6 month follow up patient developed headache, dizzy and occasional incoherent speech. Electroencephalogram (EEG) revealed no abnormality and the symptoms resolved on conservative treatment. The 1-year follow-up DSA depicted no recurrence of aneurysms and the 15-month follow up MRI did not reveal any abnormal changes at the site of surgery (Figure 1B).

Admission for Gliosarcoma

The patient developed nonfluent speech at postoperative three years. On neurological exam the patient was mildly disoriented with mild aphasia and memory impairment. The T1-weighted MRI depicted a hypointense lesion in the vicinity of the left basal ganglia with peripheral heterogeneous enhancement and T2-weighted MRI showed mild peripheral edema (Figure 2A-C). DSA did not reveal the recurrence of the clipped aneurysms and the central branches of middle cerebral artery displayed a confluence of abnormal staining in the left basal ganglia area (Figure 3A, B). Given the past history of aneurysm rupture, the lesion was diagnosed as reactive gliosis due to hematoma organization. Pathological examination of the biopsy specimen showed lymphoid cell infiltration without any evidence of tumor cells. The progressive enlargement of lesion was evident on series of MRI performed in April, May, and June 2008 (Figure 2D-F). The patient gradually developed right limb numbness and weakness. A left frontotemporal craniotomy was performed. The tumor appeared gray-red in color, cystic, tough with yellowish surrounding tissue and no clearly boundaries. Histological exam with hematoxylin and eosin staining

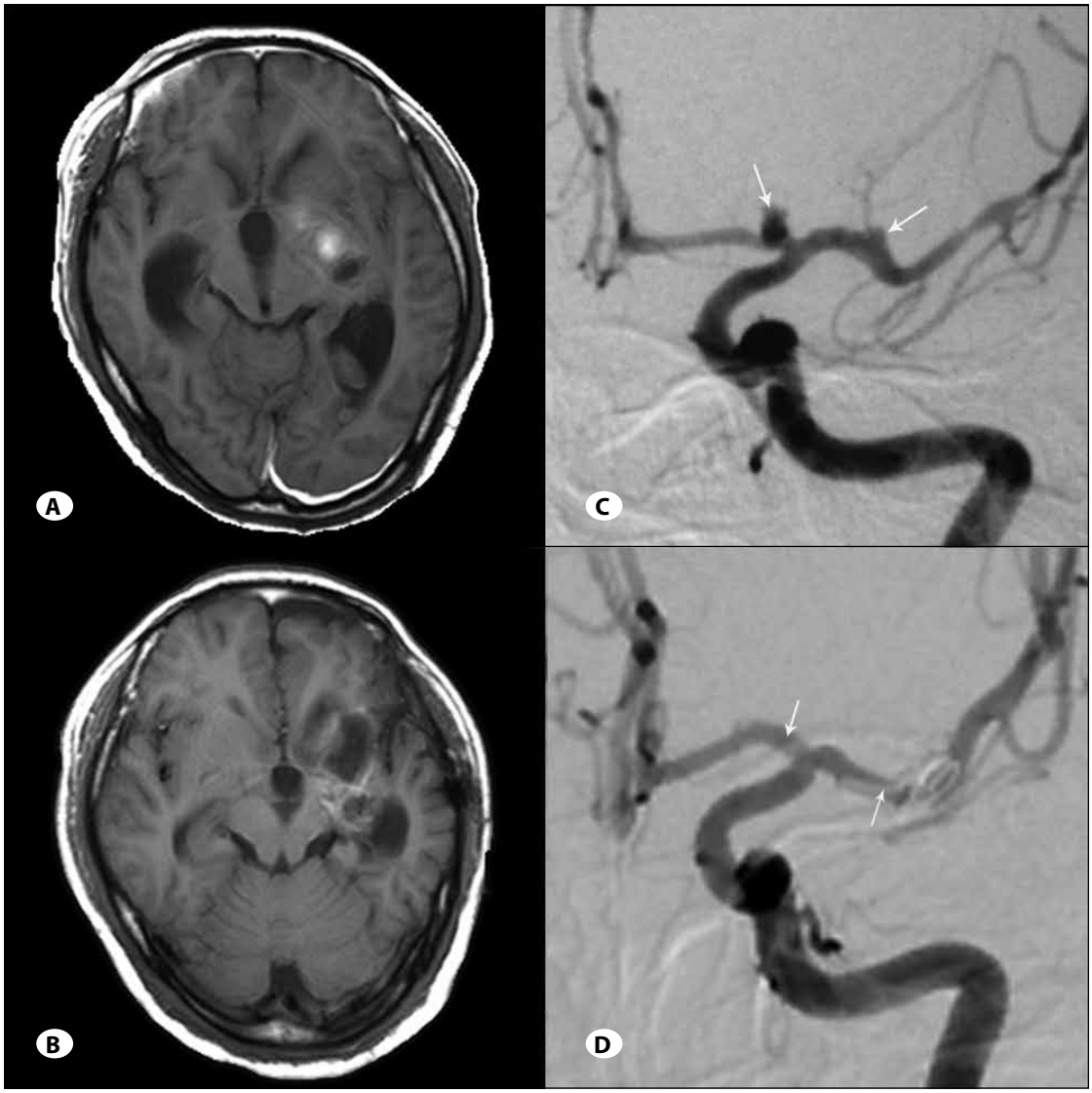

Figure 1: A) Axial T1-weighted image showing intracranial hematoma and an area of hyposignal intensity with heterogeneous margins in the left basal ganglia and the mildly dilated ventricle. **B)** 15-month post-operative axial T1-weighted image exhibiting no sign of tumor/mass. **C)** DSA displaying a saccular aneurysm located on the bifurcation of internal carotid artery, and a fusiform aneurysm on the M-1 segment of the middle cerebral artery. **D)** DSA revealing both aneurysms successfully clipped.

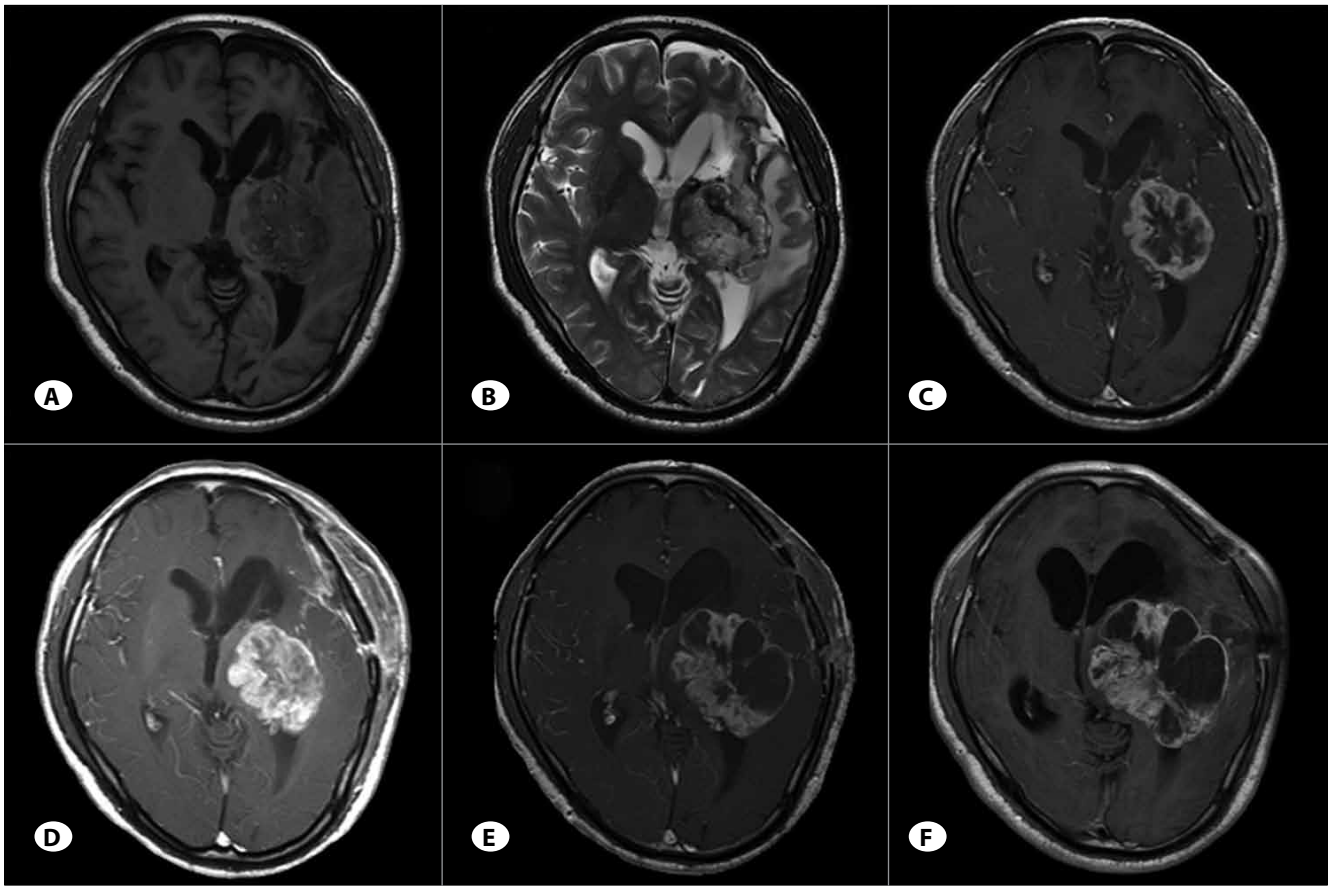

Figure 2: A) Axial T1-weighted image showing a hypointense mass lesion in the operative field. **B)** Axial T2-weighted image demonstrating mild peripheral edema surrounding the mass. **C)** Axial T1-weighted gadolinium-enhanced image showing the peripheral heterogeneous enhancement. **D-F)** a series of T1-weighted gadolinium-enhanced image revealing the progressively enlarged lesion in April, May, June 2008.

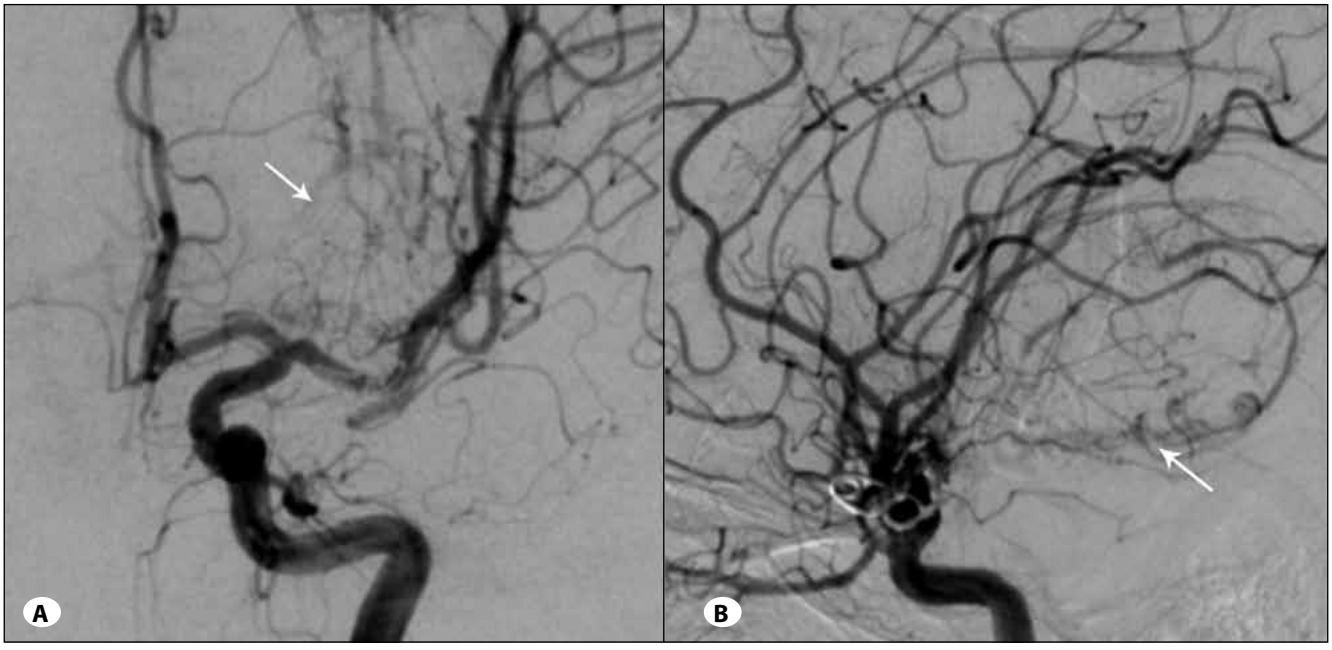

Figure 3A,B: Anteroposterior and lateral cerebral angiography exhibiting a large number of abnormal staining in the left basal ganglia area.

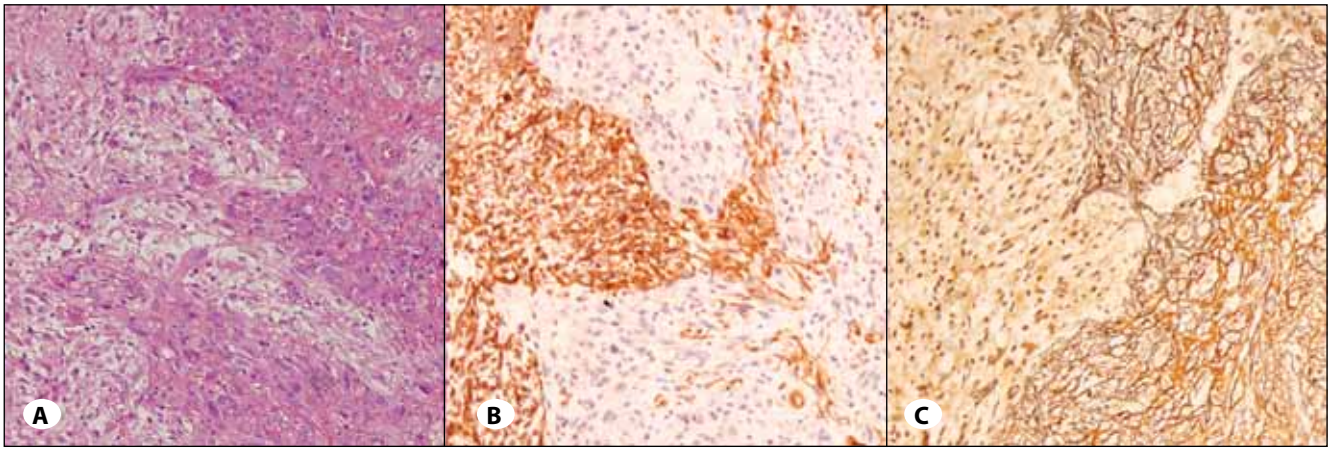

Figure 4: A) Histological section showing gliomatous elements intermingled with sarcomatous components. (H&E, ×100). **B)** immunohistochemical section showing glial fibrillary acidic protein (GFAP) positive expression within gliomatous portions. (GFAP, ×100). **C)** Gomori`s silver stain section showing rich reticulin fibers in the sarcomatous area. (Gomori's Stain, ×100).

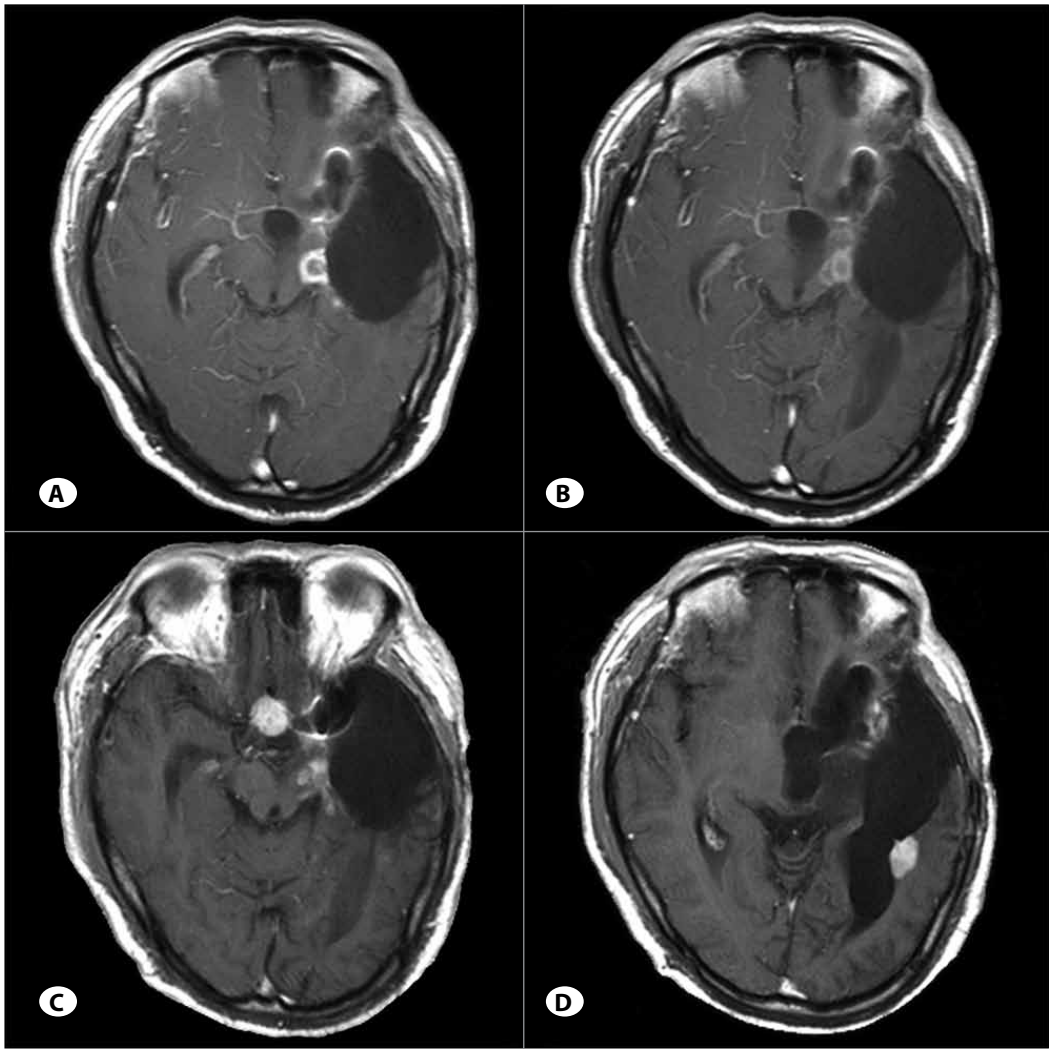

Figure 5: A) March 2009. Axial T1-weighted gadolinium-enhanced image showing the tumor recurrence in the left medial temporal lobe adjacent to the left cerebral peduncle. **B)** May 2010. Axial T1-weighted gadolinium-enhanced image displaying the recurrent tumor disappearance; **C)** May 2011. Axial T1-weighted gadolinium-enhanced image exhibiting the tumor suprasellar cistern metastasis. **D)** May 2011. Axial T1-weighted gadolinium-enhanced image showing the tumor recurrence in the operation area.

demonstrated variations in cytological composition, cell density, and stroma (Figure 4A). Immunohistological staining demonstrated positive glial fibrillary acidic portein (GFAP) expression in the gliomatous portion but not in sarcomatous element (Figure 4B); and reticulin staining was positive for collagen in the sarcomatous component of the tumor (Figure 4C). These pathological features were consistent with gliosarcoma, WHO grade IV. There was no evidence of osseous, cartilaginous, muscular, or adipose differentiation in the sarcomatous area. Postoperative sequential conformal radiotherapy with a total dose of 57 Gy and temozolomide chemotherapy was employed. The patient tolerated the procedure well. In March 2009, the tumor recurred in the left medial temporal lobe (Figure 5A). Stereotactic radiotherapy and the second temozolomide chemotherapy were implemented resulting in evanescence of the recurred tumor (Figure 5B). Unfortunately, in May 2011, the 2-year follow up MRI exam revealed multifocal tumor recurrence and subarachnoid metastasis (Figure 5C,D). Stereotactic radiotherapy was performed again. The patient has been in close follow-up.

DISCUSSION

Gliosarcoma constitutes 1.8-2.4% of all glioblastomas. Histological diagnosis of gliosarcoma is based on the 2007 WHO criteria that include: 1) dual morphological features of gliomatous and sarcomatous components; 2) positive expression of glial markers in the glial part; and 3) negative expression for glial markers but positive for mesenchymal markers in the sarcomatous part of the tumor (11). The occurrence of glioma following aneurysmal clipping is a rarity and its etiology remains elusive. An extensive review of literature could garner only 8 cases of glioma that were diagnosed after aneurysm clipping surgery (Table I) (1-3,10,19). The predisposing genetic alterations inducing tumorigenesis, and the environmental factors might play a crucial role. We elaborated four factors that can be hypothesized as the possible causes for this peculiar occurrence – traumatic glioma, coexistence of two pathologies, increased concentration of metal ion, and radiation.

Brain trauma has been speculated as the causative factor for malignant glioma and a weak correlation between head injuries and the development of gliomas has been demonstrated (7,8). Since the initial criteria for considering trauma as the etiology for brain tumor has been described, various modifications are reported (13,23) and based on contemporary medical technology, these criteria can be defined as follows:

1. No signs of intracranial lesions including epilepsy, abnormal electroencephalogram, mass lesion on CT/MRI, should be present before brain injury.
2. The brain injury should be evidenced on imaging or histology.
3. The location of tumor should correspond to the site of trauma on CT/MRI exam or intraoperatively and the tumor should be in direct continuity with the traumatic scar and not merely in its vicinity.
4. The tumor should be verified by pathological examination, magnetic resonance spectroscopy (MRS) and/or positron emission tomography (PET).
5. The latent period between the injury and the tumor formation must be long enough (minimum 1 year) to ascertain the possibility of their causal relationship.

A total of 4/8 reported cases including our case abide by these criteria for posttraumatic gliomas. In our case, MRI depicting the hypointense signal with heterogeneous margin in the left basal ganglia area can be speculated as the low-grade glioma that was present before the aneurysmal rupture. However, the tissue adjacent to aneurysm, where the gliosarcoma was diagnosed later, was pathologically verified as gliosis at the time of clipping with no evidence of tumor cells. Consequently, brain injury can be fared better as the cause of tumorigenesis in present case; even so, the possibility of the co-existence cannot be completely ruled out.

The reported cases that did not meet the criteria of posttraumatic glioma can divided into two following type:

Table I: Reported Cases of Glioma Diagnosed after Aneurysm Clipping Surgery

Report	NO.	Histology	Mother Artery	Tumor Location	interval year
Andrews et al (1985) [2]	1	Glioblastoma multiforme	L MCA	L temporal	6 M
Licata et al (1986) [10]	2	Malignant glioma	R ICA	Corpus callosum	16Y
		Malignant glioma	ACoA	L temporoparietal	3Y
Boop et al (1991) [3]	1	Desmoplastic cerebral astrocytoma	L MCA	R frontoparietal	4 M
Stendel et al (1997) [19]	1	Anaplastic oligodendroglioma	ACoA	R frontal	10Y
Abe et al (2006) [1]	2	Glioblastoma multiforme Anaplastic oligoastrocytoma	L ACA L PCoA	L frontal L frontal	10Y 14Y
Present case	1	Gliosarcoma	L ICA, MCA	L temporal	3Y

***AcoA=** anterior communicating artery, **ACA=** anterior cerebral artery, **PcoA=** posterior communicating artery, **ICA=** internal carotid artery, **MCA=** middle cerebral artery.*

I- Aneurysms located in the vicinity of the glioma, where the feeding artery was involved, and the latent period is shorter than 1 year. (1/8 cases, 12.5%). In this instance, aneurysm is more likely induced by glioma; the case reported by Andrews et al. (2) can be categorized in this type. The exact cause of aneurysm induced by gliomas is ill-defined, and the proposed mechanism includes altered hemodynamics (12), angiogenic remodification (15) and the disruption of vessel wall induced by tumor (2,22).

II- Aneurysms are remote from the tumor and the involved primary artery is not the feeding vessel of tumor. The brain tissue involved in tumorigenesis is not damaged by surgical clipping (3/8 cases, 37.5%). The cases reported by Licata et al (10) and Boop et al. (3) are example of this type. These instances show that either the occurrence of two pathologies is a mere coincidence or that the patient might have had yet absolved cytogenetic abnormality.

The hypothesis of the metal ions released from aneurysm clip contributing to the malignant transformation, is based on the fact that the prolonged exposure to metal ions can lead to cytotoxicity and genotoxicity (14). An elevated risk of carcinogenesis has been observed in post-arthroplasty osteoarthritis and rheumatoid arthritis patients, where beside the disease pathology, the implants employed in arthroplasty are considered contributive (20). The contemporary aneurysms clips are made of cobalt or titanium alloys. Although, titanium alloy (Ti-6Al-4V) is a desirable primary metallic biomaterial, the concentrations of titanium, aluminum and vanadium ions in various solutions mimicking the internal environment have been measured and elevated levels shown to damage the nucleus and DNA (6). As yet, there is no valid data of increased metal ions concentration in blood and cerebrospinal fluid (CSF) of patients after aneurysms clipping. However, it can be speculated that the presence of the blood-brain barrier, immersion of metal ions in CSF, wear of the metal due to pulsatile movement of brain and clipped artery might contribute to the increase ions concentration potentially.

Lastly, studies have demonstrated the linear dose response relationship between low-dose of ionizing radiation and cancer risk (17). A higher incidence of glioma in children treated for tinea capitis with low-dose therapeutic radiation is reported (18). Furthermore, the occurrence of gliosarcoma following radiation exposure has been documented in the literature (16,21). Brain dose from each CT scan exam range from 15 to 90 mGy (4). The effective radiation dose was measured as 14.0±8.1 mSv in a neurointerventional procedure (9). In the present case, before the diagnosis of gliosarcoma, patient received 3 CT scan and 3 cerebral angiography exams. The total radiation dose can be approximated to 102 mGy. The radiation employed in the diagnostic and treatment purpose for aneurysms might contribute to carcinogenesis.

CONCLUSION

This is the first report of gliosarcoma occurrence following the surgical clipping of the cerebral aneurysm. Cerebral trauma, co-existence of two pathologies, metal ions released from aneurysm clips, and radiation could be associated with this rare occurrence.

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