

Arteriovenous Malformation with Underlying Radiologically Silent Primary Brain Tumor: Case Report and Literature Review

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Abstract

Background: The coexistence of clearly demarcated glioma and vascular malformation is rarely identified. Astrocytomas represent the most common subtype found.

Methods: We conducted a systematic review of the literature published until December 2019, using the PubMed database, recording all histologically documented cases of AVM associated with primary brain tumor. We have reported for each case, study date, age, sex, intracranial site of the lesion, histopathological features, the neuroradiological techniques used for diagnosis, extension of surgical resection (biopsy, partial, total), adjuvant treatment (radiotherapy, chemotherapy, trans-arterial embolization) and overall survival.

Results: With our case, only 21 cases of angiographically detected arteriovenous malformation and histologically proven primary brain tumor, have been documented. The mean age was 42 years (range 8-72) with male prevalence (12 M, 9 F). Total tumor resection was obtained in 12 cases (57.1%), a partial resection in 4 cases (19.04%) whereas a biopsy was performed in 2 cases (9.5%); in 2 cases no information about the extent of resection was reported whereas in one case no tissue sampling was obtained because of the death of the patient. AVM was treated with XRT in 5 cases (23.8%), subtotal resection (STR) was performed in 2 cases (9.5%), trans-catheter embolization was performed in 2 cases (9.5%) and in 1 case no treatment was performed for the patient's death.

Conclusion: The association between primary brain tumors and arteriovenous malformation is a rare entity that presents various pathogenic hypotheses and diagnosis can be difficult. In all these cases, we recommend a detailed histological examination of the parenchyma adjacent to the AVM.

Keywords: Xanthoastrocytoma, Arteriovenous malformation, Angioglioma, Hemorrhage, Glioma.

Abbreviations:

- APXA = anaplastic pleomorphic xanthoastrocytoma
- AVM = arteriovenous malformation
- CT = computed tomography
- DWI =diffusion weighted imaging
- GTR =gross total resection
- MCA = middle cerebral artery
- MRI = magnetic resonance imaging
- PXA = pleomorphic xanthoastrocytoma

RT = radiotherapy
 STR = sub-total resection
 TOF = time of flight
 WHO = world health organization

Introduction:

The association between primary brain tumors and arteriovenous malformation (AVM) has been reported to reach 0.1% in the computed tomography (CT) scan era. Since the introduction of magnetic resonance imaging (MRI), the rate of association between these pathologies is supposed to significantly increase [1]. It includes gangliogliomas, meningiomas, hemangioblastomas, neurilemmomas, craniopharyngiomas and gliomas. The latter represent the most common tumors detected in association with AVM and among gliomas, astrocytomas represent the most common subtype found [2]. Neovascularization, the formation of blood vessels de novo, and angiogenesis, the process of new vessel formation from pre-existing vasculature, are critical steps for the development of both AVMs and glial tumors. Within the latter, it is reasonable to speculate that local angiogenic factors could potentially contribute to the development of a vascular malformation [3]. Nazek et al. stated that a proliferation of oligodendroglial cells, in the cerebral tissue involved by the AVMs and in the adjoining white matter, does not represent a sufficient criterion for diagnosis of brain glioma. For this reason, some studies could probably have overestimated this aspect also due to the absence of recurrence in cases of subtotal resection [4].

Despite the skepticism, to date the international literature regarding angiographically documented intracranial AVM associated with histologically confirmed brain gliomas, diagnosed as combined lesions, consists of twenty cases and their existence as distinct entities is controversial. We present a literature review on association between primary brain tumors and AVM, adding our experience of a 46-year-old man undergoing surgical treatment for left parietal vascular malformation with histopathology suggesting co-present Anaplastic Pleomorphic Xanthoastrocytoma (APXA).

Case report:

Clinical history and radiological findings:

A 46-year-old man was admitted to the Emergency Department of the Policlinico Umberto I ° - "Sapienza" University of Rome, due to seizures without significant pathologies or history of head trauma. On neurological examination he appeared sleepy, collaborating, with ideomotor slowdown. No focal neurological deficits were detected. CT scan showed a spontaneous intraparenchymal hemorrhage in the left parietal lobe (Fig.1). To investigate the cause of the hemorrhage, a brain MRI confirmed the presence of a voluminous left parietal hemorrhage associated; Time of Flight (TOF) sequences showed an abnormal arterial vessel originating from the left middle cerebral artery (MCA) and bearing towards the hematoma. Cerebral angiography showed a left parietal AVM, size 3.5 cm, supplied by left MCA and draining in the posterior third of the superior sagittal sinus, Grade 2 according to the Spetzler-Martin classification (Fig.1). Considering clinical and radiological status, the patient underwent surgical removal of the AVM.

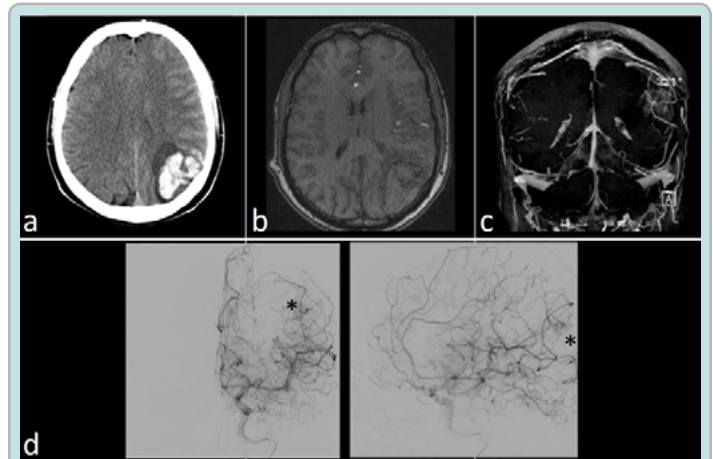


Figure 1: Preoperative radiological findings: a) CT scan showed the intraparenchymal hemorrhage in the left parietal lobe; b-c) MRI TOF and 3D angiographic reconstruction revealed the presence of an abnormal vascularization in the region of the hematoma; d) a cerebral angiography confirms the presence of the AVM (*).

Surgery:

In prone position, using craniometric landmarks, a left parietal craniotomy has been performed. Once the dura has been opened, it has been possible to appreciate the presence of a subacute intraparenchymal hematoma. A preliminary intraoperative fluoroangiography has been performed confirming the presence of the AVM. Corticectomy has been performed in the site of the hematoma. Under microscopic guidance a lesion having the characteristic of the AVM has been detected. Arterial feeders have been accurately coagulated and cut. The nidus has been dissected from the brain parenchyma and the venous drainage has been consecutively closed. After removal of the nidus, intraoperative fluor-angiography has been performed confirming the complete resection of the AVM. The hemorrhagic clot has been completely removed.

Postoperative course:

Postoperative angiography showed the disappearance of the pathological vascularization documented on preoperative investigations (Figure 2). Histopathological examination was suggestive for APXA (WHO grade III), with abnormal vascularization and BRAF V600E mutation (Figure 3). A brain MRI with gadolinium was performed for this histological finding but no pathological enhancement was detected. Adjuvant chemotherapy with Temozolomide (according to Stupp's schedule for 14 months) and radiotherapy were scheduled. Thirty-seven months later, for tumor recurrence, a new surgery was performed followed by adjuvant chemotherapy (according to Stupp's program for 7 months). Unfortunately, a new neoplastic regrowth was detected 44 months after the first surgery but with involvement of the corpus callosum. The patient died for disease progression in corpus callosum and basal ganglia, with an overall survival of 47 months from diagnosis.

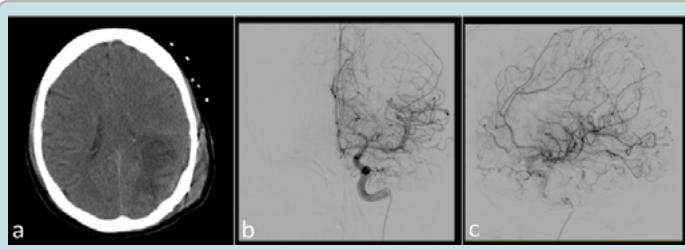


Figure 2: Postoperative CT scan (a) and angiography (b-c) showed the complete removal of the hematoma and the AVM.

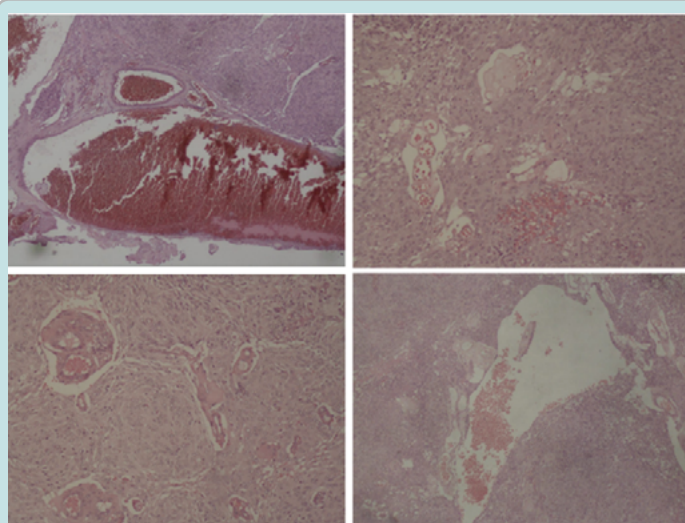


Figure 3: Microscopic examination documenting the presence of a hemorrhagic glial tumor with moderate cellularity. Cellular elements are characterized by big nucleoli and abundant eosinophilic cytoplasm and appears to be surrounded by fibrillar stroma. Some elements show pleomorphic nuclei with nuclear pseudocysts. Vascular mitosis, necrosis and proliferation are also present. All these aspects, coupled with the results of immunohistochemistry, suggested the diagnosis of anaplastic pleomorphic xanthoastrocytoma (grade III).

Materials and methods:

A systematic review of the literature has been performed using the scientific database PubMed by typing the following keywords: “xanthoastrocytoma and AVM”, “arteriovenous malformation and glioma”, “hemorrhagic brain tumor” and “angioglioma”. We only included articles written in English language. References of each article was analyzed to identify relevant manuscripts which were not identified through the initial research. We reported study date, age, sex, intracranial site of the lesion and histopathological features. In addition, the neuroradiological techniques used for diagnosis, extension of surgical resection (biopsy, partial, total), adjuvant treatment (radiotherapy, chemotherapy, trans-arterial embolization) and overall survival were also recorded.

Results:

The literature review through December 2019 revealed 20 publications for a total of 20 cases with a histological diagnosis of primary brain tumor in association with an AVM. Our case was added to those already described in the literature (Table 1). We also collected 8 publications for a total of 9 cases (including our case) of intracranial hemorrhage associated with histologically documented pleomorphic xanthoastrocytoma (PXA) (Table 2).

Table 1: Cases reported of PXA with intracranial hemorrhage.

Case No	Authors	Age	Sex	Tumor site	Hemorrhage	Diagnosis	Outcome
1	Levy 1996	46	F	Lt temporal	ICH & SAH	PXA	Dead
2	Yoshida 2005	61	F	Lt temporal	ITH	PXA	Survived
3	Asano 2006	59	F	Lt temporal	ICH	APXA	Dead
4	Lee 2007	64	M	Lt frontal	ICH	PXA	Survived
5	Wind 2009	5	F	Lt temporal	ITH	PXA	Survived
6	Yoshikawa 2010	60	F	Lt temporal	ICH & SAH	PXA	Survived
7	Naganska 2013	36	F	Rt occipital	ICH	PXA	Survived
8	Takamine 2019	11	F	Rt temporal	ICH	PXA	Survived
9	Santoro 2021	46	M	Lt parietal	ICH	APXA	Dead

ICH: Intra-cerebral Hemorrhage, ITH: Intra-tumoral Haemorrhage, Lt: left, Rt: right, SAH: Subarachnoid Hemorrhage.

Table 2: Cases reported of radiological detected AVM and histologically proven primary brain tumor.

Case No	Authors	Age	Sex	AVM/Tumor site	Neuroimaging	Treatment	Tumor histology	Outcome/ Follow-up
1	Fine 1960	15	M	Parietal/ Ventricular	ventriculogram, angiogram	TR, RT	Oligodendroglioma	NR
2	Welcker 1966	25	F	Parietal	angiogram	NR	Astrocytoma	NR
3	Heffner 1971	17	M	Subfrontal/ Meningeal	CT, angiogram	PR (tumor), TR & RT (AVM)	Low grade astrocytoma	improved
4	Crowell 1975	17	M	Temporal	CT, ventriculogram, angiogram (no shunting)	PR	Oligodendroglioma	NR
5	Zuccarello 1979	50	M	Temporal	angiogram	NR	Astrocytoma	NR
6	Ho 1981	63	F	Thalamus/ Cingulate	NR, diagnosed at autopsy	NR	Astrocytoma	NR
7	Licata 1986	60	F	Occipital/ Temporal	CT, angiogram	PR (tumor), AVM not treated	GBM	Died, months 14
8	Martinez-Lage 1986	43	M	Parietal/ Ventricular	CT, angiogram	TR, RT	Oligodendroglioma	improved
9	Goodkin 1990	9	F	Parietotemporal	CT, angiogram	TR	Anaplastic astrocytoma	NR
10	Malcolm 1991	41	M	Frontal	CT, angiogram	TR, RT	Astrocytoma	Improved months 6
11	Lee 1996	45	M	Temporo-occipital	CT, angiogram	TR	PXA	NR
12	Harris 2000	57	M	Temporo-occipital	MRI, angiogram	B, RT	Anaplastic astrocytoma	Died months 4
13	Ziyal et al., 2004	58	M	Temporo-parietal	MRI, postop angiogram	TR (tumor), PR (AVM)	high-grade glioma	Improved
14	McKinley 2008	55	F	Parietal	MRI, angiogram	TR (tumor), TAE (AVM)	Anaplastic oligodendroglioma	Died day 6
15	Pallud 2009	35	M	Frontal tumor, Rolandic AVM	MRI	TR (tumor)	APXA	Alive months 18
16	Aucourt 2012	65	M	Frontal	MRI, angiogram	TR (tumor)	GBM	NR
17	Soltanolkotabi 2012	8	F	Thalamic	MRI, angiogram	TR (tumor), TAE (AVM)	Pylocytic astrocytoma	Alive
18	Gmeiner 2013	72	F	Temporal	MRI	TR, RT & ChT	GBM	Died months 12
19	Naganska 2013	36	F	Occipital	MRI	TR	PXA	Alive
20	Lohkamp 2016	71	F	Thalamic	MRI, angiogram	B	GBM	Died months 6
21	Santoro 2021	46	M	Parietal	MRI, angiogram	TR, RT & ChT	APXA	Died months 47

APXA: Anaplastic Pleomorphic Xanthoastrocytoma, B: Biopsy, ChT: Chemo-Therapy, CT: Computer Tomography, GBM: Glio-Blastoma Multiforme, MRI: Magnetic Resonance Imaging, NR: Not Reported, PR: Partial Resection, PXA: Pleomorphic Xanthoastrocytoma, RT: Radiation Therapy, TAE: Trans-Arterial Embolization, TR: Total Resection.

Among the cases of intracranial AVM associated with primary brain tumor, the mean age was 42 ± 29 years (range 8-72) with male prevalence (12 M, 9 F). Lesions were in parietal lobe in 5 cases (23.8%), in 4 cases (19.04%) in the frontal lobe, in 3 cases (14.2%) in the temporal lobe, in 1 case (4.7%) in the occipital lobe, in 3 cases (14.2%) at the thalamic level, in 3 cases (14.2%) the extension was temporo-occipital and in 2 cases (9.5%) temporo-parietal.

In 7 cases (33.3%) a CT scan was associated with preoperative cerebral angiography, in 6 cases (28.5%) the angiogram was preceded by an MRI, in 4 cases (19.04%) surgical treatment was performed only after a brain MRI and in 3 cases (14.2%) only by intracranial angiography. In only one case (4.7%) in the pre-CT era a ventriculography was performed while in one case no images were acquired due to the patient's death.

Gross total tumor resection (GTR) was obtained in 12 cases (57,1%), a partial resection in 4 cases (19,04%) whereas a biopsy was performed in 2 cases (9,5%); in 2 cases no information about the extent of resection was reported whereas in one 1 case no tissue sampling was obtained for the patient's death.

AVM was treated with radiotherapy (RT) in 5 cases (23.8%), subtotal resection (STR) was performed in 2 cases (9.5%), trans-arterial embolization was performed in 2 cases (9, 5%), in 1 case no treatment was performed for the patient's death and in 9 cases the data was not reported.

Primary brain tumor was Glioblastoma Multiforme in 5 cases (23.8%), astrocytoma in 8 cases (38%) including in 2 cases (9.5%) anaplastic astrocytoma and in 1 case (4.7%) pilocytic astrocytoma; in 4 cases (19.04%) the histopathological examination was indicative of oligodendroglioma including 1 case of anaplastic oligodendroglioma. One PXA was found in 4 cases (19.04%) including 2 cases of anaplastic type. Among the 18 cases (85,7%) surgically treated for brain tumor, adjuvant treatment was used in 2 cases (11%) combining chemo and radiotherapy. Follow-up was reported in 8 cases with a mean survival of 13.4 months.

Among the 9 cases of cerebral haemorrhage associated to PXA, mean age was (range 5-64), with female prevalence (2 M, 7 F). In 6 cases (66%) tumor and haemorrhage were in the temporal lobe, in 1 case (11%) in frontal lobe, in 1 case in the occipital lobe and in 1 case in the parietal lobe. Histology was PXA in 7 cases (77%) and APXA in 2 cases (22%). In 2 cases (22%) subarachnoid haemorrhage was associated with intraparenchymal one. In 3 cases (33%) patients died for the haemorrhagic event.

Discussion:

PXA (WHO grade II) is an astrocytic tumor that grossly appears as a superficial solid and cystic mass with involvement of the leptomeninges, moderate cellularity, predominantly pleomorphic with foci of lymphoplasmacytic infiltration without any necrosis and rare mitoses [5,6,7]. Pleomorphic Xanthoastrocytoma (PXA), term firstly coined by Kepes et al in 1979, is a rare, circumscribed glioma composing <1% of all astrocytic tumors. It is mostly diagnosed in the second decade of life with mean age at diagnosis is 29 ± 6 years with no gender predilection [5,6,7]. Initial presenting symptoms include seizures, headaches, nausea, vomiting, diplopia and somnolence [8]. According to the World Health Organization (WHO) classification, since 2016, two different entities have been pointed out, based on histopathologic features: grade II PXA and grade III anaplastic PXA. In 1983 Weldon-Linne described the first case of recurrent PXA with malignant transformation (WHO grade III) [9]. Anaplastic Pleomorphic Xanthoastrocytoma composes 15-50% of all PXA; it has magnetic MRI features like those of other high-grade astrocytomas, namely more heterogeneous contrast enhancement, peritumoral edema, lower rADCmin ratio on DWI, and higher rCBVmax ratio on DSC-PWI [10]. The enhancement pattern of APXA could be explained by the necrosis, hemorrhage, and vascular proliferation within the tumor, which was observed by Rutkowski [11]. On histological examination it is defined by the presence of necrosis associated with high mitotic activity, usually > 5 mitosis / 10 high-power fields and increased cellularity [12]. Like our case, one of the main molecular characteristics is BRAF V600 gene mutation that have the highest oncogenic potential [13,14]. This mutation divides PXAs into two clinically relevant subgroups for natural history and response to therapy: BRAF-mutated PXA shows superior survival compared to wild type BRAF and exhibits responses to BRAF-targeted therapies [15,16]. Total resection should be the surgeon's goal, correlating with 10-year overall survival of 82% for PXA [17]. Otherwise, APXA has a 5-year OS rate of 57% [11]. A meta-analysis of 167 patients with grade II PXA does not demonstrate an association between adjuvant

therapy with better oncological outcomes while radiotherapy is useful for residual or recurrent tumor [18]. Generally traditional chemotherapy has been considered minimally effective or ineffective for the treatment of PXA [19], while in progressive disease or APXA, when surgery or radiotherapy is not always a viable option, systemic treatments are often employed [8].

The incidence of hemorrhage in gliomas is approximately 1.4-2.6% and its frequency increases with the WHO classification [1]. It is more common in high-grade gliomas such as glioblastomas and anaplastic astrocytomas, which show microvascular proliferation and necrosis. Reticular type capillaries are sometimes seen in lower grade gliomas and have been found associated with hemorrhage [20,21].

Intracranial hemorrhage associated with PXA is rare and to date nine cases have been reported in the literature, including our experience (Table 2). The lesions, consisting of mixed tumors of glial and vascular origin, particularly cavernous or arteriovenous type, have often been referred to as angiogliomas. The term "angioglioma" was coined by Councima et al. to describe a cerebellar vascular neoplasm with characteristics of what is now recognized as the cellular variant of hemangioblastoma and therefore appears to be valid for rare cases of low-grade glioma with a distinct vascular pathology. Angiogliomas should not be confused with high-grade neoplastic gliomas, which due to significant neovascularization, can be misdiagnosed with AVM [2].

Pathogenetic suggestions consider these angiogliomatous lesions as a reactive astroglial neoplastic proliferation secondary to a pre-existing vascular malformation and/or haemorrhages [1,22]. Four cases have been described in the literature, showing the initial appearance of the AVM and the subsequent finding of the tumor within it; histological examination showed hemosiderin-laden macrophages and reactive gliosis: it could represent the transition between the vascular precursor and glioma. The possibility that an anaplastic glioma could induce de-novo vascular malformation or that a bleeding vascular malformation could induce secondary neoplastic changes in perivascular glial tissue is still under discussion [1,23,24]. More studies are needed to provide an adequate answer.

The coexistence of clearly demarcated glioma and vascular malformation is rarely identified. With our case, only 21 cases of angiographically detected AVM and histologically proven primary brain tumor, have been documented (Table 1). AVM might be associated with different glial components including low- and high-grade astrocytoma, oligodendroglioma, mixed oligo-astrocytoma or glioblastoma. We have reported the case of a lesion with two separate components of APXA and AVM, which form a common tumor mass. Although the angiographic and intraoperative appearance of the lesion had the characteristics of an AVM, the definitive histopathological diagnosis revealed an APXA. Only three previous cases of this association have been reported: two cases with WHO grade III and one case WHO grade II (Table 1).

Conclusion:

The association between primary brain tumors and arteriovenous malformation is a rare entity that presents various pathogenetic hypotheses and diagnosis can be difficult. This possibility could be overestimated as reported in the literature.

However, in cases of AVM, we believe that a detailed histological examination of the adjacent brain parenchyma and adequate clinical and radiological follow-up are necessary to avoid misdiagnosis, in the possibility of coexistence of a PXA / APXA or other forms of underlying primary brain tumor.

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