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Acquired cerebral arteriovenous malformation induced by an anaplastic astrocytoma: An interesting case

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High grade gliomas foster an environment rich in angiogenic factors that promote neovascularity. We report a case of a cerebral arteriovenous malformation, which developed in the setting of a high grade astrocytoma. The patient presented with complaints of confusion and left hemiparesis. An initial cerebral angiogram was normal. Repeat angiography six weeks later demonstrated an extremely vascular lesion with arteriovenous shunting involving the right thalamus and occipital lobe. Histopathologic evaluation of open biopsy and autopsy specimens demonstrated a high grade astrocytoma in association with an arteriovenous malformation. Immunohistochemical staining with VEGF was diffusely positive. A possible role for the hyperangiogenic environment of a high grade astrocytoma resulting in the development of an arteriovenous malformation is discussed. [Neurol Res 2000; 22: 473–477]

Keyword: Angiogenesis; astrocytoma; AVM; glioma; tumor

INTRODUCTION

The rare association between high grade astrocytomas and cerebral arteriovenous malformations (AVM) has been previously reported^{1–3}. These reports describe either the development of a glioma in the setting of a known AVM or simultaneous recognition of the two lesions. Although a hyperangiogenic environment has been identified as a key component in the genesis of both intracranial lesions, a solid understanding of the co-development of these lesions is lacking. We report a patient in whom a *de novo* AVM developed in association with or subsequent to a high grade glioma, a previously unreported occurrence. The histopathology in this case also highlights the potential role of a hypervascular environment in the initiation and development of an AVM.

CASE REPORT

A 57-year-old man presented with a two-month history of headaches, mild confusion, left sided weakness and numbness. Computed tomography (CT) of the brain was negative. Carotid Doppler demonstrated complete occlusion of the left and 60% stenosis of the right internal carotid artery. These findings were confirmed by carotid angiogram, at which time a cerebral angiogram was normal (*Figure 1A,B*). The patient subsequently underwent right carotid endarterectomy as treatment for his right carotid stenosis. Despite surgery, his symptoms progressed and he developed intermittent nausea, vomiting and a 9 kg weight loss. Repeat head CT three

weeks after endarterectomy demonstrated low density in the right thalamus. A contrast MRI revealed a 5.0×6.0×4.5 cm heterogeneously enhancing hypervascular mass in the right thalamus, midbrain and medial occipital lobe, and the patient was referred for diagnosis and management. Repeat cerebral angiography two months after the initial study revealed an extremely vascular lesion with arteriovenous shunting, located within the right thalamus, medial temporal and occipital lobes (*Figure 1C,D*). A contrast MRI was repeated (*Figure 2*) and confirmed the presence of an enhancing hypervascular mass as earlier described. The lesion was approached intrahemispherically using an occipital craniotomy. Gross inspection revealed what appeared to be an AVM, which was judged to be unresectable. A small amount of gliotic-like brain immediately adjacent to this vascular lesion was biopsied, and the histopathologic findings were consistent with a malignant astrocytic neoplasm. Following an unremarkable post-operative course, the patient began radiation therapy. However his condition deteriorated and he died four months after surgery. An autopsy of the brain was performed.

PATHOLOGY

Histopathologic review of the biopsy and autopsied brain revealed a highly malignant astrocytic neoplasm localized in the right inferior temporal/occipital lobes extending into the brain stem and cerebellum with extensive leptomeningeal spread (*Figure 3A*). This fibrillary tumor was composed of enlarged, oblong cells with pleomorphic, hyperchromatic nuclei (*Figure 3B*). Occasional mitotic figures were observed. The tumor was intimately enmeshed with large arterial and venous

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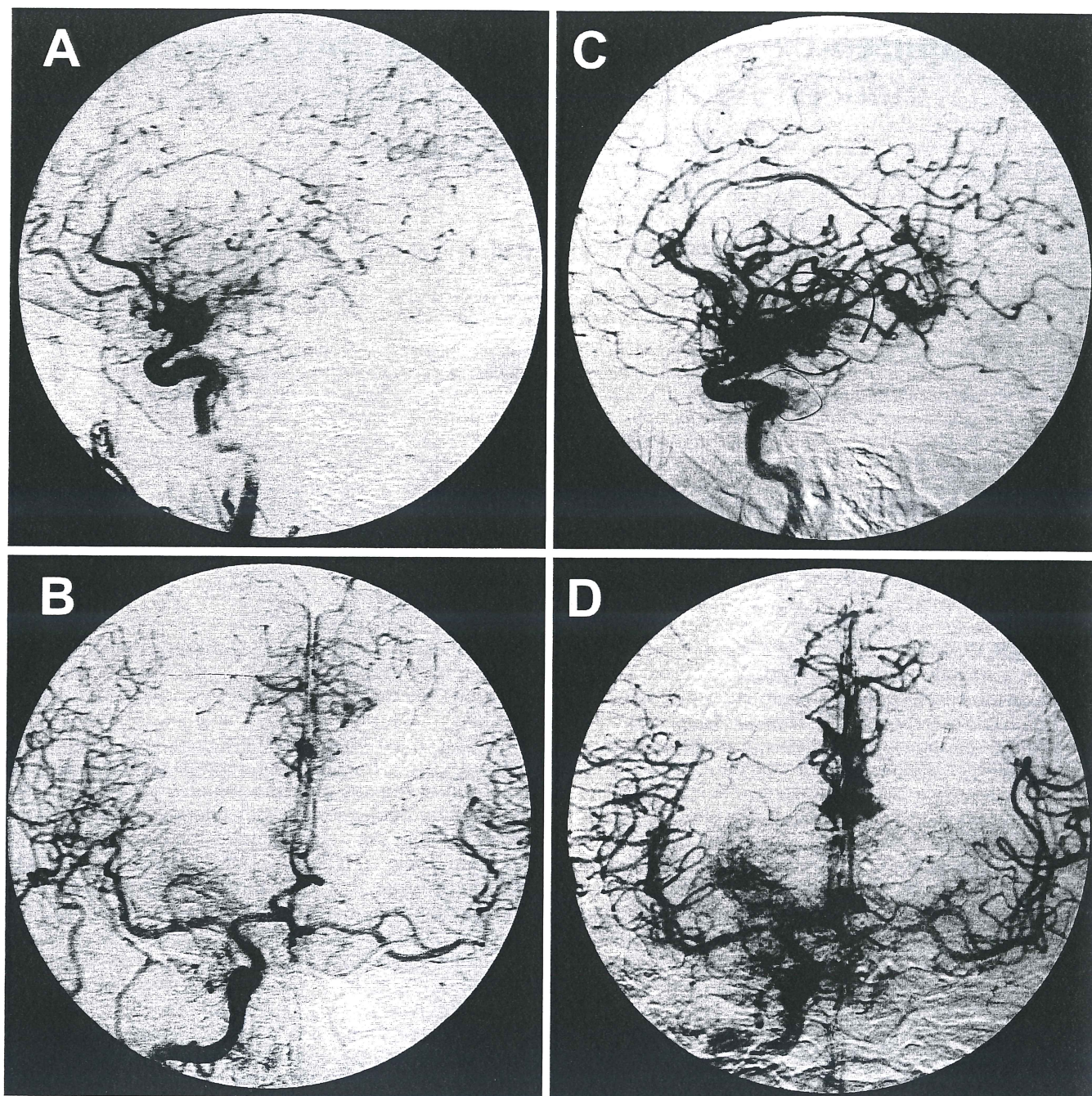


Figure 1: A,B: Initial right carotid angiogram showing A: lateral and B: anterior-posterior views. C,D: Right carotid angiogram six weeks subsequent to the first, showing an arteriovenous malformation in C: lateral and D: anterior-posterior views

channels. Elastic van Gieson (EVG) staining highlighted the internal elastica of the arterial component, which was incomplete and reduplicated in many places (Figure 3C). Such features are characteristic of arteriovenous malformations⁴.

Immunohistochemical studies demonstrate tumor cells with positive GFAP (glial fibrillary acid protein, DAKO) (not shown) and VEGF immunoreactivity (vascular endothelial growth factor, Santa Cruz Biochemical, Santa Cruz, CA, USA) (Figure 3D). The VEGF

immunoreactivity was cytoplasmic and observed with greatest intensity in tumor cells surrounding vessels.

DISCUSSION

An association between AVM and glioma has been previously described¹⁻³. However, in all these reports the arteriovenous malformation either preceded the development of the glioma or the two lesions were first identified simultaneously. What makes this case so

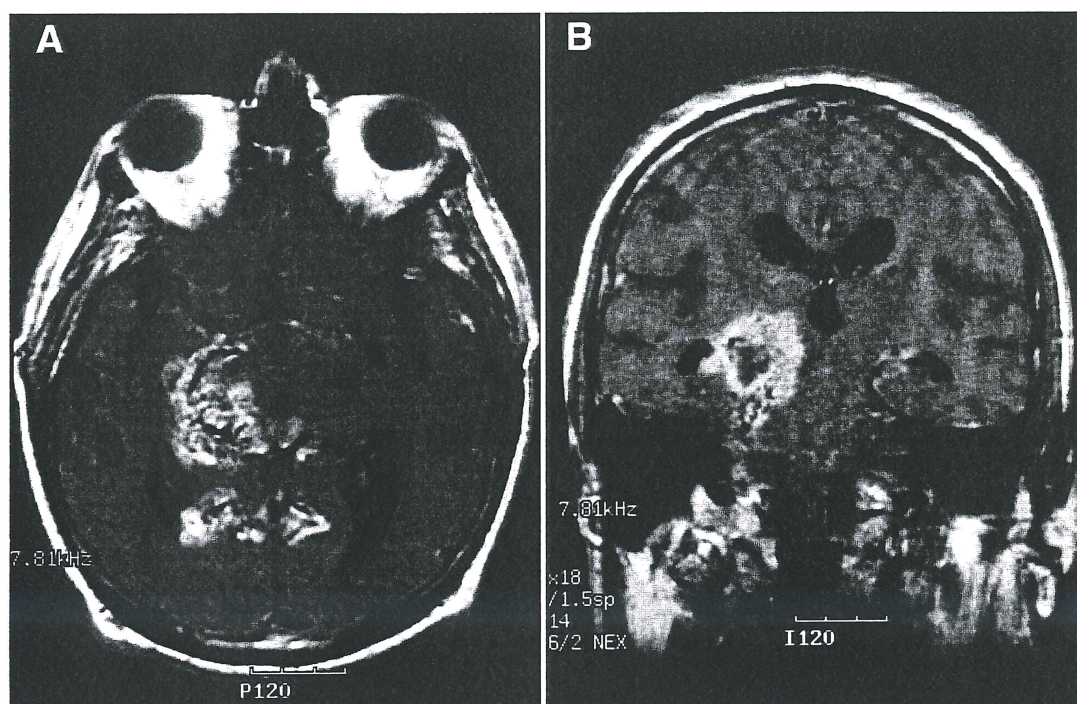


Figure 2: MRI of the brain, axial and coronal post-contrast images

unique is the *de novo* angiographic appearance of an AVM, a previously unreported observation. Goodkin *et al.*⁵, in their review of the literature, explored the question of whether these lesions were coexistent or sequential. Of 14 cases, none described an AVM developing after the identification of a glioma. In contrast, acquired AVMs have been reported in non-neoplastic settings. Examples include the development of an AVM following a cerebral infarct⁶ or at the site of a previously resected lesion with a normal post-operative angiogram⁷. In such cases the theories regarding the etiology of an acquired AVM focus on an environment of enhanced angiogenesis^{6,7}.

Gliomas are currently believed to arise as a result of multiple unique combinations of genetic aberration, including the loss of tumor suppressor genes and amplification of angiogenic factors⁸⁻¹². Meanwhile, cerebral AVMs are thought to arise from congenital failure of capillary development during gestation, resulting in a direct communication between arteries and veins¹³. 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.

The process of angiogenesis and the role of angiogenic factors in the pathogenesis of central nervous system vascular malformations and malignancies have been a focus of several studies in recent years. Causative

factors identified to date include basic fibroblast growth factor (bFGF), angiogenin, tumor necrosis factor α , vascular endothelial growth factor (VEGF) and a number of structural and matrix vascular wall proteins^{8-10,12,14}.

VEGF, also known as vascular permeability factor (VPF), is a cytokine with numerous functions including induction of angiogenesis and microvascular hyperpermeability¹⁵. Multiple studies have established an association between angiogenesis and microvascular permeability to upregulated levels of VEGF in various tissues and settings, including several human tumors. VEGF appears to be a major factor in the neovascularization and growth of high grade gliomas^{8,12,15-18}. In particular, tissue hypoxia results in the upregulation of VEGF mRNA and protein levels¹⁶, and according to Shweiki *et al.*¹⁶ may be the mechanism for triggering angiogenesis in high grade gliomas.

Because VEGF is specific for vascular endothelium and is shown to be an endothelial cell mitogen both *in vitro* and *in vivo*¹⁵, it is thought to play a pivotal role in the initiation of angiogenesis and AVM growth⁷. In the previously reported cases of acquired cerebral AVM, a hyperangiogenic environment characterized the pathology^{6,7}. Sonstein *et al.*⁷ identified increased focal cellular VEGF staining within a population of recurrent AVMs, patients theorized to be undergoing active angiogenesis. Their conclusion was that VEGF, in concert with other processes, played an integral role in AVM development.

Although the specific stimuli for angiogenesis are as yet unidentified, it is clear that VEGF plays a key and necessary role. Numerous studies have concluded that VEGF is common to both high grade astrocytomas

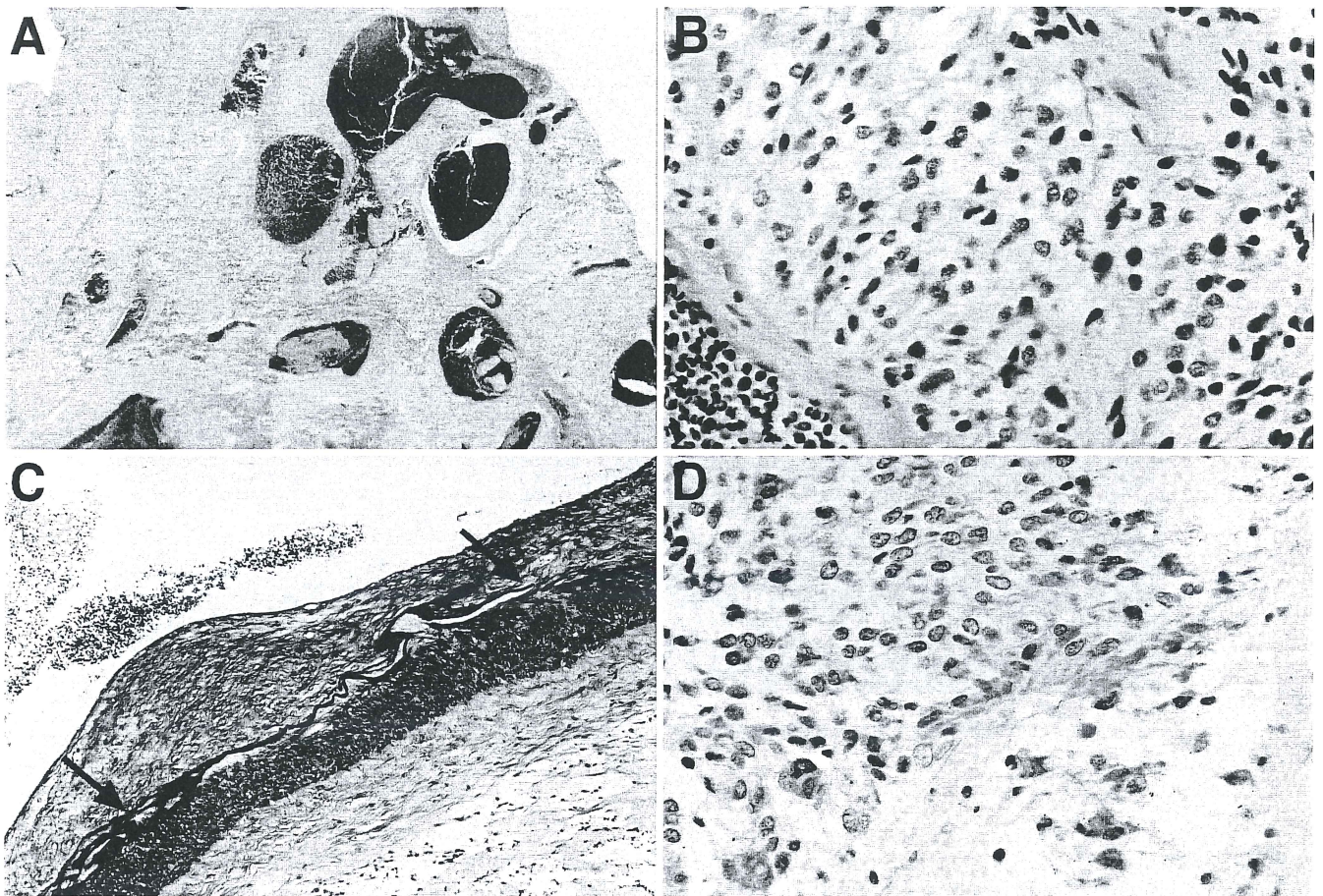


Figure 3: Arteriovenous malformation (AVM) associated with anaplastic astrocytoma. **A:** Enlarged and dilated arterial and venous channels course through leptomeninges filled with neoplastic cells (original magnification $\times 100$). **B:** Anaplastic astrocytoma cells (H&E, original magnification $\times 400$). **C:** Representative wall of the AVM showing reduplication and discontinuity of internal elastica (arrows) (Elastic van Gieson stain, original magnification $\times 200$). **D:** Immunohistochemical staining for VEGF showing abundant cytoplasmic staining of tumor cells (original magnification $\times 400$)

(initiating and supporting their hypervascularity and increased permeability) and to AVMs (initiating and maintaining growth). Because VEGF has been implicated in the induction and/or proliferation of both AVM and malignant glioma, we elected to perform immunohistochemical stains in the case being presented. The intense staining for VEGF, which was detected in this case, provides further support for the notion that this cytokine may play an important role in triggering the *de novo* generation of AVM. Further neuropathologic evaluation of the tissue failed to demonstrate arterialized vessel components along with alteration in the elastica, as is commonly seen in high grade gliomas. This further supports this case as a true arterialized vascular malformation.

CONCLUSION

In this reported case we describe a *de novo* AVM developing subsequent to an astrocytoma. We hypothesize that the enhanced angiogenic environment fostered by the tumor, as measured by the upregulation of VEGF,

may be a critical stimulus for the development of an AVM.

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