Surgical Neurology International

SNI: Unique Case Observations, a supplement to Surgical Neurology International

OPEN ACCESS

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Editor: James I. Ausman, MD, PhD University of California, Los Angeles, CA, USA

Arteriovenous malformation within an isocitrate dehydrogenase 1 mutated anaplastic oligodendroglioma

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Received: 02 January 15 Accepted: 23 April 15 Published: 25 June 15

This article may be cited as:
Lai G, Muller KA, Carter BS, Chen CC. Arteriovenous malformation within an isocitrate dehydrogenase 1 mutated anaplastic oligodendroglioma. Surg Neurol Int 2015;6:S295-9.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2015/6/10/295/159373

Abstract

Background: The co-occurrence of intracranial arteriovenous malformations (AVMs) and cerebral neoplasms is exceedingly rare but may harbor implications pertaining to the molecular medicine of brain cancer pathogenesis.

Case Description: Here, we present a case of *de novo* AVM within an isocitrate dehydrogenase 1 mutated anaplastic oligodendroglioma (WHO Grade III) and review the potential contribution of this mutation to aberrant angiogenesis as an interesting case study in molecular medicine.

Conclusion: The co-occurrence of an IDH1 mutated neoplasm and AVM supports the hypothesis that IDH1 mutations may contribute to aberrant angiogenesis and vascular malformation.

Key Words: Arteriovenous malformation, isocitrate dehydrogenase 1, oligodendroglioma

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/2152-7806.159373
Quick Response Code:

INTRODUCTION

The co-occurrence of cerebral neoplasms and arteriovenous malformations (AVMs) is a rare but documented phenomenon.[1,4,7,8,10,12,13,15-17,19,22,32,33] While co-occurrence of bona fide AVM and oligodendroglioma is extremely rare, histologically aberrant vasculature mimicking AVM can be found in approximately 5% of oligodendrogliomas.[14] Abnormal oligodendroglial proliferation has also been noted in white matter adjoining AVMs.[14,18] These results in the context of increased hemorrhage risk for patients afflicted with oligodendrogliomas[25] suggest pathophysiologic interactions between oligodendroglioma and cerebral vascular biology. Whether the inciting event for the co-occurrence involves vascular formation or tumorigenesis remains an open question. The absence of increased oligodendroglioma risk in a large AVM series[14] suggests AVM formation is unlikely the inciting event. In contrast, increased prevalence of hypervascularity mimicking AVM in oligodendroglioma patients supports the notion that the tumor microenvironment facilitates the pathogenesis of vascular malformation.[10]

In this context, we present a case of *de novo* AVM within an isocitrate dehydrogenase 1 (IDH1) mutated anaplastic oligodendroglioma (WHO Grade III). IDH1 encodes for a metabolic enzyme that catalyze the conversion of isocitrate to α-ketoglutarate, the first step of the citric acid cycle.[28] Nearly all IDH mutations in oligodendrogliomas involve substitution of R132 of IDH1.[28,29] This mutation results in the loss of native enzymatic activity in the production of α-ketoglutarate and confers novel activity in the production of 2 hydroxyglutarate (2HG).[24,5]

Accumulation of 2HG ultimately triggers changes in the epigenetic landscape of the tumor and consequent tumor physiology. Our results indicate that the IDH1 mutation may be associated with a tumor microenvironment that facilitates AVM. Strategies for surgical management of such co-occurrence, as well as implications pertaining to molecular medicine, are reviewed.

CASE REPORT

History and examination

The patient is a 44-year-old woman who presented with a sub-acute neurocognitive decline over a several months period, such that she was no longer able to perform routine tasks required for daily activities. Past medical history is notable for Graves disease (diagnosed 2005, treated with methimazole) and endometrial adenocarcinoma s/p total abdominal hysterectomy-bilateral salpingo-oophorectomy and chemotherapy (carboplatin and paclitaxel) in 2009, in remission since. Neurological examination was notable for difficulties recalling the events prior to the presentation and disorganized speech. However, the patient re-oriented easily. Physical examination revealed bilateral and symmetric proptosis. Laboratory values were unremarkable. Computed tomography scan of the brain showed 6.1 cm × 4.8 cm × 4.9 cm mass centered over the anterior falx cerebri with moderate surrounding hypodensity and effacement of adjacent sulci [Figure 1a]. Patchy hyper-density was seen within the mass, with Hounsfield units >200 suggestive of calcification. Magnetic resonance imaging (MRI) demonstrated an irregularly shaped, intra-axial mass with heterogeneous contrast enhancement that abut the anterior communicating artery (ACA) [Figure 1b]. Fluid attenuation inversion recovery imaging revealed complex patterns of hypointense tubular outlines within the lesion, suggestive of considerable vascularity within the lesion [Figure 1c]. MR angiogram showed multiple vascular pedicles emerging from both ACA branches penetrating the lesion as well as prominent venous drainages into the anterior and posterior superior sagittal sinus. Diagnostic cerebral angiogram confirmed extensive blood supply from the bilateral ACAs as well as the left middle cerebral artery (MCA) [Figure 2a] with a 2.4 cm × 1.4 cm × 2.3 cm AVM nidus and prominent venous drainages into the superior sagittal sinus [Figure 2b].

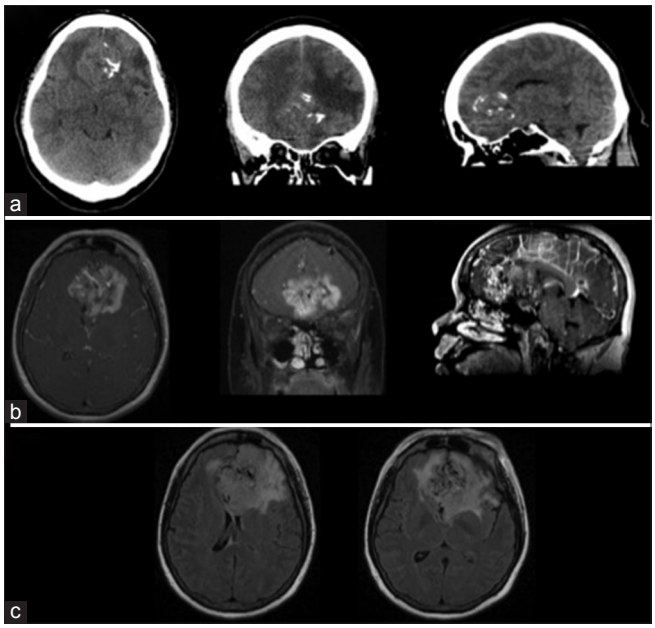

Figure 1: Pretreatment imaging: Computed tomography (a) T1 magnetic resonance postcontrast (b) and fluid attenuation inversion recovery (c) showing 6 cm × 5 cm × 5 cm bilateral frontal lobe mass with internal coarse calcifications, marked enhancement, and surrounding vasogenic edema with multiple flow voids and large draining veins.There is abnormal tissue interspersed between vascular elements and large areas of cystic changes and necrosis

Surgery

Staged embolizations were performed prior to surgical resection. The first stage involved Onyx embolization of four major pedicles arising from the right anterior cerebral artery. 3 days later, Onyx embolization of three major pedicles arising from the left ACA and two pedicles arising from the left MCA were performed. 3 days after the second embolization, the patient underwent resection of the mass through a bi-frontal craniotomy with frontal sinus exenteration. Under microscopic magnification, the plane along the inferior margin of the lesion was developed along the skull base to devascularize the dural pedicles. Branches of the ACA were identified and followed to isolate A1 and A2 branches. Under stereotactic guidance, corticectomy was made in the

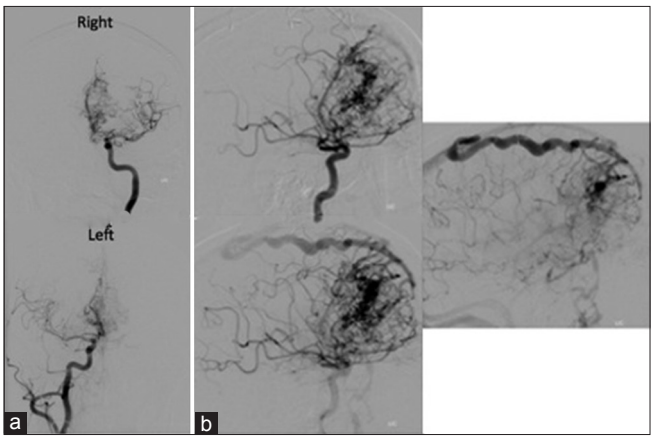

Figure 2: (a) Preembolization digital subtraction angiograms of the anterior circulation performed by injection of the left internal carotid artery and right internal carotid artery demonstrating vascular pedicles emerging from the right middle cerebral artery and right anterior communicating artery (ACA) (top), and pedicles emerging from the left ACA (bottom). (b) Mid to late phase angiogram demonstrate the arteriovenous malformation nidus and the venous outflow

right middle frontal gyrus to allow a trajectory to the superior margin of the tumor. The tumor was debulked until the distal ACAs were identified. These vessels were carefully followed until continuity to the proximal ACA was established. Tumor fragments were then carefully micro-dissected free from the ACA. Closure was performed using standard methods.

Pathological findings

An intraoperative frozen section was consistent with high-grade glioma. Subsequent hematoxylin and eosin-stained permanent sections revealed an intimate admixture of anaplastic oligodendroglioma (WHO Grade III) and AVM. The anaplastic oligodendroglioma exhibited archetypal histopathologic features including uniform cellularity with uniformly round nuclei set in perinuclear halos [Figure 3a]. Mitotic figures were numerous, with up to eight identified in one high power (×400) field, and there was multifocal microvascular proliferation. As is common in oligodendrogliomas, microcalcifications and multiple nodules of the tumor with heightened cellularity were seen [Figure 3b]. Immunohistochemistry against the most common IDH1 gene mutation (R132H) stained the tumor mass but not the AVM vessels. Fluorescence *in situ* hybridization for chromosomes 1p and 19q showed a deletion in 1p19q.

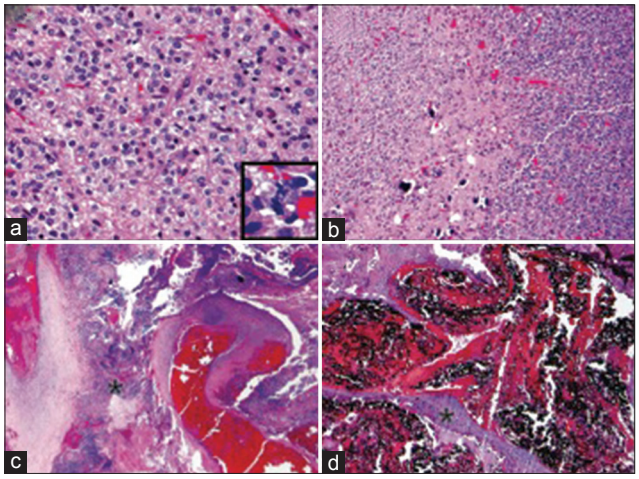

Figure 3: Photomicrographs of anaplastic oligodendroglioma and arteriovenous malformation (AVM) histology (a) anaplastic oligodendroglioma showing uniform cellularity, uniformly round nuclei, and perinuclear halos. This section shows classic delicate microvasculature, although microvascular proliferation was seen in other areas. Inset highlights an atypical mitotic figure of which many were identified (H and E; original magnification, ×200). (b) Secondary features of oligodendroglioma include scattered microcalcifications (center of the image) and clonal nodules of heightened cellularity (right side of image) (H and E original magnification, ×100). (c) Irregular large vessels of the AVM with intervening cellular oligodendroglioma (*) (H and E original magnification, ×20). (d) Irregularly contoured vessels of the AVM filled with black granular embolization material. An intimal cushion is identified in one of the fibrotic vessel walls (*) (H and E original magnification, ×50)

The AVM was set within a background of anaplastic oligodendroglioma and consisted of multiple irregularly contoured vascular lumens of varying diameters including both thick-walled muscular arteries and large thin-walled veins with variable amounts of intervening parenchyma including oligodendroglioma [Figure 3c]. Black granular embolic material filled some vessels. Irregular vessels showed intimal hyperplasia/cushions, a characteristic feature of AVMs [Figure 3d]. Due to the patient's history of endometrial adenocarcinoma and new diagnosis of a glioma, consideration was given to the possibility of Lynch syndrome resulting from a mutation in a mismatch repair gene. To test the immunohistochemistry was performed using antibodies against MLH1, MSH2, MSH6, and PMS2. However, all stains were positive in the tumor and hence there was no evidence of mutations in the common mismatch repair genes at the protein level.

Postoperative course

Postoperative MRI revealed a gross total resection of the lesion. The patient remained neurologically non-focal postoperatively. Due to cognitive dysfunction, the patient was discharged to rehabilitation. At the 1-month follow-up, the patient was oriented but had little recollection of the hospitalization. She subsequently underwent a 6-week course of radiation and temozolomide followed by a 1 year course of temozolomide. At the 2 years follow-up, she had her driver's license re-instated and resumed independent living. MRI at this time [Figure 4] showed no evidence of tumor recurrence.

DISCUSSION

Isocitrate dehydrogenase 1 mutation in an anaplastic oligodendroglioma/AVM is of significant interest. The current literature suggests that vascular malformation can be induced by focal expression of vascular endothelial growth factor (VEGF)[9,23,27] and reports have linked

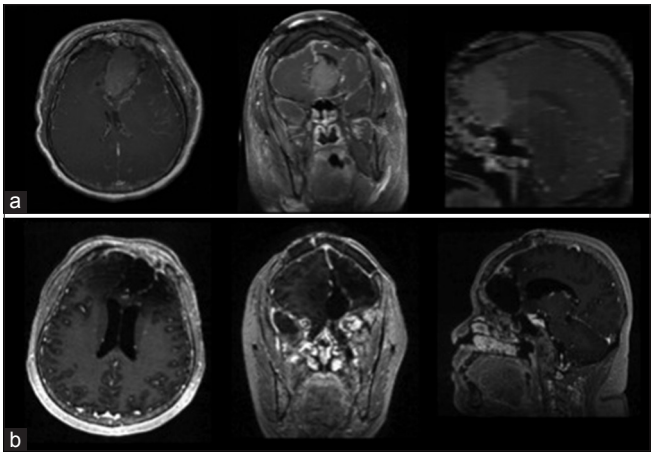

Figure 4: Immediate (a) 1 year (b) postoperative magnetic resonance imaging T1 postcontrast

VEGF expression to IDH1.[31] An early study showed that the decreased accumulation of α-ketoglutarate in IDH1 mutated cells results in increased accumulation of hypoxia-induced factor-1 (HIF-1),[31] a key transcription factor responsible for VEGF expression.[6,21] The study concluded that IDH1 mutated tumors were associated with enhanced angiogenic signaling. However, another study reported that the accumulation of 2HG in IDH1 mutated cells activated an enzyme that degrades HIF-1 and leads to decreased VEGF expression.[11] In the context of the current understanding of molecular AVM pathogenesis, the co-occurrence of an AVM and an IDH1 mutated anaplastic oligodendroglioma would support the hypothesis that IDH1 mutations can be associated with a tumor microenvironment that promotes aberrant angiogenesis.[3,30] However, a single case report is by no means conclusive and the rarity of such co-occurrence suggests that this role may be limited and modulated by other molecular events. A study of 25 IDH1 mutated tumor samples did not find increased HIF-1alpha expression in all IDH1 mutated tumor cells, but rather mostly in cells adjacent to areas of necrosis,[26] which argues for a more complex relationship between IDH1 and angiogenesis.

Surgical management of tumors harboring AVMs also warrants discussion. During surgical consideration, tumor vasculature should be deliberately and meticulously scrutinized. Any potential indication of aberrant structures should be further characterized by dedicated vascular studies. Although there are no guidelines for the management of these rare cases, preoperative endovascular embolization is recommended.[2,20] Intensive level care and monitoring should be provided postembolization, with plans for urgent surgical resection should the patient suffer a neurological decline. Surgical approach should be designed to maximally devascularize the tumor mass prior to debulking. The approach should be further designed to facilitate the visualization of the parental vessels giving rise to the tumor-specific vascular pedicles. While the finding of an AVM within a tumor mass is inherently intimidating from a surgical perspective, we believe that excellent results, as reported here, can be achieved with careful surgical planning and meticulous operative approach.

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