A low-grade cerebral arteriovenous malformation suspected of being a metastatic tumor: A case report and literature review

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ABSTRACT

Cases of low-grade cerebral arteriovenous malformations (cAVMs) showing dynamic changes and large areas of brain edema on short-term MRI follow-up have rarely been reported. This report describes an incidentally discovered and initially misdiagnosed cAVM in a patient with malignancies. The presence of abnormal signals surrounded by large areas of brain edema combined with tortuous or dilated vessels indicates the possibility of an AVM, especially in young people.

1. Introduction

Cerebral arteriovenous malformations (cAVMs) are uncommon dysmorphic vascular connections that usually present with intracranial hemorrhage, epilepsy, headaches, and focal neurological deficits. Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used non-invasive diagnostic tools. CT findings usually include punctate or linear isodensities, calcifications and/or low-density encephalomalacia. Diagnostically, MRI scans characteristically display black or low-signal areas (flow voids). Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) enable the visualization of dilated vessels. However, cAVMs are relatively rare and can easily be missed or misdiagnosed due to atypical medical imaging and nonspecific clinical manifestations. Digital subtraction angiography (DSA) is the most reliable and accurate method for cAVM diagnosis, and is capable of visualizing abnormal vessels, dilated feeding arteries, and early venous drainage. The Spetzler-Martin grading system is most commonly used that considers the size and position (non-eloquent or eloquent brain region) of lesions, and venous drainage patterns. More complex cAVMs have higher S-M grades, indicating more difficult treatment and greater risk of post-operative complications.[1] A dynamic low-grade cAVM with extensive edema is prone to misdiagnosis, particularly in patients with malignant tumors. In this case, a progressive lesion with a large area of cerebral edema was incidentally discovered in a 30-year-old woman with pulmonary metastasis of rectal cancer. The lesion, initially misdiagnosed as a metastasis, was in fact a cAVM.

2. Case report

Cerebral MRI in November 2019 incidentally detected a lesion in the right frontal subcortex (Fig. 1) of a 30-year-old female patient with pulmonary and hepatic metastases of rectal cancer who underwent routine examination. The patient underwent radiotherapy, chemotherapy (Folfox6), and surgery between December 2017 and March 2018. Targeted and immunotherapy drugs (Keytruda plus regorafenib and herceptin) were administered in November 2019.

Two months later, in January 2020, the lesion had become more extensive, with large areas of edema and dilated vessels around the lesion on cerebral MRI (Fig. 2). The initial diagnosis was an intracranial metastasis. In March 2020, MRI captured mixed signals on T1WI and T2WI (Fig. 3). During this time, the patient continued antitumor treatment as before. The patient did not present with common clinical or hereditary syndromes, and her physical neurological examination was negative.

Due to the presence of dilated tortuous vessels around the edema, medical imaging specialists recommended a DSA examination, and a low-grade cAVM was confirmed (Fig. 4). Rapid dynamic changes, artery ectasia, and a single tortuous drainage vein are predictive of a high risk of rupture. After conferring on the patient and her family, transarterial embolization treatment was decided (Fig. 4) and six-month follow-up was scheduled (Fig. 5) (see Fig. 6).
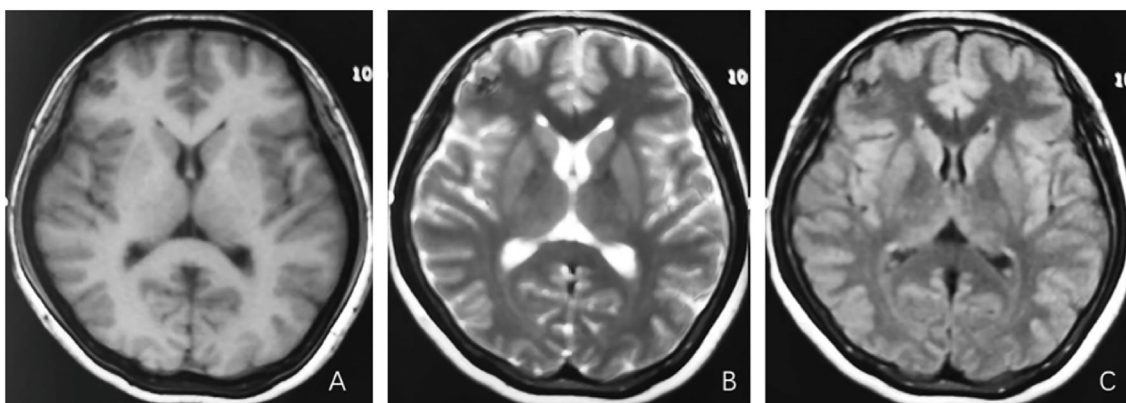
Fig. 1. Unenhanced MRI (2019.11) showed hypointensity at the right frontal subcortex. No edema was detected surrounding the small lesion.
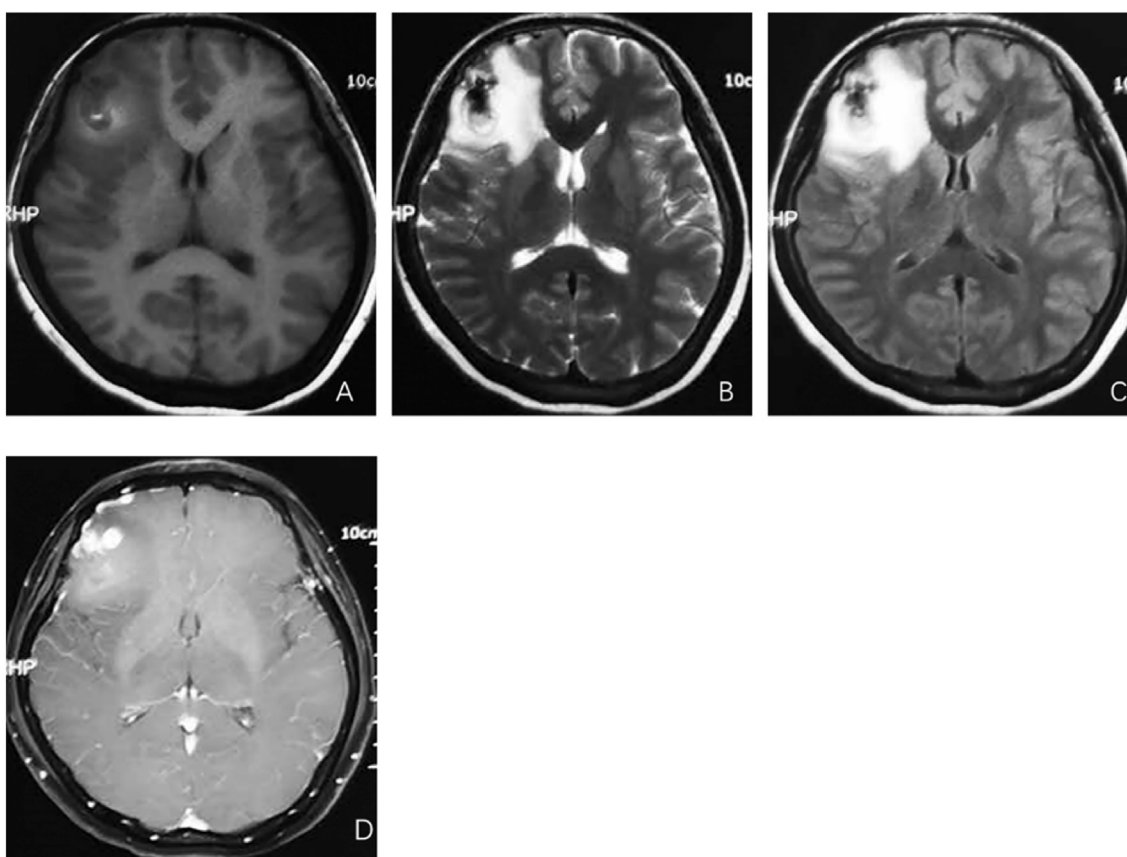

Fig. 2. Two months later (2020.01), MRI demonstrated a larger lesion with significant brain edema. Enhanced MRI (Fig. D) depicted dilated tortuous vessels.

3. Discussion

cAVM in a patient with a peripheral malignant tumor was initially misdiagnosed as a metastatic neoplasm. During the short-term MRI follow-up, dynamic changes and flow voids were observed. DSA confirmed an S-M grade I cAVM in the right frontal lobe, and embolization was performed. Roughly six months after the operation, medical imaging confirmed that the lesion was cured.

Medical imaging plays an important role in the diagnosis of cAVM. CT and MRI are important non-invasive diagnostic techniques, whereas DSA remains the gold standard. Unenhanced CT is highly sensitive in detecting hemorrhage, but is not very successful in detecting unruptured AVMs. cAVMs usually appear as isodense areas or areas of low density without a mass effect and some of them develop calcifications.

Additionally, cAVMs should be suspected in young patients with cerebral hemorrhage, particularly parenchymal hemorrhage with calcification. The literature indicates that ruptured cAVMs account for 33% of intracerebral hemorrhage in people under 40 years of age and 47% of people under the age of 20 years.[2] MRI has higher sensitivity and specificity than CT. cAVMs characteristically appear as black or low-intensity signals on the T2 weighted images. Generally, DWI does not demonstrate restricted diffusion.[3] Enhanced CT and contrast-enhanced MRI can assist in the visualization of abnormal lesions and dilated vessels. Enhanced MRA is not affected by blood flow rate, and a short time of echo (TE) reduces the turbulence influence on signals and is able to display vascular structures more clearly than unenhanced MRA. CTA and MRA are suitable for imaging feeding arteries and drainage veins.

This cAVM initially misdiagnosed as a metastasis is mainly due to
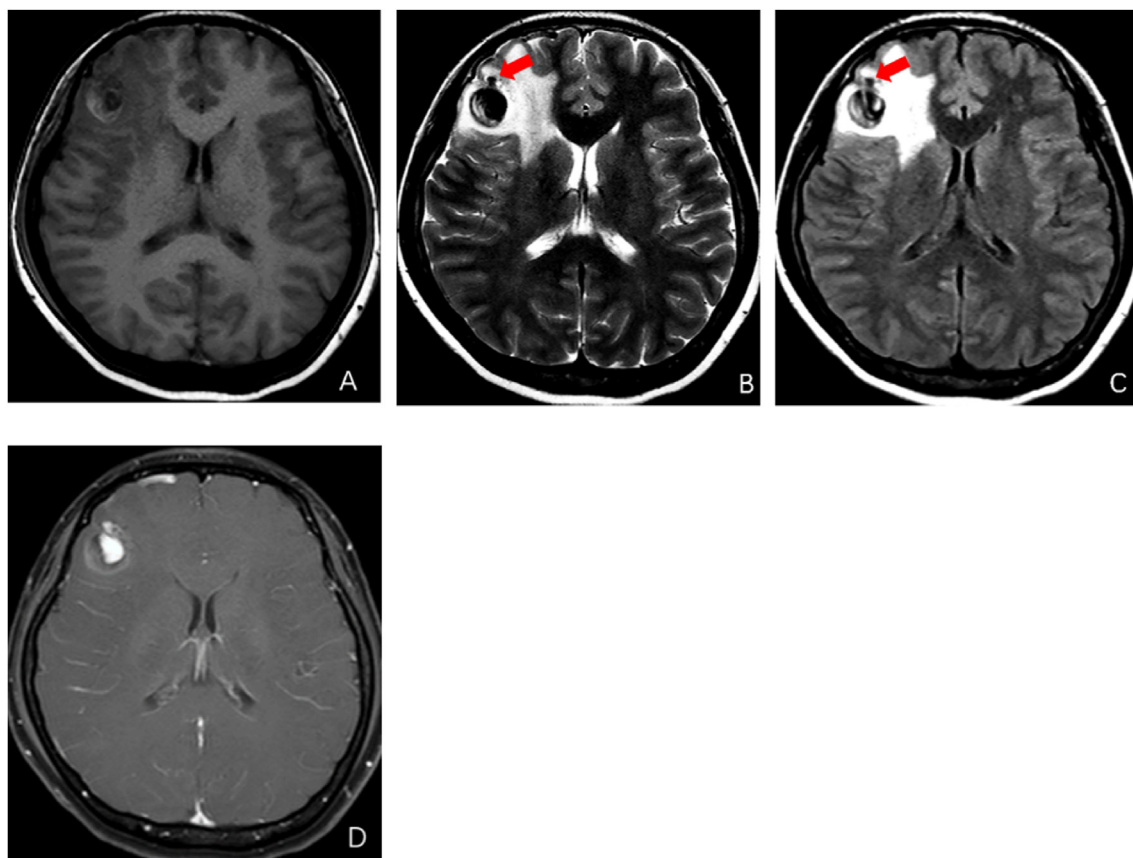
Fig. 3. Four months later (2020.03), the lesion was more extensive with pseudoaneurysm formation. Flow void was revealed on T2WI and T2-flair (arrow). Figure D exhibited thrombosis and turbulence within the ectasia.
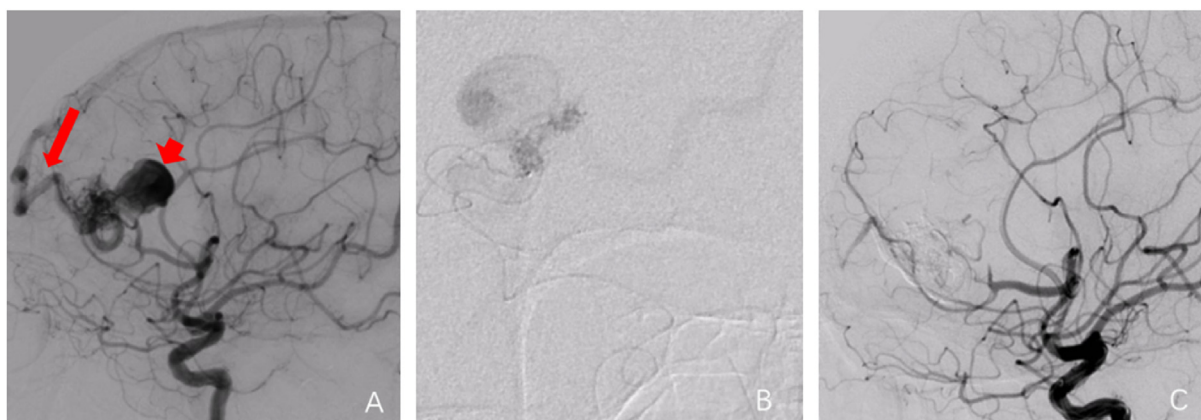
Fig. 4. Cerebral angiography and embolization were conducted in May 2020. Figure A displayed an aneurysm and single tortuous drainage vein of the low-grade cAVM, fed by the right middle cerebral artery branches with drainage into the superior sagittal sinus. Figure B showed a microcatheter advanced into the nidus via the feeding artery. Figure C revealed the cAVM was embolized successfully after 1.6ml Onyx-18 was cast into the drainage vein and nidus.

medical history and lesion imaging modalities. In terms of medical history, brain lesions are frequently misdiagnosed as cerebral metastasis by radiologists and physicians because of their atypical appearance on MRI. cAVM presents as a small lesion surrounded by a large area of edema. This presentation shows similarity to that of brain metastasis. Although multiple brain metastases are most common; however, many malignancies have a propensity for singular metastasis. With an incidence of 25–45%[4] and a tendency to be round, they are typically hypointense on T1WI with variable signals on T2WI. Metastases are often surrounded by extensive vasogenic edema, displaying a high signal on T2WI and T2-flair but a low signal on T1WI and DWI. Edema is typically confined to the white matter, and the involvement of the cortex should spur the search for other pathologies.[5] Neither plain CT scans nor enhanced CT scans were important limitations in our case. A mixed and relatively high density may help in the diagnosis of advanced lesions with aneurysm and thrombosis formation. Furthermore, a signal void caused by vessel structures containing flowing blood was absent on unenhanced MRI scans. Small cAVMs typically have low blood flow rates, making it challenging or difficult to detect abnormal vessels using routine MRI. As the cAVM grows its hemodynamics become more readily observable on
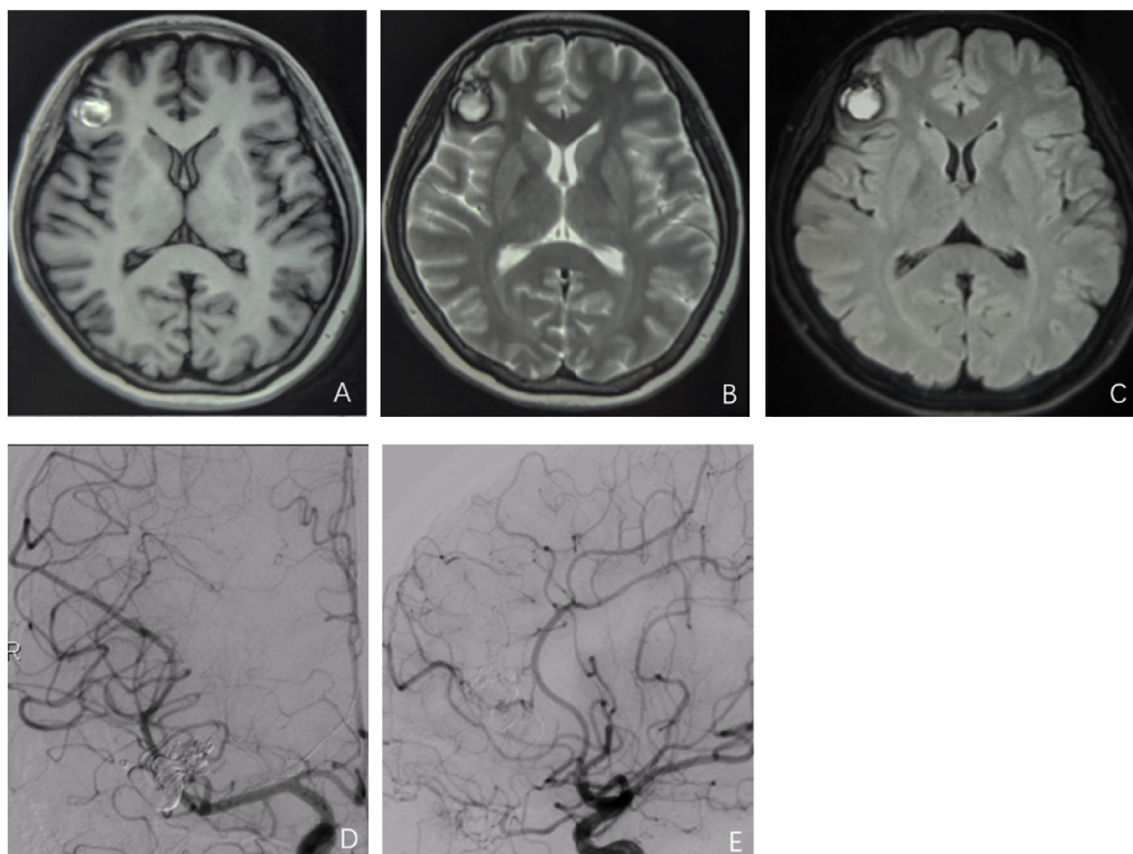
Fig. 5. Six-month follow-up after embolization (2021.12.09). Figure A, B and C showed thrombus formation in the aneurysm along with edema disappearance.
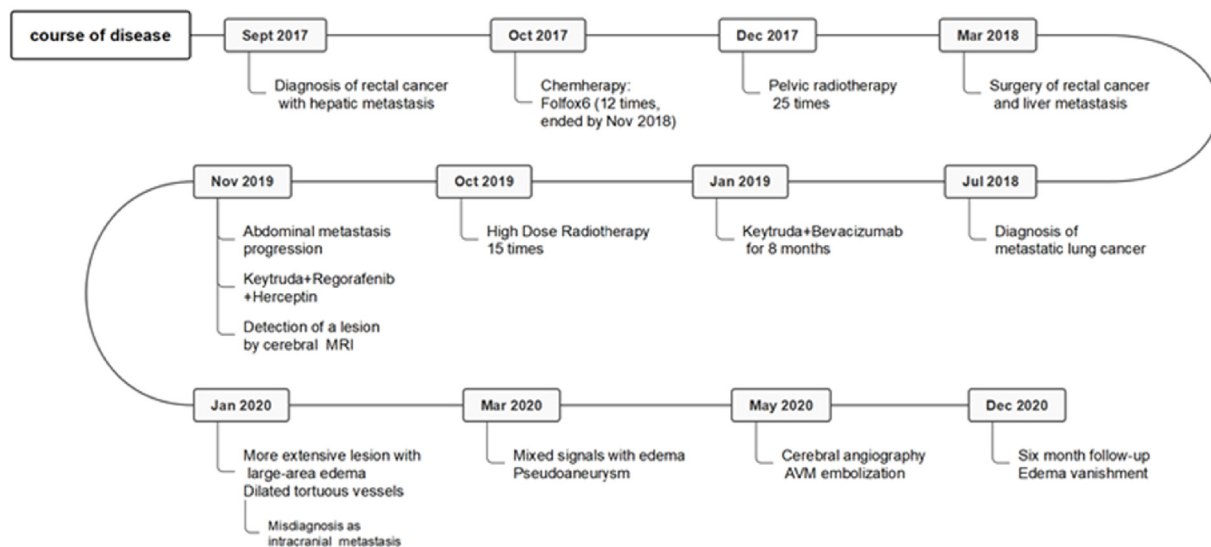

Fig. 6. The detailed information of the case.

imaging.[6,7] As the internal environment and hemodynamics change, cAVMs progress and become more detectable.

Extensive edema commonly results from a ruptured cAVM. However, low-grade cAVMs without significant hemorrhage causing large areas of edema are rare. Inadequate drainage of a single tortuous vein, high expression of vascular endothelial growth factor (VEGF), and aneurysm growth are factors that cause edema. Venous congestion, usually induced by cortical drainage, venous varicosity, and drainage vein stenosis,[8] is considered as the primary cause of congestive edema. Chen et al.[9]

reported a case of medium-sized cAVM with large-area congestive edema and main drainage venous stenosis that had not ruptured. Drainage vein stenosis and common drainage venous hypertension are also believed to cause cerebral edema. Li et al.[10] reported a high-grade cAVM with symptomatic varix. The edema and symptoms disappeared after regression of the varix by transarterial embolization. Aneurysm growth can also cause mass effects and cerebral edema.[11] Some targeted drugs such as bevacizumab and trametinib are believed to be promising for the treatment of cAVMs.[12] And some researchers believed that some sorts of

Table 1
Reported cases of metastasis to a cAVM.

Investigator	Age (years)/ Sex	Manifestation	Location	Medical imaging	Treatment	Pathology	Primary Organ	Prognosis
Scardigli et al.,[13] (1984)	65/ female	Bleeding	Brain stem	CT: Pontine high density and mass effect Enhanced-CT: Enhancing lesion.	Radiotherapy	Metastatic disease and bAVM	Breast grand	Death
Greene et al.,[14] (1980)	73/ female	Bleeding	Cerebellum	CT: Cerebellar high density and cerebral ventricle dilation	Surgery and radiotherapy	Metastatic adenocarcinoma and a bAVM	Lung	Death
Akalan et al.,[15] (1994)	41/male	Epilepsy	Parietotemporal Lobe	Enhanced-CT: Ring enhancement nodule with peripheral edema Enhanced-MRI: Mixed intensity nodule on T1WI, surrounded by edema Enhancing lesion.	Surgery		Lung	Intraoperative bleeding Hemiplegia and hemianopia post-operation
Morollon et al.,[16] (2015)	19/male	Bleeding	Frontal Lobe	CT: Hematoma and midline shift	Hematoma evacuation	Choriocarcinoma within a bAVM nidus	Testicle	Death
Sundarakumar et al.,[17] (2015)	26/male	Head Hemianopia Bleeding after chemoradiotherapy	Occipital Lobe	Enhanced-MRI and DSA: S-M IV grade AVM. One month MRI follow-up: Circular enhancement nodule and extensive edema around AVM. Two months MRI follow-up: A marked increase in the nodule size and worsening edema	Chemoradiotherapy	Choriocarcinoma metastasis to a AVM	Testicle	Permanent visual field defect
Kazama et al.,[18] (2020)	61/male	Bleeding	Occipital Lobe	Enhances-CT and MRI: Abnormal vessels. DSA: S-M III grade AVM	Embolization and surgery	Small cell carcinoma metastasized to a AVM	Lung	Death

targeted drugs may provide novel opportunities for aneurysm suppression.[13,14] Consequently, we speculated that the rapid aneurysm progression may have had little connection with the anti-tumor drugs in our case. Additionally, VEGF can lead to abnormal vascular remodeling, damage to the vascular wall structure, and impairment of the BBB. Although VEGF was not tested in this case, VEGF expression is usually observed in patients with malignant tumors, especially those with multiple metastases. Akabane et al.[15] described an unruptured cAVM generating a 4 mm blood flow-related aneurysm with surrounding edema within 3 months. The authors believed that VEGF not only promotes the occurrence and growth of aneurysms but also increases the permeability of vascular walls.

In extremely rare cases, metastasis to a cAVM has been discovered, with six pathologically verified cases on record[16–21] (Table 1). Since intracranial metastatic tumors are apt to invade blood vessels[22] and endothelial cells,[23,24] metastasis to cAVMs is prone to hemorrhage and aneurysm formation. Five of the six known cases presented with bleeding. The other patient experienced bleeding during surgery and was hemiplegic postoperatively. Hematogenous metastasis of malignant tumors requires normal capillaries and venules; therefore, the probability of tumor cell implantation in and around a cAVM is believed to be rather low.[22] Some researchers have proposed that the abundant blood vessels maintained by AVMs may provide a pathway for hematogenous tumor spread.[17,18,20] In summary, the six reviewed cases had the following

characteristics: bleeding tendency, rapid clinical progress, mass effects, and high mortality.

Without pathological examination, we were unable to confirm the occurrence of metastasis. By six-month follow-up after transarterial embolization, the edema had disappeared. MRI and DSA did not detect any abnormalities. Consequently, metastasis can be ruled out, and our case can be classified as simple cAVM.

The etiology, diagnosis, and treatment of cAVMs have always been challenging. Unenhanced CT is not sensitive for the detection of unruptured cAVMs. The presence of a flow void is a clue to the diagnosis of an AVM. In addition, dynamic follow-up by MRI, combined with other imaging modalities such as CTA and MRA, helps diagnose cAVMs, while DSA remains the gold standard. For young patients with intracranial hemorrhage, cAVMs must be considered. Despite its rarity, cAVM metastasis should not be ruled out in patients with malignant tumors or in elderly patients.

Credit authorship contribution statement

Xiaolong Zhang: Supervision, Methodology; Ting Pan: Writing-original draft preparation, Visualization; Gang Lu, Liang Ge: Conceptualization, Methodology; Yeqing Jiang, Hailin Wan: Writing-Review & Editing, Resources; Shu Xu: Data Curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Zafar A, Fiani B, Hadi H, et al. Cerebral vascular malformations and their imaging modalities. *Neurol Sci.* 2020;41:2407–2421.
2. Ruíz-Sandoval JL, Cantú C, Barinagarrementeria F. Intracerebral hemorrhage in young people: analysis of risk factors, location, causes, and prognosis. *Stroke.* 1999; 30:537–541.
3. Mills MT, Zafar A, Choudhari KA, et al. Management of concomitant moyamoya disease, arterial venous malformation, and intracranial aneurysm: case illustration, literature review, and management algorithm. *World Neurosurg.* 2018;119:262–266.
4. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322:494–500.
5. Pope WB. Brain metastases: neuroimaging. *Handb Clin Neurol.* 2018;149:89–112.
6. Santos R, Aguilar-Salinas P, Entwistle JJ, et al. De Novo Arteriovenous malformation in a pediatric patient: case report and review of the literature. *World Neurosurg.* 2018; 111:341–345.
7. Mullan S, Mojtahedi S, Johnson DL, et al. Cerebral venous malformation-arteriovenous malformation transition forms. *J Neurosurg.* 1996;85:9–13.
8. Kim BS, Sarma D, Lee SK, et al. Brain edema associated with unruptured brain arteriovenous malformations. *Neuroradiology.* 2009;51:327–335.
9. Chen X, Lu X, Yan F, et al. Spontaneous thrombosis in main draining veins of unruptured cerebral arteriovenous malformations: a case report. *Medicine (Baltim).* 2019;98, e15588.
10. Li G, Wang G, Yu J, et al. Regression of a symptomatic varix after transarterial embolization of a brain arteriovenous malformation: a case report and literature review. *Medicine (Baltimore).* 2019;98, e18418.
11. Tsang ACO, Wong DPH, Cheuk W, et al. Pseudoaneurysm formation and rupture after stereotactic radiotherapy for cerebral arteriovenous malformation: a case report and review of literature. *Br J Neurosurg.* 2021;35:116–118.
12. Raper DMS, Winkler EA, Rutledge WC, et al. An update on medications for brain arteriovenous malformations. *Neurosurgery.* 2020;87:871–878.
13. Liu B, Granville DJ, Golledge J, et al. Pathogenic mechanisms and the potential of drug therapies for aortic aneurysm. *Am J Physiol Heart Circ Physiol.* 2020;318: H652–H670.
14. Xu B, Iida Y, Glover KJ, et al. Inhibition of VEGF (Vascular Endothelial Growth Factor)-a or its receptor activity suppresses experimental aneurysm progression in the aortic elastase infusion model. *Arterioscler Thromb Vasc Biol.* 2019;39:1652–1666.
15. Akabane A, Jokura H, Ogasawara K, et al. Rapid development of an intranidal aneurysm with perifocal brain edema in an unruptured cerebral arteriovenous malformation. *Case report. J Neurosurg.* 2002;97:1436–1440.
16. Scardigli K, Biller J, Ghobrial M, et al. Brain stem vascular malformation simulating a hemorrhagic metastasis: report of a case with pathologic correlation. *Eur Neurol.* 1984;23:240–246.
17. Greene GM, Hart MN, Poor Jr MM, et al. Carcinoma metastatic to a cerebellar vascular malformation: case report. *Neurosurgery.* 1990;26:1054–1056. discussion 1056-1057.
18. Akalan N, Erbengi A, Ozgen T, et al. Carcinoma metastasis to a cerebral vascular malformation: case report. *Turkish Neurosurgery.* 1994;4:81–84.
19. Morollón N, Arrese I, Zamora T, et al. Histology of a cerebral hemorrhage: AVM as a seat of a metastatic choriocarcinoma. *Neurocirugia (Astur).* 2015;26:143–146.
20. Sundarakumar DK, Marshall DA, Keene CD, et al. Hemorrhagic collision metastasis in a cerebral arteriovenous malformation. *J Neurointerventional Surg.* 2015;7, e34.
21. Kazama H, Yoshioka H, Kanemaru K, et al. Metastasis of carcinoma to a cerebral arteriovenous malformation. *World Neurosurg.* 2021;145:278–281.
22. Wang J, Wang R, Zhao J. Ruptured cerebral aneurysm from choriocarcinoma. *J Clin Neurosci.* 2013;20:1324–1326.
23. Helmer FA. Oncotic aneurysm. Case report. *J Neurosurg.* 1976;45:98–100.
24. Lefebvre G, Toledano M, Saeed Kilani M, et al. Brain metastatic dissemination of choriocarcinoma complicated of aneurysmal rupture. *J Neuroradiol.* 2013;40:62–64.