Neurochirurgie 65 (2019) 36–39

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Short clinical case

Synchronous cerebral arteriovenous malformation and lung adenocarcinoma carcinoma brain metastases: A case study and literature review

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ARTICLE INFO

Article history:
Received 20 February 2018
Received in revised form 11 May 2018
Accepted 6 July 2018
Available online 9 January 2019

Keywords:
AVM
Adenocarcinoma
Cranial
Brain
Lung carcinoma

ABSTRACT

Introduction. – While there are numerous published cases of arteriovenous malformations (AVMs) developing in the setting of malignancy, it is extremely rare to find them concurrently associated in the brain.
Clinical case. – This is the case of a 55-year-old male who presented to the emergency department complaining of headaches, memory and visual changes. Neuro-imaging revealed a right temporal parietal AVM and an adjoining hyperenhancing occipitotemporal lobe lesion with concern for a possible evolving stroke. The patient was treated with radiosurgery for the AVM. His symptoms progressed one month later, and repeat imaging suggested interval enlargement of the previously presumed stroke that was intricately associated with the AVM, in addition to two new small enhancing lesions of the left temporal lobe. Microsurgical resection of the temporal lobe mass revealed adenocarcinoma of the lung.
Conclusion. – This case represents a previously undocumented confluence of cranial AVM that initially masked a non-small cell lung cancer brain metastasis.

1. Introduction

Arteriovenous malformations (AVMs) are tangled complexes of tortuous vessels representing fistulous connections between arteries and veins that lack an intervening capillary bed [1]. This leads to the development of high-flow lesions that are prone to rupture. When occurring in the brain, AVMs are reported in 1–2 per 100,000 persons/year, accounting for 1–2% of all strokes. The annual risk for intracranial hemorrhage (ICH) after diagnosis is approximately 2–4% per year. Unruptured AVMs are capable of causing significant morbidity including seizures, headaches and/or neurological deficits due to mass effect and involvement of neighboring brain regions [2]. Current treatment options include conservative management, surgical resection, stereotactic radiosurgery (SRS), endovascular embolization or a combination of the above. Despite a small risk of ICH and multiple accepted treatment approaches, the decision whether or not to treat unruptured AVMs remains debated. A recent retrospective trial demonstrated that long-term morbidity was often related to hemorrhagic brain damage and rarely to surgical resection itself [3]. Additionally, a large ongoing prospective randomized controlled trial comparing conservative vs. interventional modalities may provide greater clarity in the comparative efficacy between treatment options [4]. Studies such as these will help to provide certainty in the otherwise ambiguous therapeutic approaches in AVM management.

Current theories concerning AVM development are also controversial. There is a growing trend of evidence suggesting the de novo formation of AVMs [5,6]. However, most postulate that these lesions are a result of embryogenesis defects. In patients with such abnormalities, lesions remain small throughout life unless growth is stimulated by a secondary insult resulting in angiopathy or angiogenesis [7]. In a recent study by Nikolaev et al., activating KRAS mutations were identified in the majority of brain AVM tissue specimens. Additionally, the authors demonstrated that the expression of mutant KRAS in endothelial cells, in vitro, induced expression of genes related to angiogenesis and other proliferative pathways [8]. While not currently recognized as a risk factor, cranial metastatic malignancy has been described in several instances

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https://doi.org/10.1016/j.neuchi.2018.07.003
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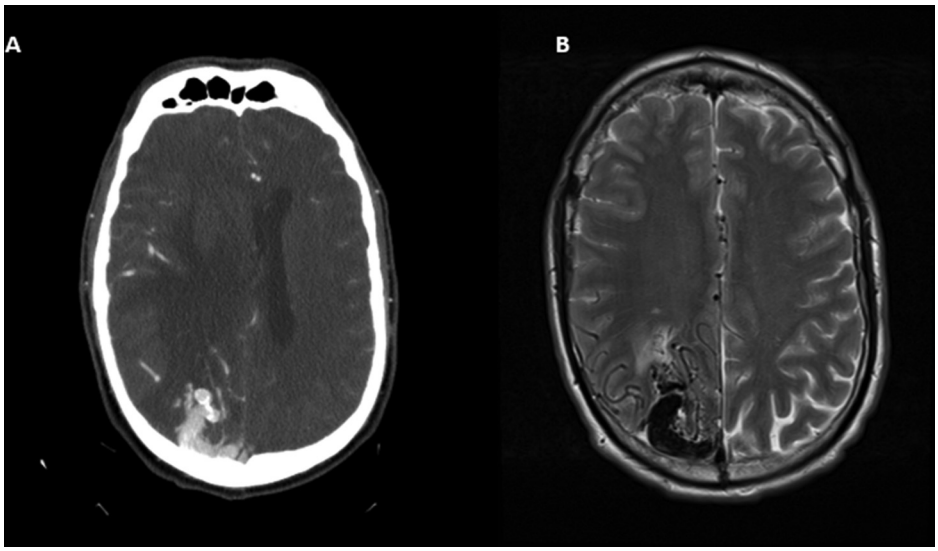

Fig. 1. A. Axial CT angiogram with contrast. B. Axial T2 MRI: AVM of the temporal parietal lobe with prominent draining vein.

as co-occurring within or adjacent to AVMs [9,10]. In either case, the brain metastases were due to a highly vascularized neoplasm (renal cell carcinoma and choriocarcinoma) with hypothesized production of angiogenic growth factors contributing to the formation of the AVM [9]. In contrast, we report herein, a case of a primarily avascular adenocarcinoma of the lung with secondary brain metastases co-occurring with an AVM in the temporal parietal lobe. To the best of our knowledge, this co-occurrence of lung carcinoma and AVM has not been previously described in the literature.

2. Clinical case

A 55-year-old male presented to the emergency room complaining of recurring headaches unrelieved by administration of opioid-like medications, in addition to memory deficits and visual changes (difficulty focusing without any focal visual field deficits). Initial cranial CT without contrast imagining, at an outside facility, demonstrated a right temporal parietal lesion consistent with pial AVM and accompanying vasogenic edema. The patient was referred to our clinic with unchanging headaches in addition to fatigue, paresthesias and an unsteady gait. A cranial CT angiogram and T2 weighted MRI showed a 3.9 cm Spetzler Martin grade III AVM, with prominent draining veins extending to the superior sagittal and right transverse sinus (Fig. 1). Axial diffusion and T2 weighted MRI with contrast demonstrates an area of restricted diffusion in the right occipitotemporal lobe with vasogenic edema, increased from prior imaging (Fig. 2). There was no evidence of dural venous sinus thrombosis or hemorrhage in this region, however this occipitotemporal finding was of concern for evolving stroke secondary to the AVM. After consultation with neurosurgery and radiation oncology, the patient elected to proceed with stereotactic radiosurgery for the AVM given the possible higher risk of visual field deficits (due to the lesion's close proximity to the occipital lobe) with surgical resection.

One month later the patient reported worsening headaches and memory difficulties. The neurological exam was otherwise normal. Postaxial T1 weighted MRI with contrast revealed an interval enlargement of the previously treated lesion. Increased vasogenic edema with 1.2 cm leftward shift of midline and mass effect on the right lateral ventricle was evident. Furthermore, two small enhancing metastatic lesions (previously undetectable on imaging) in the left temporal region with accompanying vasogenic edema were now present (Fig. 3). These new findings were highly suggestive of a malignant process and therefore, microsurgical resection of the right occipitotemporal lesion was performed with great care in order to respect the draining veins associated with the AVM. Additionally, the patient received stereotactic radiation to the resected tumor bed and other brain metastases. Radiosurgery was followed by systemic chemotherapy.

The pathology report of the resected specimen revealed a metastatic carcinoma of the lung staining positively for CK7 and TTF-1; staining for CK5 and CK20 were negative. These findings were consistent with poorly differentiated adenocarcinoma of the lung. Chest CT immediately prior to the surgery confirmed a lung primary tumor.

3. Discussion

We present a unique case of an adenocarcinoma of the lung metastasizing to the brain co-occurring with an AVM. Prior reports of metastatic cancers have been hypothesized as contributing to the formation of AVMs, but, to our knowledge, this is the first reported case of a lung carcinoma presented in this manner.

Lung cancer represents one of the most commonly diagnosed malignancies and is responsible for the largest number of cancer-related deaths worldwide. Lung cancer arises from the cells of the respiratory epithelium and can be divided into multiple subtypes, with adenocarcinoma defining 38.5% of such diagnoses [11,12]. Lung cancer spreads hematogenously, metastasizing to the brain in 10–25% of all cases. This type of spread can lead to significant morbidity and mortality with 5-year survival rates of approximately 3.6% [12,13].

AVMs are vascular abnormalities consisting of complex tangles and communications between one or more arteries of the cerebral parenchyma and one or more draining veins without an intervening capillary bed [14]. This level of angiogenesis requires interactions between various molecules that regulate cellular processes including extracellular matrix production, endothelial invasion, migration and proliferation, in addition to remodeling of the vascular network [1]. The mostly widely recognized factor involved in the aforementioned angiogenic processes is vascular endothelial growth factor (VEGF). VEGF is theorized to play a crucial role in AVM formation through stimulating growth and development of vascular endothelial cells, enhancing proliferation and differentiation, and prolonging the life of existing vessels [15]. Furthermore,

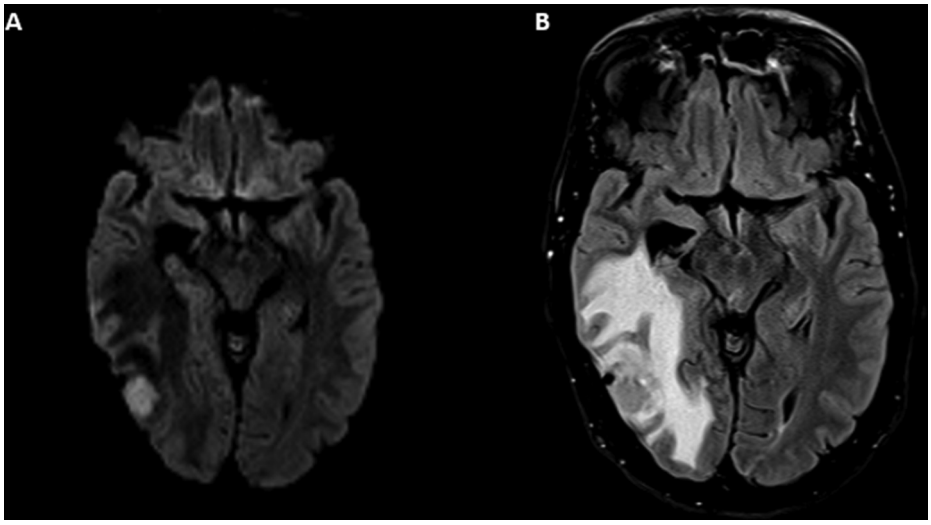

Fig. 2. A. Axial diffusion weighted MRI. B. T2 weighted MRI with contrast: area of restricted diffusion in occipitotemporal lobe with vasogenic edema.

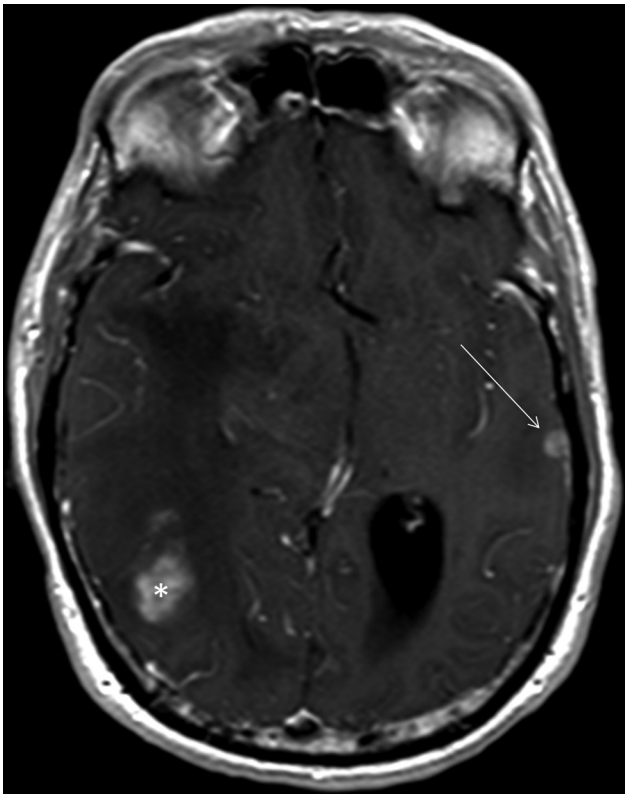

Fig. 3. Postaxial T1 weighted MRI with contrast: right occipitotemporal, cortically based, heterogeneously enhancing lesion with surrounding vasogenic edema (*). Left temporal enhancing lesion (arrow) with surrounding edema. Midline shift with increased mass effect upon right lateral ventricle.

VEGF increases vascular permeability, which is thought to be pivotal in the development of the vasogenic edema surrounding most AVMs and tumors alike [1].

While various cancers are associated with or lead to the development of AVMs, there are few reports of a non-central nervous system (CNS) tumor metastasizing to the brain with subsequent AVM formation. Case reports of a 19-year-old male with metastatic choriocarcinoma and a 45-year-old female with renal cell carcinoma (RCC) detail that in both incidents, the patient's primary cancer and clinical condition worsened, prompting imaging, which led to findings of brain metastases with co-occurring AVMs. While choriocarcinoma and RCC represent distinct cancers, each with differing cellular origin, pathophysiology and risk factors, they are both associated with elevated levels of VEGF [9,10]. Likewise, a recent study demonstrated significantly higher levels of VEGF in lung adenocarcinoma tissues compared to healthy patients, with the greatest concentrations noted for those with advanced disease (Stage III/IV) [15]. Further studies have postulated that genetic alterations and angiogenic stimulation are each independently required for AVM development. Therefore, it is theorized that the dysregulation of angiogenesis associated with increased VEGF secondary to malignancy contributes to the formation of AVMs in genetically susceptible patients [9].

4. Conclusion

In conclusion, AVMs are rare tangled fistulous connections between arteries and veins without an intervening capillary bed. Such aberrant connections can lead to many adverse events, the most feared of which is ICH. While there is significant evidence in the literature associating non-CNS malignancies with AVM formation, there is a paucity of reports demonstrating the co-occurrence of brain metastases and AVMs. Despite no unifying theories as to their association, recent evidence points to a synergistic mechanism of underlying genetic predisposition superimposed on angiogenic dysregulation in the face of malignancy. We report herein, a previously undocumented confluence of cranial AVM that initially masked a lung adenocarcinoma brain metastasis.

Financial/technical support

None to declare.

Disclosure of interest

The authors declare that they have no competing interest.

Acknowledgements

None.

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