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Review Article

# Meningioangiomatosis: A review of the variable manifestations and complex pathophysiology

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ABSTRACT

Meningioangiomatosis (MA) is a rare, complex and heterogeneous disease of meningovascular proliferation that is found primarily in the leptomeninges and cerebral cortex but can involve subcortical white matter and other brain regions such as the cerebellum and deep gray matter. MA may be found in pediatric or adult populations and may be sporadic or neurofibromatosis-associated. The presentation of MA is highly variable: it may be associated with other neurological diseases; clinically presents on a spectrum from asymptomatic to seizures or focal deficits; radiologically presents with multifocal, tumor-like, or cystic lesions, or may appear normal; and pathologically may have cellular or vascular predominance. In this article, we review the various manifestations of MA including neurofibromatosis-associated MA, multifocal MA, cystic MA, and MA associated with meningioma, other brain tumors, focal cortical dysplasia, neurodegenerative changes, and post-radiation changes. The treatment of MA is also reviewed. While the pathogenesis of MA remains elusive, we discuss the proposed theories such as developmental, dysplastic, hamartomatous or reactive ethology in given variants. It is important for physicians to be aware of MA as more research on this complex entity is needed and timely diagnosis may benefit outcomes in patients with MA.

## 1. Introduction

Meningioangiomatosis (MA) is a rare meningovascular disease which was first described by Bassoe and Nuzum in 1915 [1]. Two decades later it was named by Worster-Drought et al. [2] with reference to an association with neurofibromatosis (NF). Since that time it has also been described in association with various lesions of the central nervous system (CNS); most often with an overlying meningioma [3]. However, a growing body of literature suggests that this rare condition is primarily sporadic [3].

MA is pathologically characterized by leptomeningeal and cortical vascular proliferation with perivascular spread of meningothelial and fibroblastic cells along the Virchow-Robin spaces of small leptomeningeal and intracortical blood vessels [3–6] (Fig. 1A, B). Clinically, MA can have variable presentations with seizure being the most common, followed by headache [7]. Depending on the location of the lesion, variable neurologic deficits have also been reported including personality change, hemiparesis and cortical blindness. Finally, particularly in cases associated with NF, MA lesions may be asymptomatic [7–11].

Radiologically, MA has a variable appearance which often makes a pre-surgical diagnosis challenging. Head CT images generally show some abnormalities, with predominantly hypodensities described. Further, of those with contrast, the majority exhibit some element of enhancement [12–14]. The main advantage of a CT image, however, is in examining for evidence of calcification which has been reported as high as 90% of cases [13] (Fig. 2A). MRI is often the imaging modality of choice and typically reveals T1 hypo- to iso-intensity along with T2-hyperintensity [14, 15]. On FLAIR sequence, gyriform hyperintensities have often been described [13, 15]. Overall the majority of MA lesions show some element of Gadolinium enhancement; however enhancement patterns vary widely over the reports in the literature [14, 15] (Fig. 2C, D). Positron emission tomography (PET) scans have been used in some cases and may more accurately delineate the border of the MA lesion in comparison to gadolinium-enhanced MRI alone [16]. Although MA lesions involve vascular proliferation, cerebral angiograms are normal in the majority, with only occasional studies showing hypervascularity or abnormal vessels [13, 14] (Fig. 2F).

Although there are now approximately 200 cases of MA reported in the literature [5, 6], the precise pathophysiology of this condition remains elusive. There have been a few proposed hypotheses including developmental and hamartomatous, dysplasic or reactive etiologies [3, 12, 17]. The harmartomatous theory is supported by the association of

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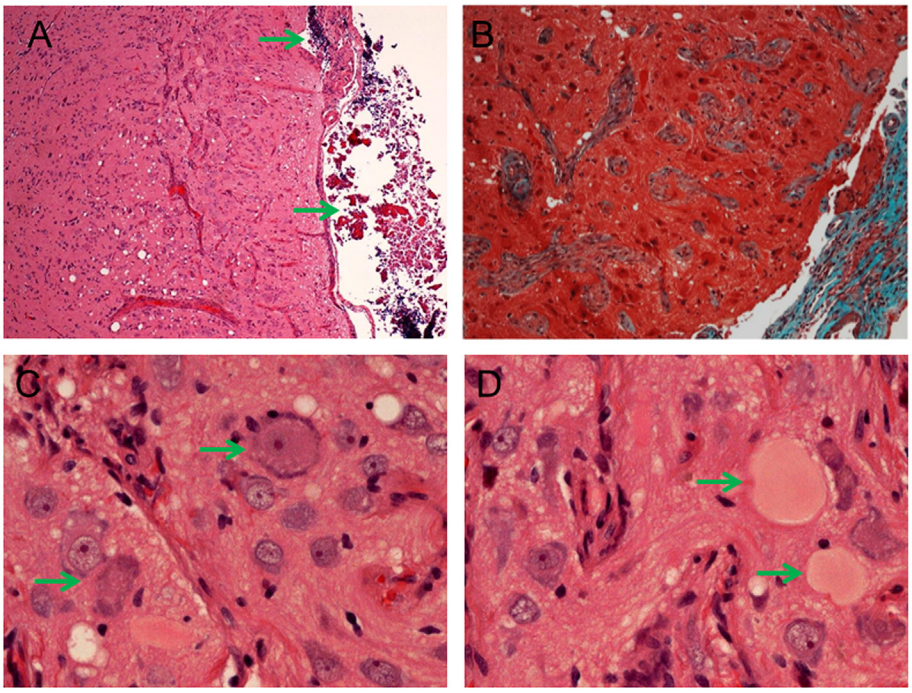


**Fig. 1.** Meningioangiomatosis associated with focal cortical dysplasia in a 60-year-old patient. Photomicrographs of a biopsy from the right parietal lobe demonstrate the leptomeningeal and cortical vascular proliferation with focal calcification in the leptomeninges (A, arrows pointing leptomeninges and calcification), marked proliferation of the leptomeninges and cerebral thick-walled blood vessels and perivascular spindled cells (B, trichrome staining), as well as focal cortical disorganization with frequent dysmorphic neurons (C, arrows) and occasional balloon cells (D, arrows). Original magnification ×100 (A). ×200 (B), ×400 (C, D).

MA with neurofibromatosis and would include it among the "neurocristopathies" as a developmental abnormality of neural crest cell migration [18]. A second theory focuses on the vascular aspect of MA, supposing the lesion begins as a vascular malformation with subsequent proliferation of meningothelial cells [12]. The third major hypothesis involves invasion by a meningioma into the brain, supported by the frequent association seen with meningiomas [3, 12]. Increasing reports of various clinicopathological presentations and associations of MA have provided new insight into the complex, heterogeneous pathophysiology of MA. In this review we will discuss the various presentations and associations of MA as well as treatment options.

## 2. Locations of Meningioangiomatosis

MA may be unifocal, multifocal or diffuse. Unifocal MA is most commonly seen and located preferentially in the cerebral cortex, but can occur anywhere in the brain. The most common location of MA is the frontal lobe, followed by the temporal lobe, parietal lobe and occipital lobe in sporadic MA cases [3, 5, 17]. In NF-associated MA cases, the parietal lobe is the second most common location. Based on a review of 100 cases of MA by Perry et al., the right cerebral hemisphere seems to be slightly favored, compared to the left hemisphere, in both sporadic and NF-associated MA cases [3]. The vast majority of MA involves the cerebral cortex; however, it has also been occasionally reported to occur in the deep nuclei and cerebellum [7, 19]. Bulut et al. [12] described a case of pathologically typical MA located in the left superior cerebellum of a 55-year-old woman who did not have NF2 or other known past medical conditions and presented with a 2-month history of vertigo. Omeis et al. [7] reported a case of cerebellar MA in a 13-year-old girl who had NF2 with supratentorial en plaque meningiomas and bilateral cerebellopontine angle schwannomas.

Multifocal or diffuse MA, despite being less frequent than unifocal or localized MA, has been reported from time to time [20]. Nearly half of NF2-associated lesions are multifocal [3]. The brain regions in which multifocal MA involves, other than the cerebral cortex and cerebellar cortex, include the third ventricle, basal ganglia, thalami, and brainstem [3, 5, 20–22]. These reports suggest that MA is not a disease confined to the leptomeninges and cortical regions. Therefore, the traditional pathological definition of MA deserves expansion to include pathological changes in these brain regions.

## 3. White matter involvement in Meningioangiomatosis

Although MA is thought to arise primarily from the leptomeninges and cerebral cortex, it is commonly reported to involve the subcortical white matter [8, 12, 17, 23–25]. Jeon et al. [12] reported 8 cases of sporadic MA, in which 7 cases (88%) showed the subcortical white matter abnormalities on neuroimaging with pathological confirmation of the white matter involvement in 6 of 7 cases (86%). In this small series, the subcortical white matter involvement was described as hypoattenuation on CT scan and T1 hypointensity/T2 hyperintensity without enhancement on MR images. All the patients with MA involving the white matter presented with seizures and after surgical resection most patients became seizure-free. Grabowski and Prayson [17] analyzed 16 cases of sporadic MA in which 11 of 13 cases with the white matter available to assess showed involvement of this tissue; of these 11 cases, 8 were associated with focal cortical dysplasia, 2 with fibrous meningiomas and 3 with meningeal hyperplasia. Based on these two small series, the white matter involvement in sporadic MA seems to be more common than previously recognized and may be as high as 80–90% of cases. On histopathological examination, the subcortical white matter changes include edema, gliosis, focal perivascular sclerosis, and/or perivascular spindled cell proliferation [12, 24]. These white matter pathological changes are compatible with the MRI finding of T2 hyperintensity and thought to be largely reactive in pathogenesis.

## 4. Sporadic and neurofibromatosis-associated Meningioangiomatosis

After its initial description, MA was thought of as a *forme fruste* of NF type 1 [1]. It has since been revealed to be associated with NF type 2 (NF2) rather than type 1 [26]. The autosomal dominant mutation in NF2 is located on chromosome 22q12 and encodes for the protein merlin which is widely expressed and important for cellular growth regulation [27]. Individuals with this mutation thus have a predisposition to develop tumors, with particular association to vestibular schwannomas and meningiomas [27].

MA cases associated with NF2 were found to have germline NF2