We report five cases of sporadic meningioangiomatosis, three males and two females, ranging in age from 12 to 36 years at diagnosis. The lesion was found incidentally by MRI after a head trauma in one case; the other four subjects had a seizure disorders, which improved following surgical resection of the cortical lesions. Grossly, the lesionectomy specimens were of a whitish color and firm consistency. Histological examination revealed that the lesions were confined to the cortex with focal involvement of the overlying leptomeninges, and revealed unifying features of meningioangiomatosis, such as proliferating microvessels with perivascular cuffs of spindle-cell proliferation within the cortex. Two cases had numerous calcifications; one was associated with a prominent fibrocalcifying component. Immunostaining results were variable among the cases. Only vimentin was consistently positive. Some of the spindle cells were weak positive for EMA in two cases. Immunoreactions with anti-CD34 detected within the cytoplasm of the spindle cells were observed in three of the five cases. The Ki-67 proliferation index of all the cases was very low, less than 0.1%. Neurofibrillary tangles were identified in only one of the five cases using the Bodian and immunostaining methods. These findings indicate that meningioangiomatosis lesions show a wide range of clinicopathological features, making diagnosis difficult. A histopathological spectrum and differential diagnoses were discussed with a review of the literature. Since this lesion is a distinct clinicopathological entity and hamartomatous in nature, it is important to make a correct diagnosis in order to avoid further aggressive treatment.

Key words: hamartomatous lesion, histopathology, meningioangiomatosis, neurofibrillary tangles, seizures.

INTRODUCTION

Meningioangiomatosis (MA) is a rare, benign, meningo-vascular hamartomatous condition affecting the cerebral cortex and leptomeninges. Approximately 90 cases of MA have been reported since the first description in 1915.1 The majority of the cases are sporadic but the association of this lesion with familial neurofibromatosis type 2 is well known.2–8 MA usually appears in young patients. Focal seizures and/or headaches are the most common presenting symptoms. A few cases with neurofibromatosis may be asymptomatic, and have been found incidentally after a head trauma or at autopsy. Histopathologically, the condition is characterized by cortical meningo-vascular proliferation, perivascular spindle-cell proliferation through Virchow-Robin spaces, fibrosis, hyalinization, calcification and even osseous metaplasia. The pathogenesis of MA is still obscure. Previous reports have suggested that the origin of MA lesions is most probably a hamartomatous proliferation of meningothelial cells.9–11 In this study we present the histopathological features of five cases without stigmata of neurofibromatosis type 2. The histopathological spectrum and differential diagnoses are discussed with a review of the literature.

MATERIALS AND METHODS

We reviewed the neuropathological records at our department to find all cases of MA that were recorded from 2000 to 2004. Five cases were identified, three patients are male and two are female, ranging in age from 12 to 36, mean 21.6. One, whose lesion was found incidentally after a head trauma, was asymptomatic. Four had histories of seizures. No stigmata of neurofibromatosis type 2, including bilateral acoustic Schwannomas or masses of the spinal cord,
were found using MRI or family history in any of the cases. General physical and neurological examinations were normal. Follow-up duration ranged from 10 to 48 months. In one case (patient 1) follow-up was not possible after surgery. Detailed clinical information is summarized in Table 1.

The resected tissues were fixed in 10% neutral formalin solution. Paraffin-embedded 6-µm thick sections were then stained with HE, Klüver-Barrera (KB), reticulum fiber and Bodian methods. Immunohistochemical examinations were performed using the standard streptavidin technique with appropriate positive and negative controls. The following antibodies were employed: epithelial membrane antigen (EMA, M0613, DAKO, Glostrup, Denmark, 1:100), Vimentin (M0725, DAKO, 1:100), CD34 Class II (M7165, DAKO, 1:50), S-100 protein (Z0311, DAKO, 1:100), Smooth Muscle Actin (SMA, M0851, DAKO, 1:200), Cytokeratin (M3515, DAKO, 1:100), Glial Fibrillary Acidic Protein (GFAP, M0761, DAKO, 1:100), Synaptophysin (A0010, DAKO, 1:200), Neurofilament Protein (M0762, DAKO, 1:100) Ubiquitin (Z0458, DAKO, 1:100), Tau (A0024, DAKO, 1:100) and Ki-67 (M7240, DAKO, 1:50).

### RESULTS

#### Clinical summary

**Case 1**, a 26-year-old man with an unremarkable medical history, was admitted to our hospital in March 2000 due to an incidental head trauma. Head computed tomography (CT) scan revealed a well-demarcated calcific lesion in the right temporal lobe with surrounding low density. Clinically, calcific lesion was suspected. Intraoperatively, the leptomeninges and subarachnoid space overlying the right temporal region contained a 2.5-cm spherical calcification filling a sulcus and compressing the cortical surface. The calcific lesion and surrounding infiltration were totally removed. Unfortunately, after the operation its follow-up was not possible.

**Case 2** was a 15-year-old girl with a history of complex partial seizures for 3 years who was admitted to our hospital in August 2000 as a result of headache and vomiting. Head CT scan revealed a low-density lesion in the right occipital lobe. On MRI, the cortical lesion was hypointense on T1-weighted images and showed low signal on T2-weighted images with surrounding hyperintense lesion. Radiologically, arteriovenous malformation was suspected. The lesion and adjacent cortex were resected. The postoperative course was uneventful and no neurological deficits were noted. A 4-year follow-up did not reveal any recurrence of the lesion.

**Case 3**, a 36-year-old woman with an unremarkable medical history, was admitted to our hospital in August 2001 due to generalized seizures, which had developed 6 months previously. Brain MRI revealed a left frontal mass lesion whose signal was hypointense on T1-weighted images and hyperintense on T2-weighted images, with surrounding increased T2 signal. A low-grade glioma was suspected. She underwent left frontal craniotomy and lesionectomy. The lesion appeared gray, firm, and well demarcated. Gross total removal of the lesion was achieved. The postoperative course was uneventful and no neurological deficits were noted. A 3-year follow-up did not reveal any recurrence of the lesion.

**Case 4**, a 19-year-old man with an unremarkable medical history, was admitted to our hospital in June 2004 due to generalized seizures, which had developed 6 months previously. Brain CT revealed a 2.0-cm well-demarcated ovoid mass without peritumoral edema in the left superficial gyrus of the parietal lobe (Fig. 1). Clinically, cavernous angioma was suspected. Intraoperatively, the mass was a well-demarcated, gray and stony, hard, globular lesion. Gross total removal of the lesion was achieved. During the 10-month follow-up, there was no recurrence of seizure or tumor.

**Case 5**, a 12-year-old boy with progressively intractable complex partial seizures since the age of 5, was admitted to our hospital in July 2004 as a result of headache and vomiting. There was no history of perinatal problems, fever-related seizures or developmental delay. A brain MRI revealed a cystic lesion with increased cortical signal in the

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Duration of illness (years)</th>
<th>Clinical presentation</th>
<th>Neurological examination</th>
<th>Location</th>
<th>Clinical diagnosis</th>
<th>Surgical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>26/M</td>
<td>–</td>
<td>Asymptomatic</td>
<td>Normal</td>
<td>Right temporal lobe</td>
<td>Calcific lesion</td>
<td>Gross total resection</td>
</tr>
<tr>
<td>2</td>
<td>15/F</td>
<td>3</td>
<td>Refractory seizures</td>
<td>Normal</td>
<td>Right occipital lobe</td>
<td>AVM</td>
<td>Gross total resection</td>
</tr>
<tr>
<td>3</td>
<td>36/F</td>
<td>0.5</td>
<td>Seizures</td>
<td>Normal</td>
<td>Left frontal lobe</td>
<td>Low grade glioma</td>
<td>Gross total resection</td>
</tr>
<tr>
<td>4</td>
<td>19/M</td>
<td>0.5</td>
<td>Seizures</td>
<td>Normal</td>
<td>Left parietal lobe</td>
<td>CA</td>
<td>Gross total resection</td>
</tr>
<tr>
<td>5</td>
<td>12/M</td>
<td>7</td>
<td>Reconstructive seizures</td>
<td>Normal</td>
<td>Left frontal lobe</td>
<td>Low grade glioma</td>
<td>Gross total resection</td>
</tr>
</tbody>
</table>

AVM, arteriovenous malformation; CA, cavernous angioma.
Sporadic meningioangiomatosis

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left frontal lobe on T1-weighted image, interpreted as low-grade glioma or cystic encephalomalacia (Fig. 2). The patient underwent left frontal craniotomy and lesionectomy. Postoperatively, he continued to take anticonvulsant medication and has remained seizure-free with no evidence of lesion recurrence for 10 months.

**Histopathological findings**

All five cases showed similar histopathological features. The main histopathological findings are summarized in Table 2.

In case 1, the lesionectomy specimen contained a 3.0-cm calcification largely filling a sulcus in the leptomeninges. The adjacent cortex was of a whitish color and firm consistency. Microscopically, the calcified leptomeningeal mass was composed of multilobulated amphophilic nodules with a concentric arrangement of acellular lamellae, some were centrally dense, hyalinized and resembled fibrocalcifying component (Fig. 3A). The adjacent cortex showed rows of proliferating oval to spindle cells with hyperchromatic nuclei, psammoma bodies, and numerous slit-like capillaries. Neither mitosis nor necrosis was found. Histopathology confirmed the diagnosis of MA.

In case 2, the surgical specimen, measuring 1.0 cm in diameter, was gray. Microscopically, the lesion was confined to the cortex with focal involvement of the overlying leptomeninges. The adherent cortex showed prominent

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**Fig. 1** Axial CT scan showing a nodular, calcific mass in the left parietal lobe.

**Fig. 2** Sagittal MRI T1-weighted image showing a cystic lesion with increased cortical signal in the left frontal lobe.

**Table 2** The main histopathological findings of five cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Meningiovascular proliferation</th>
<th>Perivascular cuffs of spindle cells proliferation</th>
<th>Perivascular connective tissue proliferation</th>
<th>Reticulum fibrerde position</th>
<th>Calcification</th>
<th>Nervous tissue Gliosis</th>
<th>NFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>(fibrocalcifying formation)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+ (dominant)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+ (dominant)</td>
<td>+ (dominant)</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
<td>+ (dominant)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+ (dominant, involving the white matter)</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

NFT, neurofibrillary tangles.
Fig. 3  Light microscopic features of the MA: (A) case 1, fibrocalciifying nodule with spindle cells proliferation in the adjacent cortex (HE, ×40); (B) case 2, predominantly vascular case with numerous capillaries and venules in the cortex (HE, ×200); (C) case 3, highly cellular area showing fascicular pattern; there is complete effacement of cortical architecture (HE, ×100); (D) case 4, some vessels of the cortex with thickened vascular wall and minimal cuffs of spindle-cell proliferation (arrows) (HE, ×100); (E) case 5, cut sections revealed a pale, rubbery and gritty intracortical lesion with cystic formation; and (F) case 5, perivascular spindle-cell proliferation presenting in the white matter (HE, ×100).
proliferation of microvessels, mainly capillaries and venules (Fig. 3B). Cuffs of spindle cells surrounded them. No calcification was noted. These findings were similar to MA with a predominant vascular pattern according to the classification of Wiebe et al. 12

In case 3, the lesionectomy specimen, measuring 3.5 × 2.5 × 1.2 cm, was of a whitish color and firm consistency. Microscopically, the most prominent feature of the transcortical plaque was a complex of small-caliber blood vessels lined by a single layer of endothelial cells and encircled by spindle cells in cuffs as well as parallel bundles (Fig. 3C). Neither cellular atypia nor necrosis was found. Some blood vessels had fibrosed or hyalinized vascular walls. A dense reticulum and collagen fiber network was aggregated around the bigger blood vessels. No calcification was noted. These findings suggested MA with a predominant cellular pattern according to the classification of Wiebe et al. 12

In case 4, the lesionectomy specimen, measuring 1.2 cm in diameter, had leptomeningeal calcific deposits and a cortical plaque. The main histopathological features of this case were similar to case 3. It was characterized by a proliferation of leptomeningeal vessels and perivascular cuffs of spindle cells within the cortex. The perivascular arrangement of spindle cells was more evident in the periphery of the lesion. Some vessels were surrounded by two or three layers of concentrically arranged spindle or oval cells (Fig. 3D). Sparse lymphocytic infiltrations were present in the leptomeninges and near some cortical vessels. Multiple calcified depositions were found in the leptomeninges and cerebral cortex. Abundant reticulum fiber with a pericellular distribution was observed. MA with a predominant cellular pattern was established in this patient.

In case 5, The lesionectomy specimen measured 4 × 3 × 2 cm. Cut sections revealed a pale, rubbery and gritty intracortical lesion with cystic formation (Fig. 3E). Microscopically, the lesion was composed of elongated spindle cells with wavy nuclei, forming moderately- to highly-cellular, focally palisading zones around fibrillar areas in which cell nuclei were scarce. Although the compact areas were mainly localized to the cortex perivascular spindle-cell proliferation was also observed in the white matter (Fig. 3F). No calcification was noted. The appearance was that of MA with a predominant cellular pattern.

On immunohistochemical analysis, the proliferating spindle-cell population expressed vimentin uniformly. Results for other markers varied: two cases (patients 4, 5) showed focal EMA positivity and three (patients 1, 3, 4) were focally positive for CD34. All were negative for cytokeration, S-100 protein, SMA, GFAP and neurofilament. The Ki-67 proliferation index for all the five cases was very low, less than 0.1%.

All the cases showed gliosis and neuronal loss with residual neurons presenting with chronic non-specific degenerative changes within the lesion areas and in the neighboring cortex. Bodian staining and Ubiquitin, Tau immunostaining demonstrated neurofibrillary tangles (NFT) in the cortex adjacent to the lesion only in one case (patient 1) (Fig. 4).
dominant cellular pattern was to show moderate to high
cellularity, as in our present cases (patient 3, 4, and 5).
Varying architecture was noted, consisting of focal areas
of storiiform, rhythmic palisading and fascicular patterns.
All cellular cases had lesional cells that, in some areas,
appeared to emerge from a perivascular location and infil-
trate the cortex. This occurred centrally within the lesions,
where cellularity was most dense. Peripherally, the perivas-
cular relationship of the cells became evident. Moreover,
patient 5 showed the white matter involved. The predom-
inantly vascular pattern, as in our patient 2, contained
thick-walled, hyalinized blood vessels and increases in
numbers with minimal perivascular cell proliferation.
Different forms of calcification are usually encountered in
MA. Our patient 1 showed the arrangement of concentric
lamination of calcific concretions. Similar changes were
also recorded in previous reports, termed fibro-osseous,
fibrocalcifying component or focal bony metaplasia.22–27 So,
the histopathological feature of patient 1 suggested MA
with a predominant fibrocalcifying formation. Our cases
indicated that the morphological changes of the MA
lesions were variable. Depending on the age of the lesion,
we consider that MA might be divided into three types,
predominantly cellular type, vascular type and fibrocalcify-
ing type.

The histopathological diagnosis of MA depends on its
localization, size, and the chronicity of the lesion.11,14,22
Many cases showed proliferating perivascular cells infil-
trating the cortex in association with marked cellularity
and reactive gliosis. Unless the pathologist is familiar with
the histopathological features of MA, these features may
lead to an erroneous diagnosis. The histopathological
differential diagnoses include meningiomas with cortical
invasion, vascular malformation and gliomas. Meningio-
mas exhibit a predominance of meningothelial cells and do
not have the pronounced vascularity seen in MA. An angi-
omatous meningioma contains numerous mature blood
vessels with meningothelial cells in varying proportions,
but neurons and glial cells are absent. An apparent menin-
gothelial component may raise suspicion of an atypical or
anaplastic meningioma with cortical invasion, but a lack
of cellular atypia, mitotic activity, necrosis and cortical
destruction favor MA. Vascular malformation tends to
bleed, which is an extremely rare feature of MA since the
lesion is firm due to the presence of a variety of mesenchy-
mal and neural elements.28,29 The presence of small-sized
vessels, their uniform distribution, lack of hemorrhage,
normal intervening tissue, associated spindle-cell prolifera-
tion and superficial location should preclude diagnosis of
vascular neoplasms. The elongated, spindly cells may be
mistaken for astrocytes. Furthermore, prominent endothe-
lial proliferation might result in an erroneous diagnosis of
a high-grade glioma. However, the absence of the typical
‘copper wire’ appearance of astrocytic fibrils and glomer-
uloid vessels and the presence of neurons within the lesion
should preclude that diagnosis. On the other hand, we
should pay great attention to recent reports concerning
MA coexisting with meningioma, oligodendroglioma and
vascular malformation.30–38

The origin of the MA lesion is not clear. Basically, it
was considered a hamartomatous proliferation of menin-
gothelial cells, blood vessels and fibroblasts in variable
proportions.11,29 Foci of meningothelial hyperplasia are
known to appear in the context of von Recklinghausen's
disease,40 and this could be a plausible origin for those
cases of MA associated with neurofibromatosis. On the
other hand, the observation of abnormal local vasculariza-
tion in some cases has led several authors to regard MA
simply as a vascular malformation with added meningo-
thal reaction.33 However, recent immunohistochemical
studies did not support a meningothelial origin for the
perivascular cells, but suggest that pluripotent cells may
differentiate into various cell types found in MA.12,15,41–43
Immunohistochemistry has limited diagnostic value as
staining patterns vary among MA cases. Our immu-
nohistochemical results parallel those in the literature. Only
vimentin, as a non-specific marker of the mesenchymal cell
was consistently positive. EMA expression, as a marker
for arachnoid cap cells was noted in two of the five cases.
These findings indicated that perivascular mesenchymal
components, such as fibroblasts and perivascular connec-
tive tissue might be playing an important role in the patho-
genesis of MA.

Neurofibrillary tangles have been described in a wide
spectrum of diseases and are seen in the setting of degen-
eration within neuronal cytoplasm. These changes were
identified in only one of our five cases. In the largest
reported series of MA, Halper et al.13 described the pres-
ence of NFT within cortical neurons in five of their six
reported cases. Only rarely have tangles been noted by
others in the literature.12,41,44 Therefore, Halper and his
colleagues hypothesized that the presence of NFT in
MA more likely represented a secondary degenerative
phenomenon rather than an intrinsic component of the
lesion.13 Finally, the diagnosis of MA is important since it
is a hamartomatous condition that presents as a mass-
occupying lesion within the cortex. It should be considered
in differential diagnosis of intracortical lesions, especially
in children and young adults. The superficial location,
perivascular cuffs of spindle-cell proliferation with variable
involvement of the overlying leptomeninges and calcifica-
tion, and small plump vessels, should clinch the diagnosis.
It is important to make a correct diagnosis in order to avoid
further aggressive treatment.

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