RESEARCH ARTICLE

Insights into Meningioangiomatosis with and without Meningioma: A Clinicopathologic and Genetic Series of 24 Cases with Review of the Literature

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Meningioangiomatosis (MA) is a rare seizure-associated lesion of presumed hamartomatous or developmental origin. It is occasionally combined with a neoplasm, most commonly meningioma (MA-M). In the current study, we examined 24 cases (14 pure MA, 10 MA-M) using immunohistochemistry for merlin, protein 4.1B, progesterone receptor (PR), and MIB-1, as well as FISH for *NF2* and *4.1B* gene dosages. Nine cases of MA-M (90%) had gene deletions (*NF2/4.1B*), protein losses (merlin/protein 4.1B), and/or PR positivity, with a similar or identical phenotype in both components. No PR positivity or gene deletions were seen in pure MAs, though merlin and/or protein 4.1B were immunonegative in six cases. Our data suggest that in most MA-Ms, the MA component is neoplastic, likely representing an exuberant perivascular pattern of spread from the meningioma, rather than an underlying hamartoma. This pattern of spread may be facilitated by meningiomas that are predominantly leptomeningeal or intracerebral in origin. It remains important to distinguish this pattern from true brain invasion, given the more ominous prognostic significance of the latter. In contrast, most perivascular spindled cells of pure MA are genetically and immunohistochemically similar to non-neoplastic meningothelial cells, consistent with current histogenetic theories.

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INTRODUCTION

Meningioangiomatosis (MA) is a rare entity characterized by a plaque-like, cerebral hemispheric mass, most often involving the temporal and/or frontal lobes. It was first described by Bassoe and Nazum in 1915 (4) and later named by Worster-Drought and colleagues in 1937 (85). There is a male predominance and to date, there have been roughly 90 cases reported (1, 2, 4-7,9, 11-14, 16, 17, 20, 21, 23, 24, 27-30, 33, 34, 36-38, 40, 41, 43, 44, 48, 49, 51, 53-58, 63-65, 67, 68, 70, 71, 74, 76, 77, 79-81, 83, 85). Histologically, MA consists of an intracortical and leptomeningeal collection of small blood vessels with perivascular spindled cells and variable degrees of cellularity, hyalinization, calcification, and even ossification. The intervening glioneuronal parenchyma appears mature but apparently disorganized. Reactive gliosis varies. Entrapped cortical neurons may show neurodegenerative changes, such as neurofibrillary tangles, granulovacuolar degeneration, and Pick-like bodies. Occasionally, neurons may appear slightly enlarged or dysmorphic, though frank cortical dysplasia is rare. Both

Parameter	MA-NF2 (N=14)	MA-Sporadic (N=86)	MA-M (N=27)
Patient Age (Years)	15-43 (Median 25)	0.8-71 (Median 17)	0.8-58 (Median 20)
Gender (M:F ratio)	2.3	1.9	5.5
Presentation			
Seizures	0%	81%	68%
Incidental	93%	4%	11%
Location			
Frontal	55%	47%	60%
Temporal	27%	47%	35%
Parietal	45%	23%	5%
Occipital	9%	7%	5%
Side of Brain			
Right	100%	62%	56%
Left	25%	46%	50%
Number of Lesions			
Single	57%	94%	100%
Multiple	43%	6%	0%

Table 1. *Comparison of published MA cases including current study.*

Case	Age	Sex	Site	NF2	PR	MIB1	Merlin	4.1B	*NF2*	*4.1B*
1 MA	25	M	NS	No	-	ND	+	+	N	N
NG					-		+	+	N	N
2 MA	27	M	L FL	No	-	ND	+	+	N	N
NG					-		+	+	N	N
3 MA	NA	M	NS	No	-	1.1%	+	+	N	N
NG					-	0	+	+	N	N
4 MA	19	M	R TPL	No	-	0.1%	+	+	N	N
NG					-	0	+	+	N	N
5 MA	12	M	R TL	No	-	0.2%	-	-	N	N
NG					-	0	+	+	N	N
6 MA	6	M	L FL	No	-	ND	+	+	N	N
NG					-		+	+	N	N
7 MA	4	M	R FL	No	-	0	-	-	N	N
NG					-	0	+	+	N	N
8 MA	23	M	NS	No	-	0	-	+	IND	IND
NG					-	0	+	+	IND	IND
9 MA*	26	M	L TL	No	-	0	-	-	IND	IND
NG					-	0	+	+	IND	IND
10 MA*	38	F	R TPL	Yes	-	0	+	+	IND	IND
NG					-	0	+	+	IND	IND
11 MA	18 mo.	F	L TL	No	-	3.4	ND	ND	N	N
NG					-	0.4			N	N
12 MA	22	F	R TL	No	-	1.8	ND	ND	N	N
NG					-	0.3			N	N
13 MA	17	M	R FL	No	-	0.7	-	-	N	N
NG					-	3.2	+	+	N	N
14 MA	37	M	FL	Yes	-	ND	-	-	IND	IND
NG					ND		+	+	IND	IND

Table 2. *Immunohistochemical and FISH results in cases of meningioangiomatosis.* M = meningioma, MA = meningioangiomatosis, NG = entrapped neuroglial cells within the MA, Age is in years, unless otherwise indicated, mo. = months, NA = not available, M = male, F = female, R= right, L = left, FL = frontal lobe, TL = temporal lobe, TPL = temporoparietal lobe, NS = cerebral, not specified, ND = not done, Del = deletion, N = normal (not deleted), IND = indeterminate, * Cases 9 and 10 were previously reported as cases 1 and 2 in (20).

sporadic and neurofibromatosis 2 (NF2)-associated forms of MA are recognized. The former accounts for roughly 75% to 80% of cases, is usually solitary, and most often comes to clinical attention due to seizures. The latter is often multifocal and is typically asymptomatic, with most cases identified as incidental autopsy findings. Given that both forms involve neocortex, it is unclear why NF2-associated cases lack the seizure association so common in the sporadic form. Electrophysiological studies in patients with sporadic MA show that epileptogenic activity may arise from the lesion itself, perilesional cortex, and/or a remote cortical site. This explains why the seizures are not always cured by removal of the MA alone (81).

The nature of MA remains unresolved. A developmental, dysplastic, hamartomatous, or reactive etiology is favored based on its typically benign clinical course and lack of significant proliferative activity in most cases. The histogenesis of the perivascular spindled cells is somewhat elusive. The occasional presence of Verocay-like bodies, lack of significant epithelial membrane antigen (EMA) positivity, and variable staining for actin, S-100 protein, and/or CD34 immunoreactivities in some cases have led to speculations that the perivascular cells arise from Schwann cells, fibroblasts, pericytes, or primitive progenitor cells. However, as the name implies, a meningothelial origin is favored, based on the presence of focal whorls or nests, epithelioid cytology, psammoma bodies, EMA expression, and/or classic meningothelial ultrastructure. The shared predisposition of NF2 patients to both meningiomas and MA also supports a meningothelial derivation. Lastly, a histologic pattern resembling that of MA may be seen adjacent to other lesions, including arteriovenous malformation (AVM), oligodendroglioma, encephalocele, cystic encephalomalacia, and cortical dysplasia (20, 30, 44, 65, 80, 81). Nonetheless, the most common association has been with meningioma (MA-M); 17 cases have been reported (7, 8, 15, 25, 30, 31, 39, 46, 50, 52, 73, 84). The leading hypothesis to explain this concurrence is that the meningiomas arise from neoplastic transformation of perivascular meningothelial cells within the MA component (8, 52). Alternatively, the MA pattern may represent cortical perivascular spread of an overlying meningioma (60, 73). Recent studies suggested the possibility that MA may be neoplastic in nature. Although the largest genetic series to date found no *NF2* gene mutations in 12 sporadic cases of MA (74), an example with *NF2* loss of heterozygosity (LOH) was recently reported (77). Similarly, *NF2* deletion was recently reported in both elements of an MA-M (73). In the current study, we explored 24 pure MA and MA-M specimens using immunohistochemistry and fluorescence in situ hybridization (FISH) to screen for proliferative activity and alterations associated with meningioma tumorigenesis, including progesterone receptor expression, loss of merlin and protein 4.1B expression, and deletions of the *NF2* and *4.1B* genes. To our knowledge, this series represents the largest clinicopathologic and genetic study to date. Our data support the hypothesis that most cases of MA are non-neoplastic, whereas most examples of MA-M represent perivascular spread of the meningioma along Virchow-Robin spaces, rather than neoplastic transformation of MA. Therefore, MA likely represents a distinct diagnostic entity in some situations and a histologic mimic of MA in others.

MATERIALS AND METHODS

Patient/tumor cohort. All available surgical and autopsy pathology slides from cases previously diagnosed as meningioangiomatosis were retrieved from the authors' in-house and consultation files, including those associated with adjacent meningio-

mas. Archival paraffin blocks or previously cut unstained paraffin sections were utilized for additional immunohistochemical and fluorescence in situ hybridization (FISH) studies. Sections were cut at 5 µm onto positively charged slides. Existing clinical, radiology, and pathology reports were reviewed in accordance with local Institutional Review Board guidelines at each individual medical center and gross pathology and radiographic images were retrieved in selected cases, where they were available. All slides were reviewed and meningiomas were classified and graded according to 2000 World Health Organization (WHO) criteria (45). The diagnosis of neurofibromatosis type 2 (NF2) was based on current NIH criteria (18).

Immunohistochemistry. Immunohistochemical studies were performed as previously published (19, 59, 61) using a Dako autostainer® (Carpinteria, Calif). Noncommercial affinity purified rabbit polyclonal antibodies against merlin (WA30) and protein 4.1B (3A1; previously referred to as DAL-1) were each applied at a 1:500 dilution (19, 59, 61). Antigen retrieval was achieved using 0.4% pepsin in 0.01 N HCl for 30 minutes at 37°C. Commercially available monoclonal Ki-67 (MIB-1; Dako, 1:80 dilution) and progesterone receptor (PR) antibodies (PR88; BioGenex, San Ramon, Calif; 1:500 dilution) were also applied after utilizing microwave antigen retrieval for 8 minutes in EDTA buffer (pH 8.0, 1.0 mM). Tumors were considered positive when neoplastic cells displayed nuclear staining for PR or cytoplasmic staining for merlin or protein 4.1B. For the latter 2 stains, brain parenchyma and cortical neurons provided an internal positive control. MIB-1 proliferative indices were expressed as percent staining and based on manual counts of 1000 nuclei in regions of greatest tumoral staining. All immunostains were separately scored in regions of meningioma (if present), perivascular spindled cells within the meningioangiomatosis, and intervening neuroglial tissue.

FISH. FISH was performed as previously published (61). Sections were deparaffinized, steamed in 10-mM citrate buffer, pH 6.0, and pepsin digested. Paired cosmid clones localizing to the *NF2* gene on 22q12.2 (n3022 and n24f20, UK HGMP Resource Centre, *http://www.hgmp.mrc.ac.uk*; gift from Dr Mia MacCollin, Massachusetts General Hospital, Boston, Mass) were directly labeled with rhodamine using nick translation. A P1 clone localizing to the *4.1B* region on 18p11.3 (gift from Dr Irene Newsham, Henry Ford Hospital, Detroit, Mich) was similarly labeled with fluorescein. Paired *NF2/4.1B* probes were diluted (1:25) in DenHyb buffer (Insitus; Albuquerque, NM), applied to each slide, and co-denatured with the target DNA at 90°C for 13 minutes. Hybridization was carried out via overnight incubation at 37°C in a humidified oven. The following day, the slides were washed with 50% formamide/1× SSC, followed by 2 washes in 2× SSC for 5 minutes each. Nuclei were counterstained with DAPI and fluorescent signals were enumerated under an Olympus BX60 fluorescent microscope with appropriate filters (Olympus; Melville, NY). For each hybridization, 100 non-overlapping nuclei were assessed for numbers of green and red signals. Cutoffs for *NF2* and *DAL-1* deletions were each set at 50% nuclei with one signal (mean plus 3 standard deviations for non-neoplastic control nuclei with one signal). Hybridizations were considered non-informative if the FISH signals were either lacking or too weak to interpret. All FISH signals were scored in separate regions of meningioma (if present), perivascular spindled cells within the meningioangiomatosis, and intervening neuroglial tissue.

Case	Age	Sex	Site	NF2	PR	MIB1	Merlin	4.1B	*NF2*	*4.1B*
15 M	28	M	L TL	No	-	0.8%	+	+	Del	Del
MA					-	0.1%	+	+	Del	Del
NG					-	0	+	+	N	N
16 M	17	M	FL	No	-	ND	+	-	IND	IND
MA					-		+	-	IND	IND
NG					-		+	+	IND	IND
17 M	20	F	R TL	No	-	3.1%	-	-	N	Del
MA					-	0.6%	-	-	N	N
NG					-	0	+	+	N	N
18 M*	9 Mo.	M	NS	No	-	6.2%	+	-	Del	N
MA					-	4.1%	+	-	Del	IND
NG					-	0	+	+	N	N
19 M*	16	M	NS	No	-	4.6%	+	-	Del	N
MA					-	2.1%	+	-	Del	N
NG					-	0	+	+	N	N
20 M	35	M	NS	No	-	ND	-	-	Del	Del
MA					-		-	-	Del	Del
NG					-		+	+	N	N
21 M	23	M	NS	No	-	ND	+	-	N	N
MA					-		+	-	N	N
NG					-		+	+	N	N
22 M	14	F	L TL	No	+	0.3%	-	-	N	N
MA					+	0.4%	-	-	N	N
NG					-	0	+	+	N	N
23 M*	16 mo.	M	L FL	No	-	2.6%	+	+	N	N
MA					-	0.7%	+	+	N	N
NG					-	0	+	+	N	N
24 M	7	M	L FL	No	Focal	7.1%	-	-	N	N
MA					-	1.2%	-	-	N	N
NG					-	0	+	+	N	N

Table 3. *Immunohistochemical and FISH results in cases of combined meningioma and meningioangiomatosis.* M = meningioma, MA = meningioangiomatosis, NG = entrapped neuroglial cells within the MA, *atypical meningioma component, Age is in years, unless otherwise indicated, mo. = months, M = male, F = female, R = right, L = left, FL = frontal lobe, TL = temporal lobe, NS = cerebral, not specified, ND = not done, Del = deleted, N = normal (not deleted), IND = indeterminate.

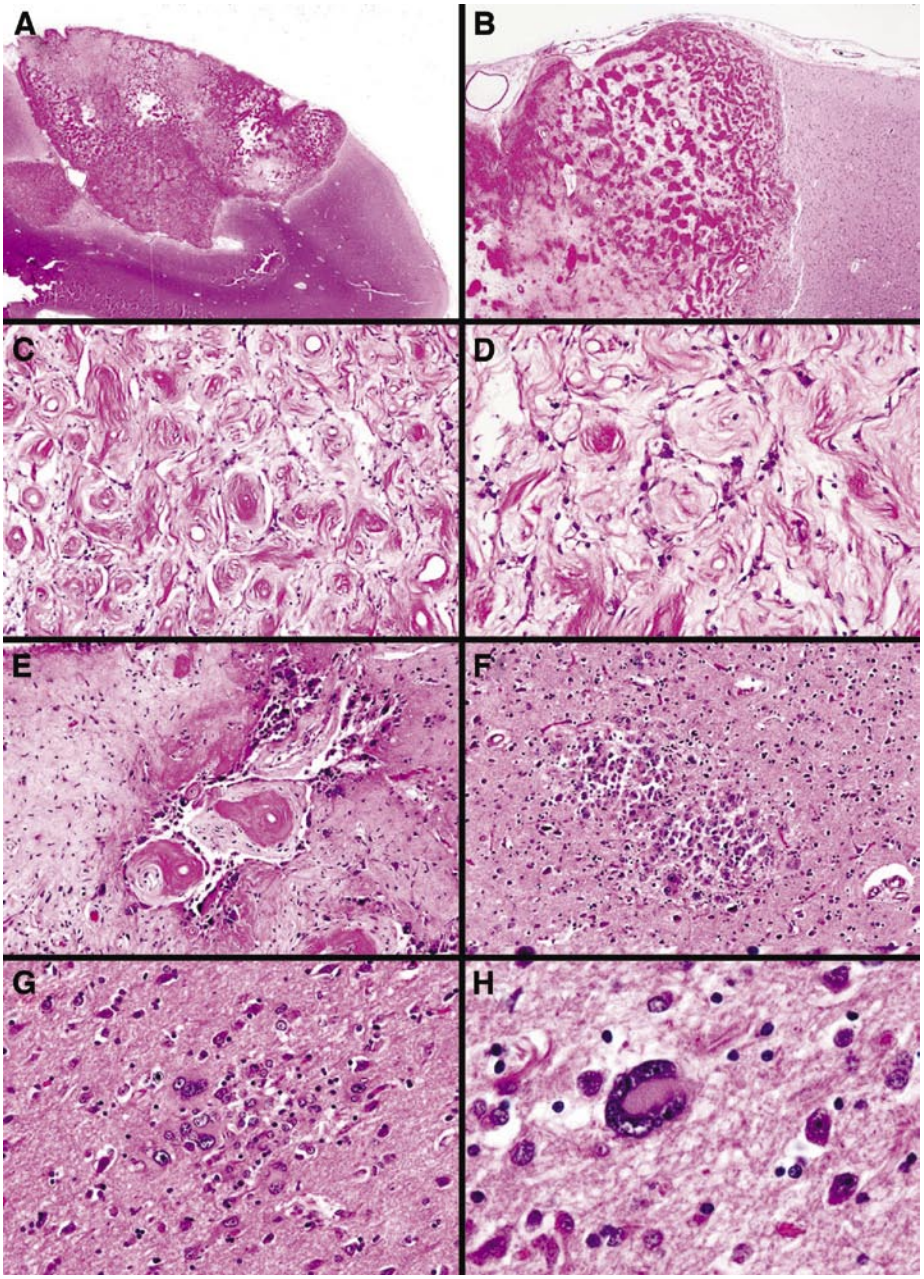

Figure 1. NF2-associated MA cases 10 (**A-D**) and 14 (**E-H**). The tumor involves leptomeninges and cortex (**A, B**), with extensively hyalinized vessels, scattered hyalinized whorls, and cords of small epithelioid or meningothelial-appearing cells (**C, D**). Unique to the NF2 cases was the presence of perilesional (**E**) and remote (**F-H**) glial microhamartomas forming microscopic nests of dysmorphic cells within the cortex.

Literature review. A search of the term meningioangiomatosis was performed using the Medline database from 1966 through July, 2004. The citations within those articles were further reviewed in order to obtain references published prior to 1966. Both text and figures were reviewed for diagnostic accuracy using current WHO criteria. A few of the cases previously included by some authors as examples of meningioangiomatosis were excluded from the current summary, based on features that suggested other diagnostic entities (eg, calcifying pseudotumor of the neural axis). The remainder were reviewed for demographic data, presence or absence of NF2, clinical presentation, location of disease, and multifocality.

RESULTS

Clinicopathologic features. The clinicopathologic features of 127 published NF2-associated MA, sporadic MA, and MA-M cases are summarized in Table 1, including 22 new cases from our study. The features of the 24 cases from the current series are further detailed in Tables 2 and 3. Our cases 9 and 10 had previously been reported as cases 1 and 2 in the study of Halper et al (20). A wide age range, as well as a predilection for children and young adults, was similar in all 3 categories of MA. NF2 patients were slightly older on average. The latter finding is almost certainly a bias introduced by the fact that the NF2 cases were detected at autopsy, rather than during life. All 3 categories also demonstrated a male predisposition, particularly in the combined MA-M group. All but one of the NF2-associated MA cases were asymptomatic and considered incidental autopsy findings. The single "symptomatic" 43-year old patient presented with headaches and drowsiness. Although reportedly an NF1 patient, few clinical details and no figures were provided (24). Therefore, the diagnosis in this case remains unclear. In contrast, sporadic MA cases were nearly always symptomatic, 81% presenting with seizures and most having a long history of epilepsy. Frontal or temporal cortex was most often involved. The right side was slightly favored in sporadic examples. This predilection was exaggerated in the 14 NF2-associated cases, many of which had multiple lesions. Nearly all the sporadic MA cases presented with a single lesion, whereas nearly half of NF2-associated lesions were multifocal.

Representative histologic features are illustrated in Figures 1 to 5. The MA pattern common to all 24 of our cases was that of intracortical and/or leptomeningeal hypervascularity with perivascular spindled cells exhibiting variable degrees of cellularity, hyalinization, and calcification. Both cases of NF2-associated MA exhibited a nodular, markedly fibrotic sulcal mass featuring peripheral cords of epithelioid-appearing cells (Figure 1A-D). The adjacent cerebral cortices were in part surrounded by glial microhamartomas (Figure 1E). In both cases, the latter were also evident in other neocortical regions and characterized by nests of enlarged, dysplastic-appearing neuroglial cells with irregular, sometimes multilobulated nuclei and variable quantities of amphophilic cytoplasm (Figure 1F-H). As in prior reports, these microhamartomas were limited to grey matter, mitotically active, and lacked the glassy eccentrically placed

eosinophilic cytoplasm of "balloon" cells encountered in tubers and focal cortical dysplasia.

The majority of sporadic MA cases consisted of plaque-like or gyriform, variably calcified and predominantly intracortical masses with focal leptomeningeal thickening (Figures 2, 3A). The lesions were either enhancing or non-enhancing, the radiographic differential often including diffuse glioma, ganglioglioma, and cortical dysplasia. Histologically, the MA varied greatly in terms of perivascular cellularity and hyalinization, most cases exhibiting a mixture of both (Figure 3A-E). Invariably, close inspection revealed entrapped ganglion cells and psammoma bodies (Figure 3E). Full blown meningothelial nests or whorls were encountered in only a minority of cases (Figure 3F). The intervening neuroglial tissue was markedly gliotic. In a subset of cases, neurons showed neurodegenerative features, such as granulovacuolar degeneration (Figure 3G) and neurofibrillary tangles (Figure 3H).

Cases of MA-M included a transition zone between the 2 components (Figure 4). Perivascular meningothelial nests resembling those of the adjacent meningioma were often evident at this site (Figure 4B). The meningiomas were mostly of the transitional subtype (7 cases), though there were 2 fibrous and one meningothelial tumors. Seven were considered histologically benign (WHO grade I) and three (cases 18, 19, and 23) qualified as atypical (WHO grade II), based on increased mitotic activity (4-6 per 10 high powered fields in all three), necrosis, hypercellularity, and macronucleoli (Figure 5A-B). No anaplastic (WHO grade III) meningiomas were encountered. The majority of the meningiomas were predominantly leptomeningeal-based with little to no dural involvement. Not surprisingly, it was often difficult to radiographically determine whether a lesion was intra-axial, extra-axial, or both. Two meningiomas were primarily intracerebral and in some areas, it was difficult to distinguish an extremely cellular MA pattern from an intracerebral meningioma with perivascular spread (Figure 5C-D). The latter interpretation was favored. All 10 cases also had areas that were indistinguishable from sporadic MA without associated meningioma (Figures 4, 5E-F).

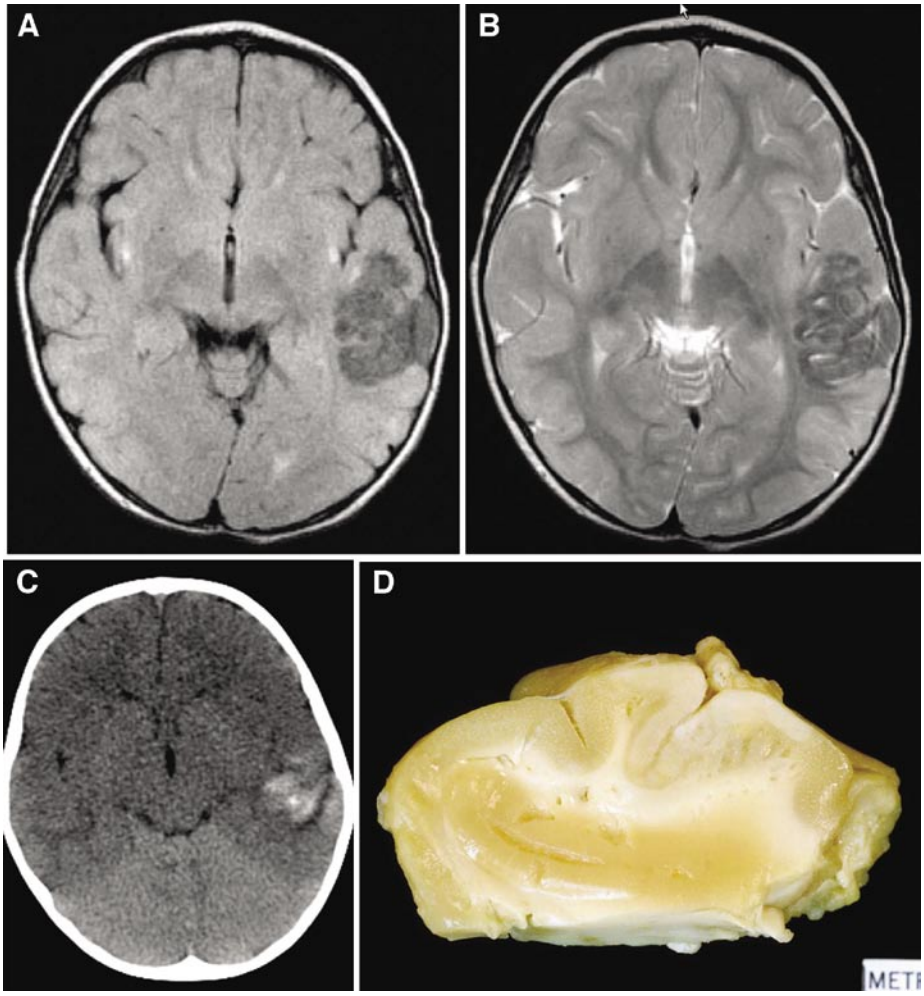

Figure 2. Neuroimaging studies in sporadic MA case 11 revealed a gyriform low-density left temporal lesion with calcifications (**A** = MRI-FLAIR, **B** = T2-MRI, **C** = CT). Case 9 was characterized by a pale, gritty intracortical lesion on cut surface (**D**).

Immunohistochemical and genetic features. The results of immunohistochemistry and FISH are summarized in Tables 2 and 3, with representative images in Figures 6 and 7. Progesterone receptor was negative in all cases of MA and was only positive in 2 of the 10 meningiomas.

As in prior studies (63), MIB-1 (Ki-67) labeling was either low (<2%) or completely negative in nearly all cases of pure MA examined. However, there were labeling indices as high as 3.4% in the perivascular spindled cells of case 11 and 3.2% in the intervening neuroglial tissue in case 13 (Table 2). In cases of MA-M, the labeling index was consistently higher in the meningioma than in the MA component, though there was always some degree of activity in the latter (Table 2; Figure 6A-B). Three meningiomas (cases 18, 19, and 24) had indices >4%, 2 of which were considered atypical (WHO grade II) by routine histology.

Six (50%) of 12 pure MA cases were immunoreactive for both merlin and protein 4.1B, whereas the perivascular spindled cells lacked expression in the other 6. Most of the latter were negative for both markers (Figure 6C-D), though case 2 was negative only for protein 4.1B (Table 2). In meningiomas, there were frequent (80%) losses of merlin and/or protein 4.1B expression (80%), with the corresponding MA component always showing the identical immunophenotype (Table 2; Figure 6E-H). The intervening neuroglial tissue was appropriately immunoreactive in all cases tested.

FISH analysis was informative in 19 (79%) of 24 cases. Most of the non-informative cases were performed on older slides or blocks (7-28 years in storage) and/or autopsy specimens, where the success rate is known to be reduced. No deletions were detected in pure MA (Table 2). In contrast, deletions of NF2 and/or 4.1B were found in 5 (56%) of 9 informative meningiomas

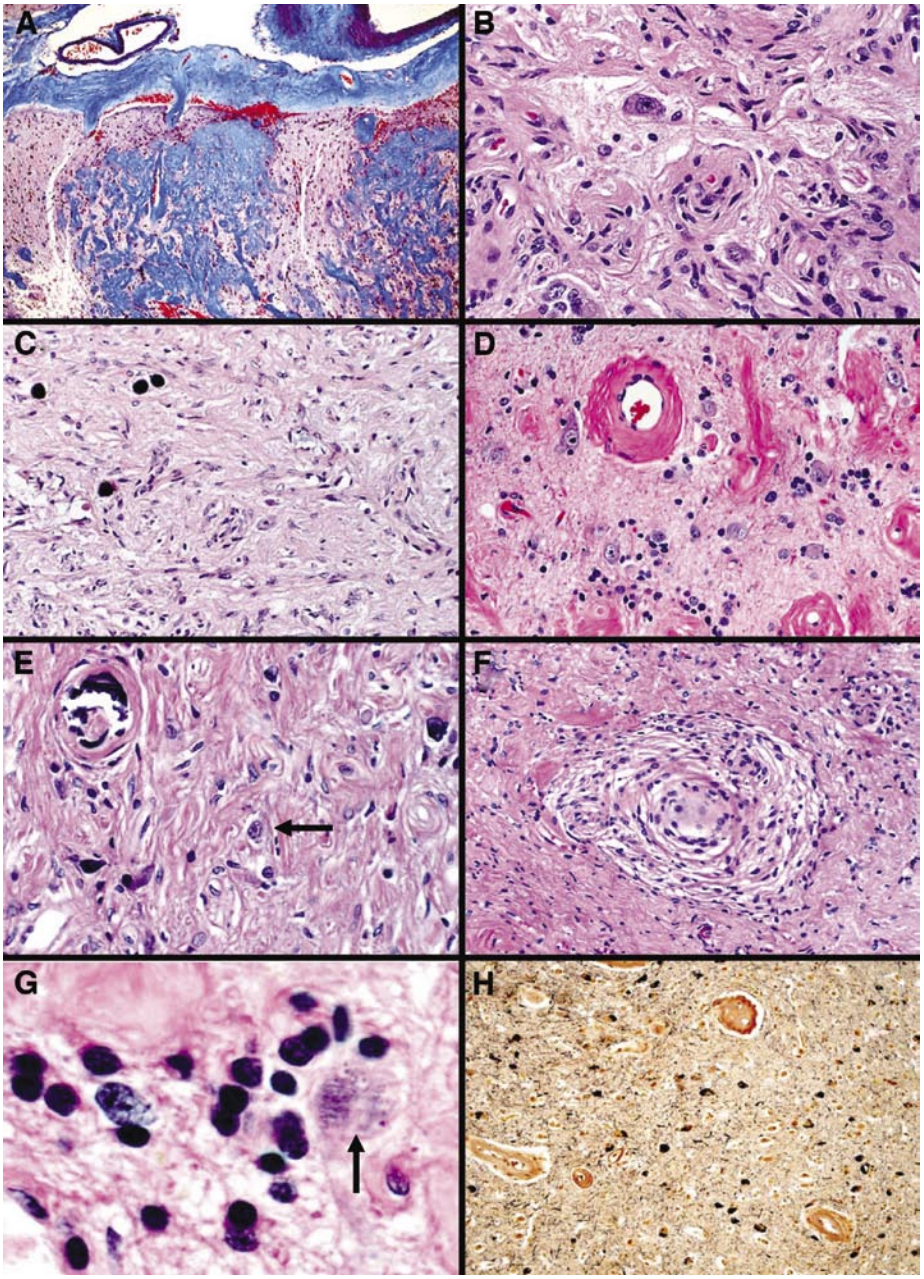

Figure 3. Representative light microscopic findings in sporadic MA from cases 13 (**A, D, G, H**), 11 (**B**), 3 (**C**), and 2 (**E, F**), including leptomeningeal and intracortical fibrosis by trichrome stain (**A**), perivascular spindled cells (**B**), psammoma bodies (**C**), hyalinized vessels (**D**), confluent "dura-like" zones of fibrosis with entrapped neurons (arrow) and scattered psammoma bodies (**E**), and meningothelial nests/whorls (**F**). Intervening cortical neurons showed neurodegenerative changes in a subset of cases, including granulovacuolar degeneration (**G**; arrow) and neurofibrillary tangles (**H**; Bielschowsky stain).

(Table 3; Figure 7). In all but one (case 17), the identical alterations were found in the MA component as well. No deletions were found in the neuroglial component of either MA or MA-M. In all, 9 (90%) cases of MA-M showed one or more meningioma-associated alterations. The remaining case was an atypical meningioma in a 16-month-old boy (case 23), which showed no detectable alterations by either immunohistochemistry or FISH.

DISCUSSION

Sporadic and NF2-associated MA are clinically and histologically distinct. The first cases of MA were reported in patients with neurofibromatosis (4-6, 85). Although initially considered a component of NF1, review of the clinical descriptions clearly showed them to be the central or NF2 form (74). Sporadic MA was not described until a half century later. Initially, it was believed that MA was so rare in the absence of NF2,

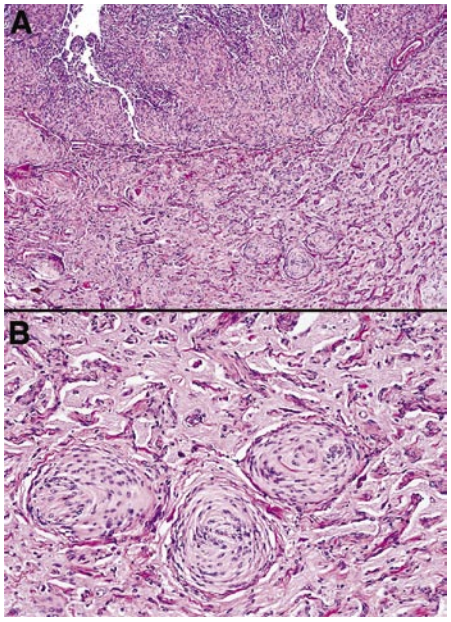

Figure 4. Transition zone in MA-M case 17 with the meningioma situated primarily in the leptomeninges and the typical cortical hypervascularity and perivascular spindled cells of MA below (**A**). Perivascular meningothelial nests resembling the adjacent meningioma were evident at higher magnification (**B**).

that the lesion represented a form fruste of the syndrome. However, the more recent literature has the opposite bias; the vast majority of patients lack features of NF2. Since sporadic lesions are encountered mainly in surgical specimens and NF2-associated cases are found at autopsy, the shift in the literature may simply reflect the changes in pathology practice over time. With the dramatic fall in autopsy rates, few pathologists today examine postmortem brains from NF2 patients. Therefore, the true incidence of this entity remains unclear. Nonetheless, Rubinstein found MA in 4 (36%) of 11 NF2 autopsy brains, suggesting that it may be considerably more prevalent in this population than was once thought (64). Of additional interest, all four of his cases had adjacent glial microhamartomas, and one additional case had these hamartomas in the absence of meningioangiomatosis (see discussion below).

Although NF2-associated and sporadic MA are often considered histologically identical, close inspection reveals some rather striking differences, evident in both published cases and in examples in our study. In general, the NF2-associated cases include cords of small epithelioid cells, and often, a nearly complete replacement of the

lesion by hyalinized scar tissue. The latter may simply reflect the fact that these lesions are identified at autopsy and may thus be "burnt out" at that point in time. Much more specific for the NF2 association is the presence of glial microhamartomas in perilesional cortex and at more remote cortical sites, as well as subcortical gray matter and even spinal cord. To our knowledge, this has never been described in sporadic MA or, in fact, in any other condition aside from NF2. In early reports, these dysplastic nests were likened to tubers and white matter lesions in the tuberous sclerosis complex (TSC). The glial microhamartomas do not, however, include classic "balloon" cells. Furthermore, in TSC and focal cortical dysplasia of the Taylor type, the dysplastic cells are most prominent at the corticomedullary junction and in subcortical white matter, rather than being limited to the cortex. These findings agree with the contention of Wiestler et al., that glial microhamartomas are pathognomonic of NF2, and their presence should be considered diagnostic of this disorder (82).

There are also clinical differences between NF2-associated and sporadic MA. All reported patients with NF2-associated MA have had other classic features of the syndrome. Nearly all have early onset of disease, bilateral vestibular schwannomas, multiple meningiomas, and death at a young age. Thus, most of these patients appear to have the more severe, Wishart variant of NF2 (3). Lastly, in contrast to the sporadic form of MA, NF2-associated MA is often multifocal, nonepileptogenic, and is an incidental autopsy finding. Despite their often extensive cortical involvement, it is unclear why neither the MA nor the glial microhamartomas of NF2 induce seizures. Nevertheless, there is clinical significance to these clinical and pathological differences. In contrast to pediatric meningiomas, which can be the presenting sign of NF2 (61), it is extremely unlikely that a child with seizure-associated MA unassociated with glial microhamartomas or other stigmata of NF2 will ever develop this syndrome. Thus, further study of the patient and screening of family members is probably not necessary.

Pure MA lacks neoplastic features in most cases. Based on the benign clinical behavior and lack of significant proliferative activity, pure MA has generally been considered a non-neoplastic lesion rather than an en plaque meningioma with extensive perivascular spread within Virchow-Robin spaces. Given the number of common clonal alterations occurring in meningiomas, this hypothesis is testable, though few genetic studies have been performed to date. Stemmer-Rachamimov et al. found no evidence of *NF2* gene mutations in 12 sporadic cases of MA (74). However, Takeshima recently reported an example with loss of heterozygosity (77). In the current study, we found no evidence of either *NF2* or *4.1B* deletions in 10 informative cases, further suggesting that the majority of pure MA cases are non-neoplastic. The presence of both merlin and protein 4.1B expression in half the cases supports both a non-neoplastic nature and meningothelial derivation of pure MAs. The lack of progesterone receptor positivity in these cases further support for this notion, since this marker is normally expressed in over half of benign meningiomas. More difficult to explain are the 6 cases lacking expression of merlin and protein 4.1B. Thus, the possibility of a neoplastic or preneoplastic form of MA with loss of expression in meningothelial cells cannot be entirely excluded. However, another potential explanation is that these cases are composed predominantly of fibroblasts or have been replaced by fibroblasts over time, since these cells do not normally express these markers. The fact that there was a lack of expression for both markers simultaneously in all 6 cases makes this possibility more probable, since there would be less chance that both genes would be inactivated in every example, none involving deletions as a contributing mechanism.

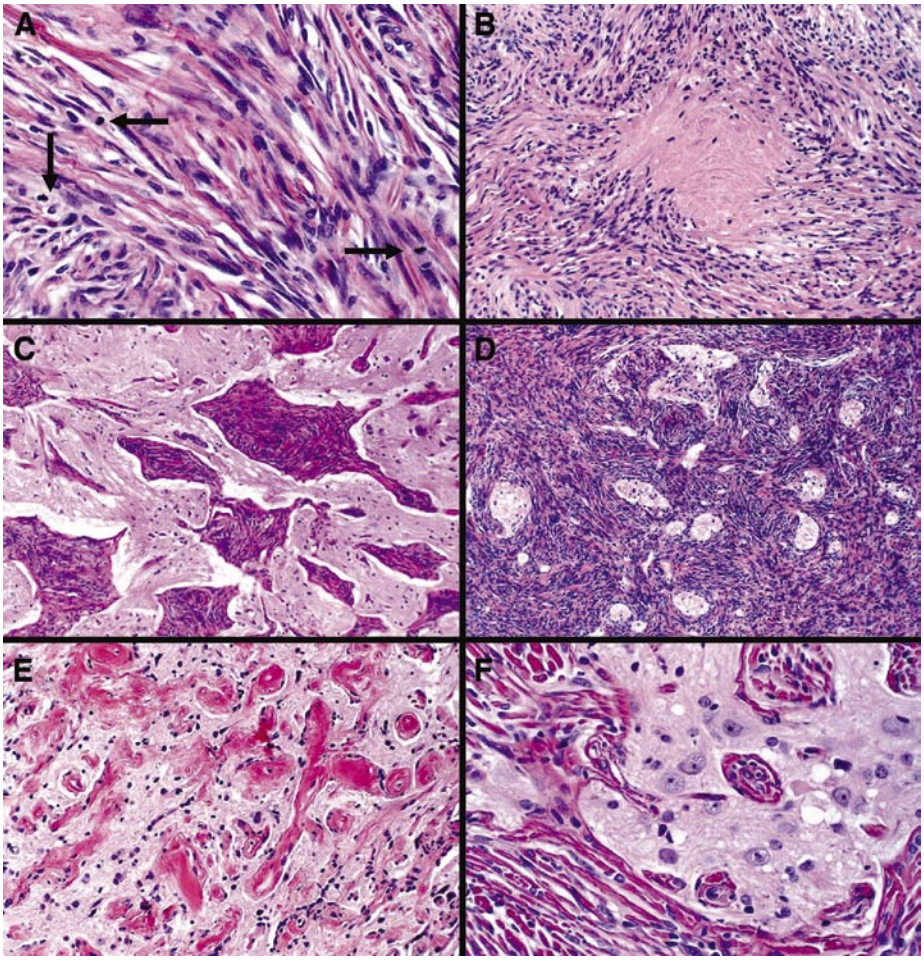

Figure 5. MA-M cases 19 (**A, F**), 18 (**B**), 21 (**C**), 20 (**D**), and 24 (**E**). Atypical meningiomas included frequent mitotic figures (**A**; arrows) and foci of necrosis (**B**). Two of the cases were intracerebral with increased cellularity in both the MA (**C**) and meningioma (**D**) components. As with the pure MA cases, there were often mixtures of nearly completely hyalinized vessels (**E**) and more cellular foci with perivascular spindled cells (**F**).

The MA component of MA-M is neoplastic in most cases. Based on the presence of

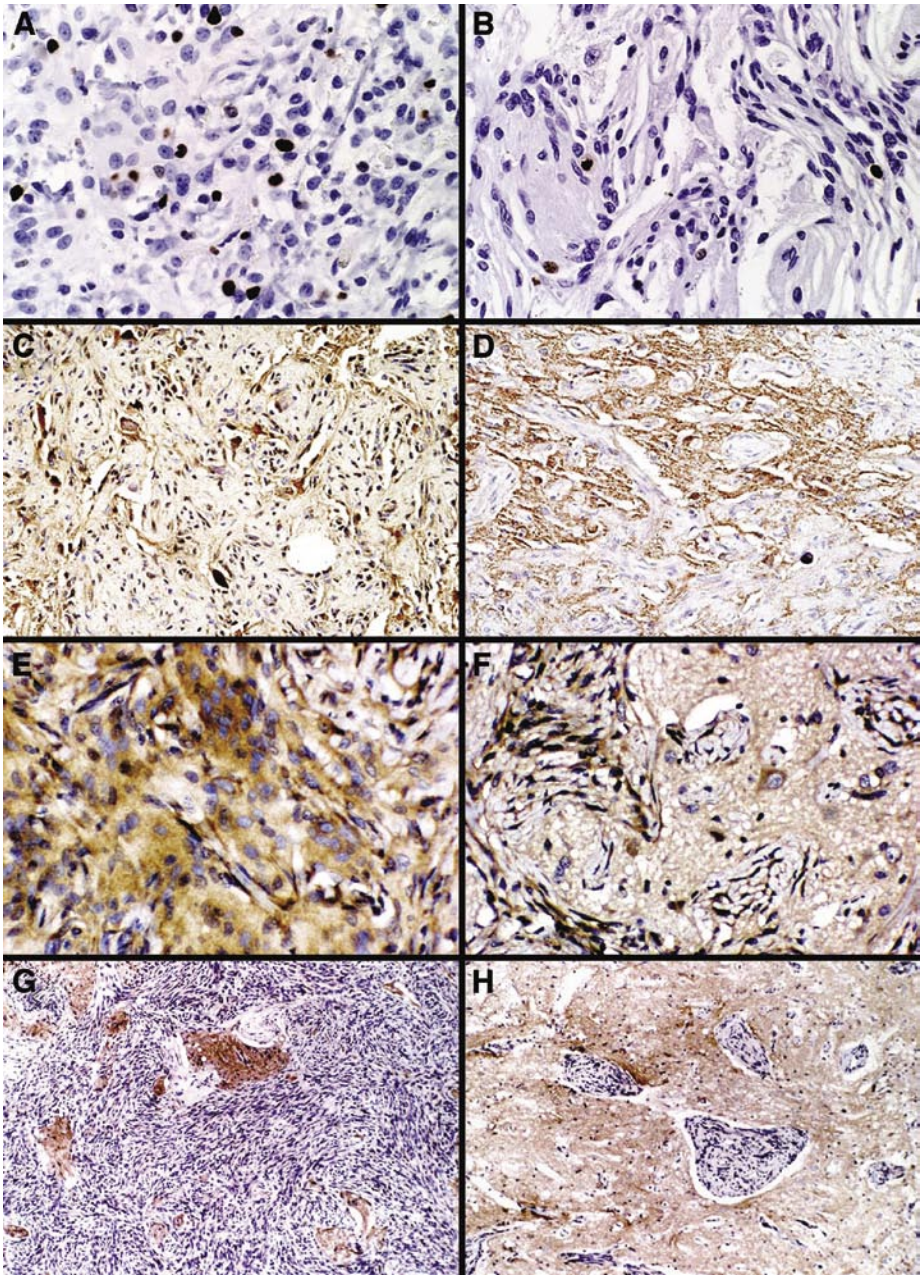

Figure 6. Representative immunohistochemical results. The MIB-1 labeling index was higher in the meningioma (**A**) compared with the adjacent MA (**B**) component of case 24. The spindled perivascular cells of MA in case 9 were negative for both merlin (**C**) and protein 4.1B (**D**), though the intervening neuroglial tissue was appropriately positive. MA-M case 19 showed retained merlin expression in both the meningioma (**E**) and MA (**F**) components. In contrast, case 20 showed loss of protein 4.1B expression in both the intracerebral meningioma (G) and adjacent MA (H) elements.

common meningioma-associated genetic alterations in nine of our ten MA-M cases and the fact that they were nearly always found in both components, our data supports the neoplastic nature of the perivascular cells in most MA-Ms. In other words, it supports the hypothesis that the meningioma simply spreads along perivascular Virchow-Robin spaces to create a MA-like pattern, rather than the more popular perception that a meningioma arose via transformation of a single cell within a pre-existing MA. Our results are similar to those of a recent case report demonstrating *NF2* deletion in both components of a MA-M (73). Even careful review of the routine histology supports this notion in that the transition zones commonly show perivascular nests that resemble the adjacent meningioma (see Figure 4). The mechanisms of inactivation are not entirely clear from our data, since there was not always good concordance for the status of individual genes at the DNA versus the protein levels. Nevertheless, this is similar to our experience with FISH and immunohistochemistry on conventional meningiomas as well (59). It suggests that some of the deleted chromosomal regions with intact expression may be targeting other genes, whereas losses of expression with intact DNA dosages may be due to other mechanisms of inactivation, such as mutations, small intragenic deletions, or hypermethylation of promoter regions.

The meningiomas in the current study differed from conventional ones in being primarily leptomeningeal rather than dura-based. This location may facilitate the MA-like pattern of tumor spread. This makes sense not only from an anatomic perspective, but also from the observation that MA-M predominates in the pediatric and young adult population in which meningiomas lacking dural attachment are relatively common (60). Interestingly, 2 of our MA-M cases were primarily intracerebral. Intracerebral meningiomas, with or without an MA-like component, have been previously reported but are extraordinarily rare (35, 42, 47, 52, 66, 69, 72, 75, 78). In the current cases, there was some overlap between MA-M and highly cellular MA alone (eg, Figure 5D). This was a difficult distinction at the time of diagnosis, though the degree of cellular accumulation was felt to be beyond that allowable for MA alone. In the current study, this interpretation was further supported by the presence of meningioma-associated alterations by immunohistochemistry and FISH. One potential explanation is that such intracerebral tumors arise from arachnoidal cap cells within the Virchow-Robin spaces and then spread peripherally in a pattern mimicking MA.

Confusion between MA and Brain invasion in pediatric and "sclerosing" meningiomas. In a prior study of MA-M in children and young adults, Giangaspero et al, stressed the excellent prognosis of these patients and cautioned against overinterpreting the MA pattern as evidence of brain invasion (15). The latter, once considered prima facie evidence of malignancy (WHO grade III) is now known to impart a similar risk of recurrence and death as atypical meningioma (WHO grade II) (62). The histologic pattern of MA differs considerably from the ragged tongue-like intracerebral protrusions of brain-invasive meningioma.

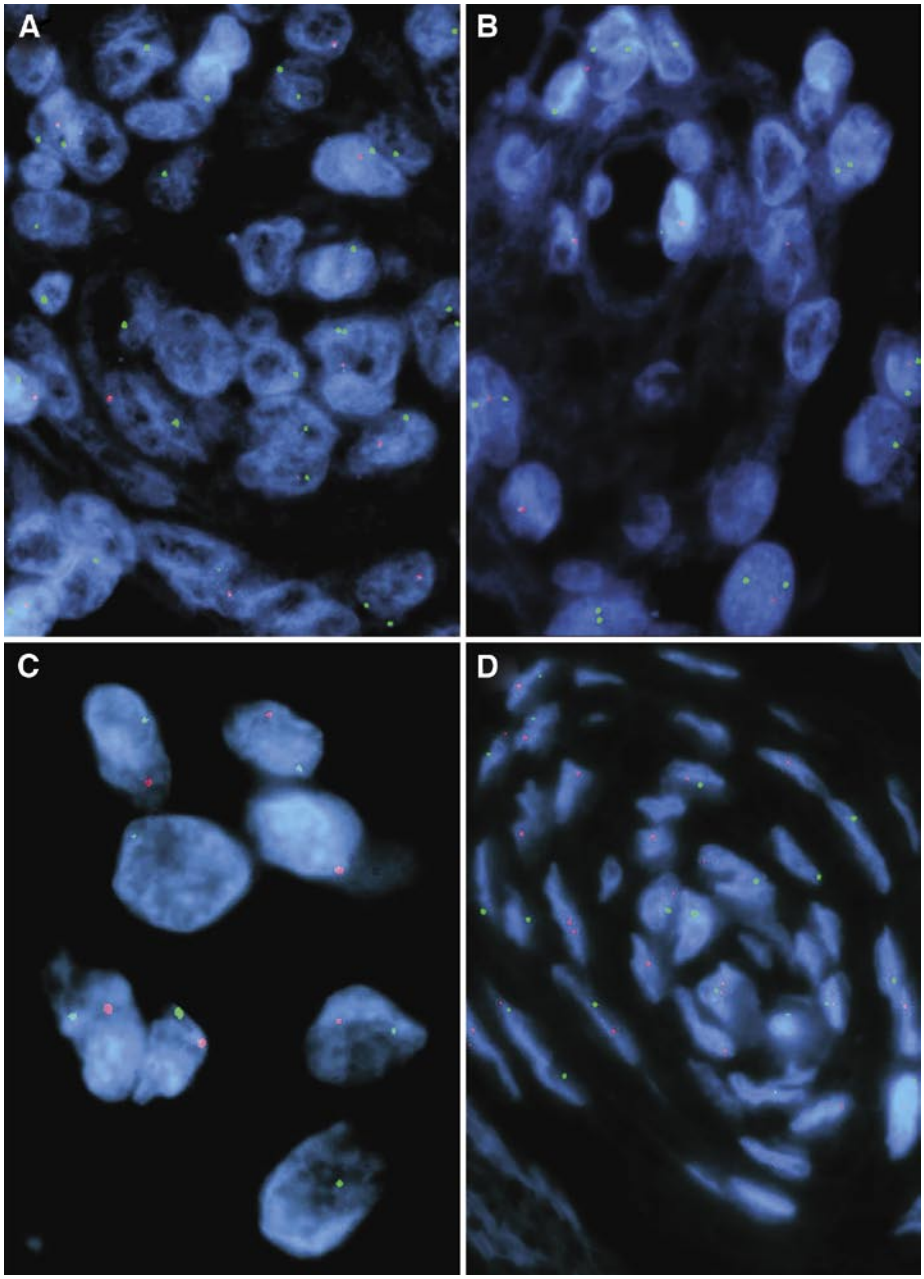

Figure 7. Representative FISH results. MA-M case 19 showed one red *NF2* and 2 green *4.1B* signals in the majority of nuclei from both the meningioma (**A**) and MA (**B**) regions, consistent with *NF2* deletion. MA-M case 15 had only one red and one green signal in the majority of nuclei from both the meningioma (**C**) and MA (**D**) components, consistent with deletion of both genes. The majority of intervening neuroglial cells showed two signals for each marker (not shown). Occasional signals are beyond the plane of focus and some nuclei have fewer than expected signals due to nuclear truncation.

Nonetheless, a review of the pediatric meningioma literature reveals several examples of MA mistaken as "brain invasion." One notable example is the "sclerosing variant" of meningioma (10, 22, 26, 31, 32). This mostly pediatric variant with a reportedly favorable prognosis despite frequent "brain invasion" has been defined by the predominance of hyalinized acellular tissue with discernable whorls. To some extent, this is highly reminiscent of the collagenized vessels encountered in MA and in fact, the authors' illustrations of brain invasion show a perivascular intracerebral pattern of spread, consistent with MA. Therefore, it is likely that at least some of these cases are examples of MA-M, rather than true brain invasive meningiomas. Kim et al similarly included one example of sclerosing meningioma in their series of five MA-M (31). Since meningiomas normally undergo variable degrees of fibrosis, additional experience is needed to determine whether or not the rare sclerosing meningioma should be considered a distinct variant and if so, how much hyalinization is required to make the diagnosis. Currently, it is not recognized as such by the WHO, and an example of the problem is illustrated in the study by Kim et al (32), wherein one sclerosing meningioma also showed features of the clear cell variant. Clear cell meningiomas often exhibit extensive collagenization (86), but they are considered WHO grade II lesions (45).

SUMMARY

The true nature of MA remains elusive. As our study showed, it represents both a specific, non-neoplastic process and a tumor pattern, wherein the meningioangiomatosis-like element shows the same genetic alterations as the overlying meningioma and apparently represents a form of perivascular tumoral spread. This pattern of spread may be facilitated by meningiomas that are predominantly leptomeningeal or intracerebral in location. Given prognostic differences, it remains important to distinguish simple MA pattern from true brain invasion in association with meningioma.

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