RESEARCH ARTICLE

Meningothelial Hyperplasia: A Detailed Clinicopathologic, Immunohistochemical and Genetic Study of 11 Cases

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Meningothelial hyperplasia is a poorly characterized entity, often associated with advanced age, chronic renal failure, trauma, hemorrhage, and neoplasia. In order to elucidate the nature of this lesion, 11 cases defined by the presence of nests of 10 or more cell layers thick, were compared with normal arachnoidal cap cells and meningiomas. Immunohistochemistry and FISH were performed to determine *NF2* (merlin), protein 4.1B, EMA, progesterone receptor (PR), EGFR, survivin, VEGF, PDGF-BB, PDGFR-β, E-cadherin, and cathepsin D status. All cases had at least one putative predisposing factor, including hemorrhage (7), chronic renal disease (5), old age (5), trauma (1), and an adjacent optic nerve pilocytic astrocytoma (1). There was typically a discontinuous growth pattern, with no invasion of surrounding normal tissue. No gene deletions were found, though scattered polyploid cells were seen in 2 cases. The immunoprofile was similar to normal cap cells with one exception; whereas normal cells were uniformly negative for PR, nuclear positivity was seen in 64% of hyperplasias, a frequency similar to that of benign meningiomas. Our data suggest that meningothelial hyperplasia is a reactive process that is usually distinguishable from meningioma based on clinicopathologic and genetic features. It may be preneoplastic in some, though further studies are needed to test this hypothesis.

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INTRODUCTION

Although not uncommonly encountered as an incidental surgical or autopsy finding, meningothelial hyperplasia represents a poorly characterized entity, and occasionally causes diagnostic difficulties due to its overlapping histologic features with meningioma. Furthermore, it is unclear whether this hyperplastic lesion represents a true precursor stage in meningioma tumorigenesis, though at least one recent animal model provides support for this hypothesis. By conditionally inactivating the neurofibromatosis 2 (*Nf2*) gene in meningothelial cells, Kalamarides and colleagues induced both meningothelial hyperplasia and meningiomas in roughly 30% of their mice (14). To our knowledge, the most recent studies focusing on human meningothelial hyperplasia were published more than 2 decades ago (3, 6, 19, 24, 25, 29) and no molecular studies have been performed to determine whether meningothelial hyperplasia shares biologic features with normal or neoplastic tissue.

In clinical practice, meningothelial hyperplasia has been reported in association with advanced patient age, chronic renal failure, trauma, hemorrhage, and neoplasia. In the setting of neoplasia, it may be particularly prominent adjacent to optic nerve pilocytic astrocytomas, where it has the potential to be misdiagnosed as an orbital meningioma (6, 24, 29). Other known meningeal-based reactive entities include granulation tissue/scar formation, inflammation, and vascular proliferation. In this regard, the enhancing dural tail at the margin of most meningiomas often consists of nothing more than hypervascular fibrous tissue (22). Further confusion may arise when small meningothelial nests are detected within a submitted "dural margin" of a resected meningioma, making it difficult to reliably distinguish normal or hyperplastic foci from tumor spread. Likewise, in cases of chronic intracranial hypotension, diffuse dural enhancement is associated with a thin subdural layer of granulation tissue, but may also include meningothelial hyperplasia (17). Similarly, we have encountered rare patients presenting with thin layers of meningeal enhancement of unknown etiology, wherein biopsy revealed thickened meninges with nests of arachnoidal cap cells. In these cases, it was difficult to distinguish hyperplasia from "meningothelial tumorlets" or meningioma *en plaque*. Such cases prompted us to re-examine the issue of meningothelial hyperplasia in greater detail using immunohistochemical and molecular techniques.

In previous studies, meningothelial hyperplasia has either not been specifically defined or was classified as meningothelial nests of 3 to 4 cell layers thick or greater (3, 19). However, since normal meningothelial clusters often exceed this limit (22), we chose a more conservative cutoff of 10 cell layers to examine the clinicopathologic features of 11 such cases. Many of the most common immunohistochemical and genetic markers used in the molecular diagnosis of meningioma were also applied (1, 4, 5, 7-13, 16, 18, 20, 21, 23, 26-28). We found that in contrast to meningiomas, hyperplastic meningothelial proliferation usually has recognizable inciting factors, typically grows in a multicentric pattern, and does not invade adjacent structures. Additionally, there was no evidence for deletions of either *NF2* or a related Protein 4.1 family member on chromosome 18, *4.1B* (previously designated *DAL-1* for "differentially expressed in adenocarcinoma of the lung"). Similarly, expression of merlin and protein 4.1B was always retained. However, meningothelial hyperplasia overlapped immunohistochemically with meningiomas in terms of progesterone receptor (PR) expression in 64% of cases. Chromosomal gains were also encountered in 2 cases. This was in contrast to normal cap cells that were uniformly

Antibody	Dilution	Source	City
PR	1:20	Biogenex	San Ramon, Calif
EMA	1:400	Dako Corporation	Carpinteria, Calif
Cathepsin D	1:40	Biogenex	San Ramon, Calif
E-cadherin	1:50	Zymed	San Francisco, Calif
PDGFR-β	1:50	R&D Systems	Minneapolis, Minn
PDGF-BB	1:20	R&D Systems	Minneapolis, Minn
Survivin	1:100	Alpha Diagnostics	San Antonio, Tex
EGFR	1:80	Zymed	San Francisco, Calif
VEGF	1:100	Zymed	San Francisco, Calif
Merlin (WA 30)	1:500	Homemade	St. Louis, Mo
Protein 4.1B (3A1)	1:500	Homemade	St. Louis, Mo

Table 1. Antibody dilutions and sources.

Case	Age	Sex	Location	Other Medical Conditions
1	7	M	Optic sheath	Adjacent pilocytic astrocytoma of optic nerve
2	4	M	Choroid plexus	Ventriculoperitoneal shunt obstructed by choroid plexus (ie, presumed to be traumatized), aqueductal stenosis, cerebral palsy
3	83	F	Choroid plexus	Thrombotic thrombocytopenic purpura, hypertension, nephrosclerosis, cardiomegaly, prior intracerebral hemorrhage and cerebral infarcts
4	40	F	Choroid plexus	Adjacent intraventricular hematoma, asthma, degenerative joint disease, syncope, migraines
5	71	F	Convexity	Adjacent subdural hematoma, hypertension, Parkinson's Disease, atrial fibrillation, diabetes
6	51	F	Sella turcica	Sickle cell disease, pulmonary infarcts/hypertension, cardiomegaly, nephrosclerosis, hepatitis C
7	84	M	Convexity	Adjacent subdural hematoma, cerebral infarct, bladder carcinoma
8	36	F	Base of brain	Adjacent subarachnoid hemorrhage, lupus, hypertension, cardiomegaly, pulmonary hypertension, nephrosclerosis with end-stage renal disease, cardiac cirrhosis
9	89	F	Sella turcica	Hypertension, cardiomegaly, nephrosclerosis, diabetes, coronary artery disease, cerebral infarct, pulmonary emboli
10	15	F	Temporal lobe	Adjacent subarachnoid hemorrhage and arachnoid cyst
11	94	F	Convexity	Adjacent subarachnoid hemorrhage and cerebral infarct, cardiomegaly, myocardial infarct, hypertension, nephrosclerosis, pseudomembranous colitis

Table 2. Summary of meningothelial hyperplasia cases.

negative for PR and showed no chromosomal abnormalities. Collectively, our data support the notion that meningothelial hyperplasia is a reactive process that is usually distinguishable from meningioma, but one that potentially may also represent a preneoplastic precursor in some.

MATERIALS AND METHODS

Study cases. Eleven examples displaying one or more microscopic foci of meningothelial nests of less than 10 cell layers thick were identified from tissue specimens removed for other reasons and encountered routinely by a single neuropathologist (AP) over roughly a 2-year period. Six specimens containing unremarkable arachnoidal cap cells from various sites were also obtained as a normal control group. These included 2 arachnoid mater strips from cerebral convexity (42-year-old male and 53-year-old male), 2 arachnoid granulation-rich dural strips from the parafalcine region (43-year-old male and 66-year-old female), and 2 tela choroidea-containing choroid plexus specimens from the lateral ventricles (17-year-old female and 82-year-old male). A second comparison group consisted of a tissue microarray with 41 meningiomas, including 8 incidental, 5 benign (WHO grade I), 18 atypical (grade II), and 10 anaplastic (grade III) meningiomas, recently studied with many of the same antibodies (16). For comparisons with merlin and 4.1B immunohistochemistry, as well as *NF2* and *4.1B* fluorescence in situ hybridization (FISH), data from 2 prior studies using the same antibodies and probes were utilized (20, 21). All studies were performed on formalin-fixed paraffin-embedded tissue cut at 5 micron thickness.

Immunohistochemistry. Immunohistochemical studies were performed and interpreted as previously published (9, 16, 20), with antibody sources and dilutions outlined in Table 1. Slides were deparaffinized with xylene, rehydrated with alcohol, and most were subjected to antigen retrieval by boiling for 8 to 10 minutes in 10-mM citrate buffer. Progesterone receptor (PR) was subjected to EDTA buffer antigen retrieval and epithelial growth factor receptor (EGFR) underwent 8 minutes of Pronase treatment. Antigen retrieval for the non-commercial, affinity purified rabbit polyclonal antibodies, merlin (WA30) and protein 4.1B (3A1) was achieved using 0.4% pepsin in 0.01 N HCl for 30 minutes at 37°C (9, 20). Slides were stained using a Dako autostainer (Carpinteria, Calif) with DAB as the detection chromogen, with the exception of survivin, detected using an ABC kit by Vector Laboratories (Burlingame, Calif) with DAB as the chromogen. All slides were counterstained with hematoxylin, dehydrated, cleared, and mounted. Omission of the primary antibody was used as a negative control and appropriate positive controls were utilized as recommended

by the manufacturers for the commercial antibodies. For merlin and 4.1B, mouse brain was used as a positive control.

Fluorescence in situ hybridization (FISH). FISH was performed and interpreted as previously published (21). 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) 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 isothiocyanate (FITC). Commercial probes against BCR on 22q11.2 (labeled in SpectrumGreen) and CEP18 (chromosome 18 centromere enumerating probe; labeled in SpectrumOrange) were also utilized (Vysis, Inc., Downers Grove, Ill). Paired *NF2/BCR* and *CEP18/4.1B* 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 overnight 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 meningothelial nuclei were assessed for numbers of green and red signals.

RESULTS

Patient cohort. Clinical data from the 11 patients with meningothelial hyperplasia are summarized in Table 2. Six were derived from surgical and 5 from postmortem specimens. Patients ranged in age from 4 to 94 years of age, though there were clusters at the 2 extreme ends of the spectrum, including 3 pediatric (4-15 years old) and 5 elderly (71-94 years old) patients. There were 8 female and 3 male patients, yielding a 2.7:1 ratio. All patients had at least one previously described predisposing or inciting factor, including hemorrhage (7), chronic renal disease (5), advanced age (5), trauma (1), and an adjacent optic pathway glioma (1). Additionally, hypertension, cardiomegaly, and arteriolar nephrosclerosis were encountered in 5 cases each, likely being interrelated in most of these cases. Cerebral infarcts were also common, identified in 4 of the cases. The meningothelial hyperplasia was most often seen in the convexity (3), choroid plexus (3), and sella turcica (2).

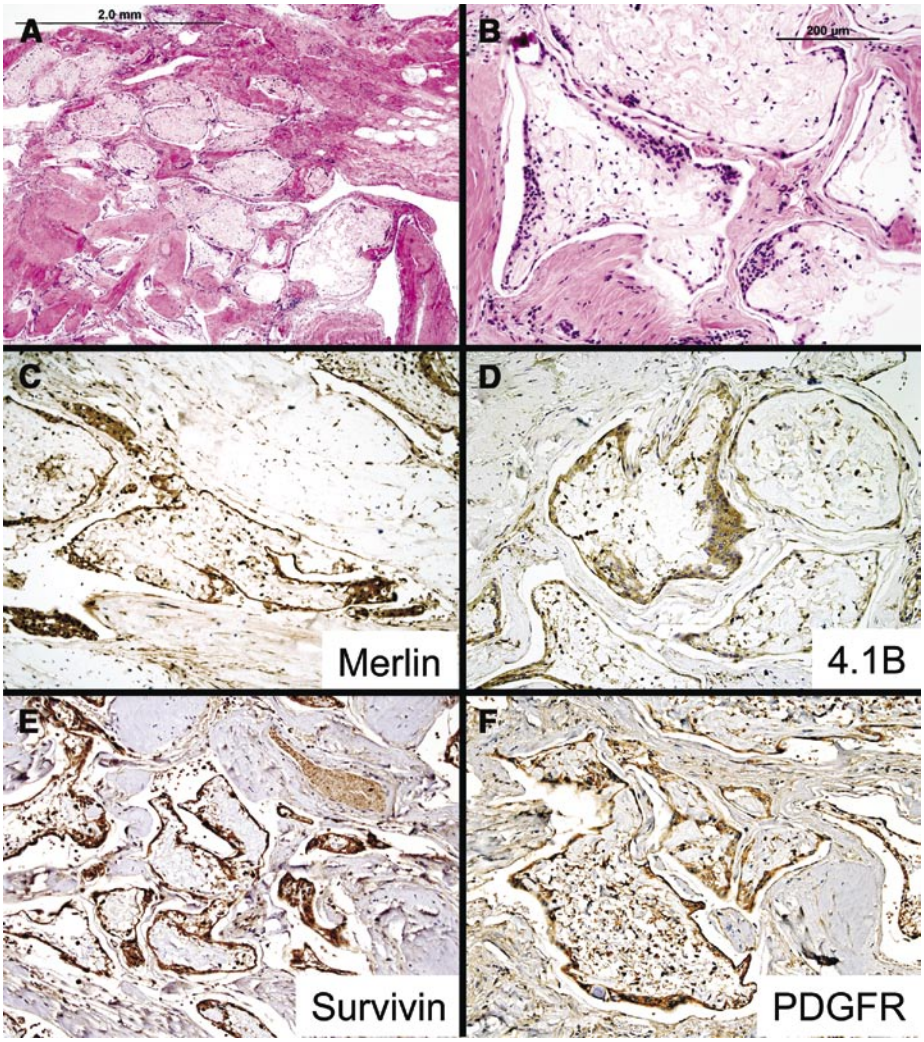

Figure 1. Examples of normal arachnoid granulations (**A, B**) with strong immunoreactivity to merlin (**C**), 4.1B (**D**), survivin (**E**), and PDGFR-β (**F**) within the cap cells.

Histology. Representative cases of arachnoidal granulations and foci of meningothelial hyperplasia are illustrated in Figures 1 to 3. Although all examples of hyperplasia were only detected microscopically, the most florid examples measured several millimeters in greatest dimension and therefore, could have conceivably been detected grossly. The majority of cases had a multicentric growth pattern with discontinuous patches of hyperplastic nests. The hyperplastic nests were seen in close proximity to the presumed inciting factor in the cases of hemorrhage and neoplasia (pilocytic astrocytoma). In others (eg, elderly patients, chronic renal failure), there was no recognizable inciting pathology adjacent to the hyperplastic nests. In the latter examples, foci of meningothelial hyperplasia were often seen in more than one site, although the full extent of disease was not possible to determine, since these represented incidental microscopic autopsy findings and only a small portion of the patients' meninges were routinely sampled. As with normal arachnoidal cap cells, hyperplastic foci were encountered in the arachnoid mater, base of the choroid plexus, or within a subdural location. Unlike meningiomas, dural invasion was not encountered in any of the cases. Cells were predominantly po-

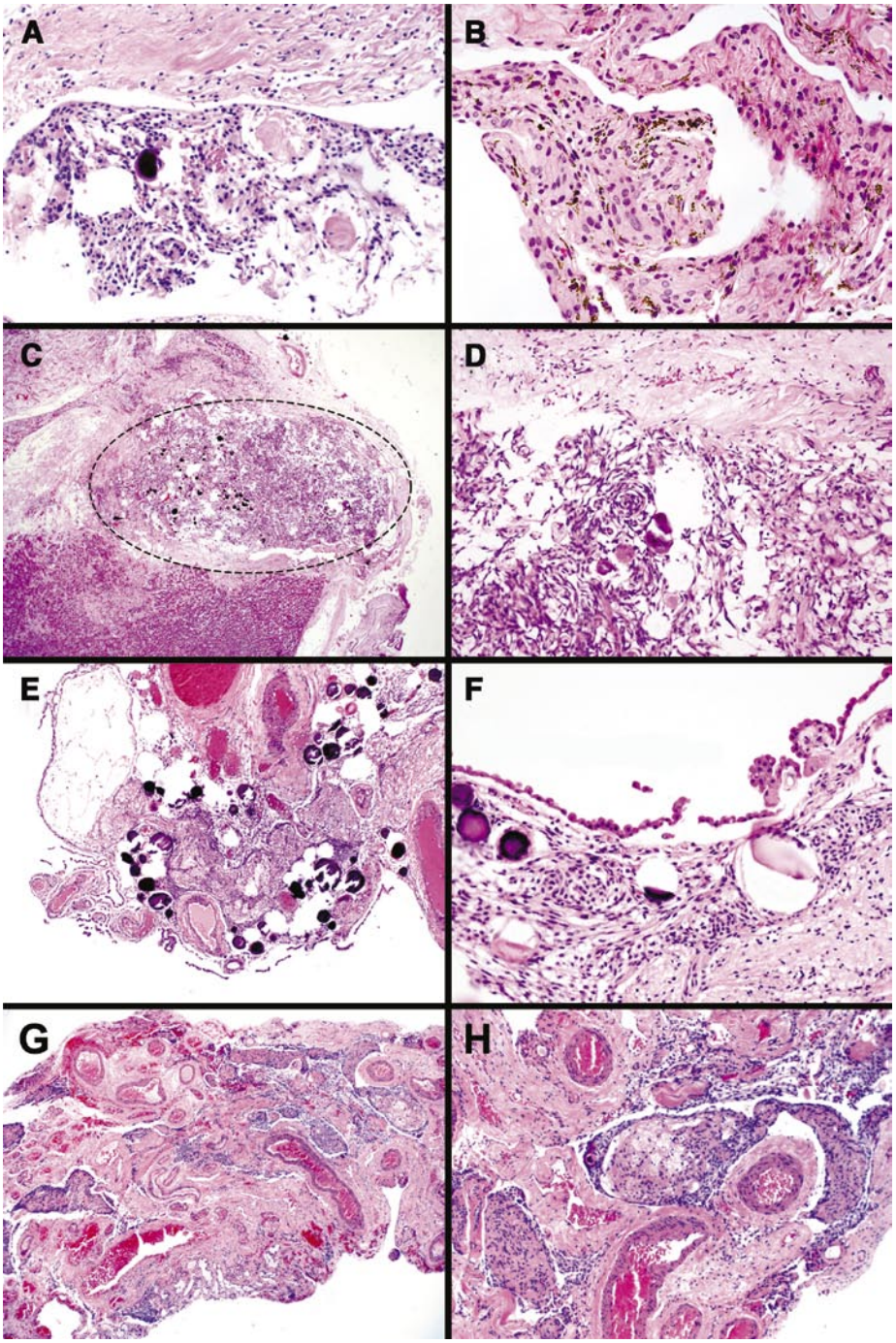

Figure 2. Examples of meningothelial hyperplasia. Cases 8 (**A**) and 10 (**B**) involved the arachnoid mater adjacent to foci of subarachnoid hemorrhage. Hemosiderin was seen within the meningothelial hyperplasia of case 10 (**B**). Case 9 was seen in the pituitary region under the diaphragma sella (outlined region) bilaterally, suggesting either multifocality or a circumferential growth pattern (**C, D**). Cases 3 (**E, F**) and 2 (**G, H**) showed multifocal meningothelial proliferations within the tela choroidea of the choroid plexus.

lygonal or epithelioid and arranged in nests and whorls, although fascicles of spindled cells were occasionally seen as well. Psammoma bodies were seen in the majority of cases. There was minimal cytologic atypia in most, though rare enlarged hyperchromatic nuclei were encountered in cases 5 and 11. Mitotic figures were either rare or not found.

Immunohistochemistry. Immunohistochemical data is summarized in Table 3 and illustrated in Figures 1 and 3. As with meningiomas in general, the majority of antibodies tested yielded positive results in most examples of both normal arachnoidal cap cells and hyperplastic foci. Most were strongly and diffusely positive, though some variability was encountered. Of particular note, PR positivity was only seen in meningothelial hyperplasia, with a 64% frequency of positivity, similar to that of meningiomas (Table 3; Figure 3B). In contrast, normal arachnoidal cap cells were uniformly immunonegative. The difference in PR immunoreactivity between cases of meningothelial hyperplasia and arachnoidal cap cells was statistically significant ($p = 0.035$; Fisher's Exact test). Similarly, hyperplasia differed from meningioma in their uniform retention of both merlin and protein 4.1B expression ($p<0.001$ for each marker; Fisher's Exact test).

FISH. FISH results are summarized in Table 3 and illustrated in Figure 4. In contrast to meningiomas, no deletions of either *NF2* or *4.1B* were seen in cases of meningothelial hyperplasia ($p<0.001$ for each marker; Fisher's Exact test). However, both cases 5 and 11 had scattered cells (5%-10% of total) with polysomies (chromosomal gains) of both 22q and 18 (Figure 4C). Given that these cells were often larger than their diploid neighbors and that both chromosomes tested were gained, these data demonstrate an overall state of polyploidy within a small subset of meningothelial cells.

DISCUSSION

Definition of meningothelial hyperplasia and its distinctions from normal cap cell clusters and meningioma. Searching for the reported diagnosis of meningothelial hyperplasia at most major medical centers, including ours, one would likely conclude that this is not a diagnostic entity. Nonetheless, it has long been recognized that meningothelial cells are capable of proliferating in response to a variety of stimuli and that such "reactive" proliferative states may be difficult to distinguish from neoplasia (meningioma). In surgical cases, this distinction has important clinical implications, since a hyperplastic proliferation is a self limited process, whereas a neoplasm has the potential to grow, eventually leading to neurologic complications and requiring therapeutic intervention. Only a few studies on meningothelial hyperplasia have been published and even fewer have

attempted to define it. Using a cutoff of 4 or more meningothelial cell layers, Bellur et al identified meningothelial hyperplasia in 184 (20%) of 922 consecutive autopsy cases (3). Similarly, Perez and colleagues studied 52 intracanalicular optic nerves from 26 consecutive cadavers (19). They considered clusters of 3 or more cell layers thickness to be hyperplastic, with 77% of their specimens fulfilling these criteria. For the current study, we chose a more conservative cutoff of 10 layers, with 11 surgical and postmortem cases fulfilling this criterion over a 2-year period at Washington University. In all cases, the meningothelial hyperplasia represented an incidental microscopic finding, with either the specimen or the brain removed for other reasons.

The most florid examples of meningothelial hyperplasia were 100 or more cell layers thick and several millimeters in greatest dimension. In contrast to most meningiomas, they often displayed a multicentric growth pattern (discontinuous nests) and never invaded the adjacent dura. They also lacked evidence of *NF2* and *4.1B* gene deletions or loss of their protein products, merlin and protein 4.1B. In contrast, utilizing the same DNA probes and antibodies, we previously found *NF2* and *protein 4.1B* losses in the vast majority of meningiomas of all histologic grades (9, 20, 21). Therefore, in clinical cases where the distinction is difficult, losses of either genes or their protein products strongly argue in favor of meningioma. In contrast, the lack of such alterations supports meningothelial hyperplasia, though it is not absolutely definitive, since rare meningiomas show no detectable abnormalities with these markers.

Of interest, hyperplastic proliferations shared a similar frequency of PR positivity with benign meningiomas (11, 20) and 2 cases had polyploid cells. These features were not seen in any of the normal controls. In this regard, meningothelial hyperplasia overlaps partially with meningioma. Polyploidy often results from a defect in cell division, wherein DNA replicates but the nucleus fails to divide. This process is seen most often in neoplasia and therefore, this finding in meningothelial hyperplasia is intriguing. For example, a study of another reactive process, gliosis, showed that reactive astrocytes exhibit an increase in nuclear volume proportional to the increase in overall cell volume without evidence for polyploidy (15). Nevertheless, polyploidy does not represent absolute proof of either a neoplastic or preneoplastic condition. Similarly, the presence of PR immunoreactivity is not irrefutable evidence of neoplasia. It is possible that PR expression is upregulated in reactive meningothelial proliferations and may be retained during neoplastic transformation to meningioma. In this regard, the finding of both meningothelial hyperplasia and meningioma in a recent animal model provides some support for an association between the 2 entities (14). Loss of *Nf2* in mouse leptomeningeal cells results in meningioma formation, some examples coexisting with hyperplastic

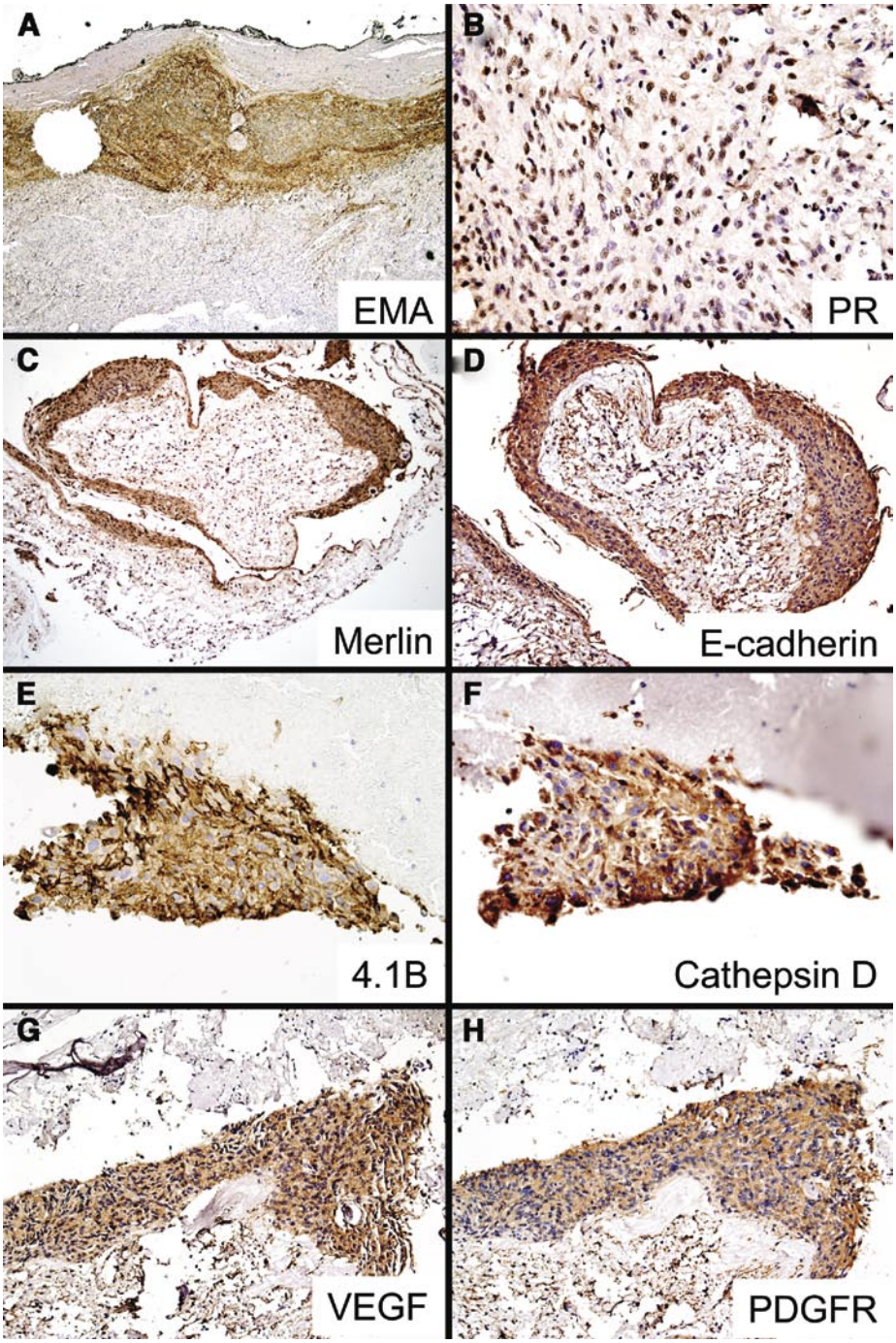

Figure 3. Representative immunohistochemical results. EMA in case 1 highlights the discrete localization of the meningothelial hyperplasia between the dura above and the optic nerve glioma below (**A**). The defect on the left represents a site of prior 0.6-mm core sampling for a tissue microarray. Strong nuclear PR expression was seen in a subset of the meningothelial cells (**B**). There was immunoreactivity for merlin and E-cadherin in case 6 (**C, D**), 4.1B and cathepsin D in case 5 (**E, F**), and VEGF and PDGFR-β in case 9 (**G, H**).

Antibody/Probe	Normal Cap Cells % (n=6)	Men. Hyperplasia % (n=11)	Meningioma % (n=41*)
PR	0	64	63
EMA	100	100	100
Cathepsin D	67	55	62
E-cadherin	100	91	90
PDGFR-β	100	100	98
PDGF BB	50	64	100
Survivin	83	100	88
EGFR	83	73	58
VEGF	83	73	75
Merlin Loss	0	0	74% (of 175) Ref 20
4.1B Loss	0	0	76% (of 175) Ref 20
NF2 Deletion	0	0	82% (of 51) Ref 21
4.1B Deletion	0	0	82% (of 51) Ref 21

Table 3. Summary of immunohistochemical and FISH data. * 41 meningiomas from tissue microarray (16), unless otherwise stated.

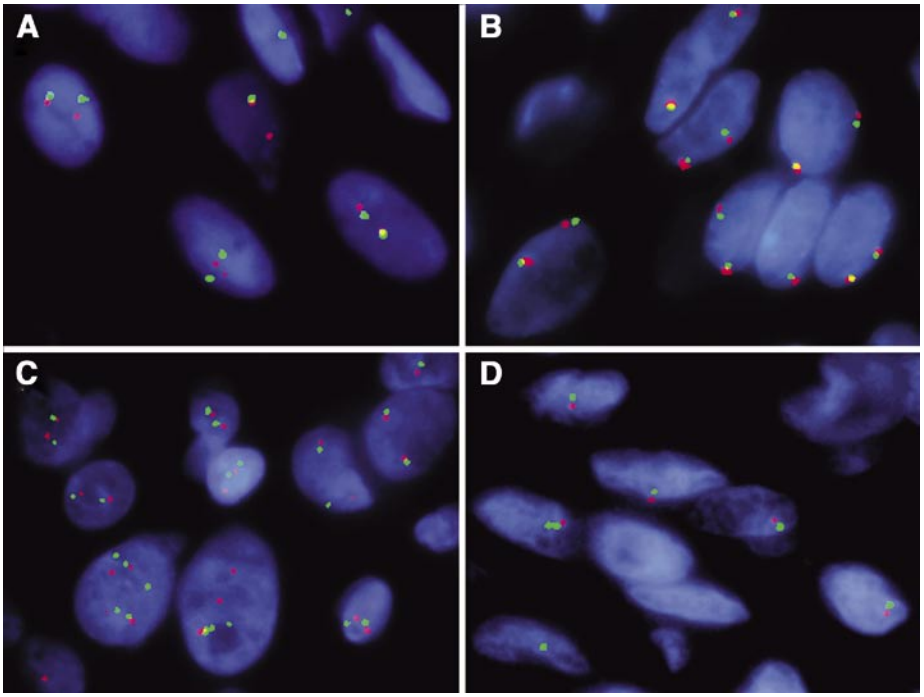

Figure 4. Representative FISH results. Normal dosages of 22q (**A**: 2 green *BCR* and 2 red *NF2* signals in most nuclei) and 18 (**B**: 2 green *4.1B* and 2 red CEP18 signals in most nuclei) were seen in case 10. In case 5, the majority of cells showed normal dosages of 22q, though scattered cells were polysomic (**C**: 2 cells in lower left with >2 green *BCR* and >2 red *NF2* signals). A meningioma with 22q deletion is shown for comparison (**D**: 1 green *BCR* and 1 red *NF2* signal in most nuclei).

proliferations. Clearly, this animal model likely differs somewhat from the human examples described in the current series. Nevertheless, in a recent mouse model of optic nerve glioma resulting from neurofibromatosis 1 (NF1) inactivation in astrocytes, we also have observed a preneoplastic hyperproliferative state in the evolution of these tumors (2). Taken together, the data suggest that meningothelial hyperplasia may represent a preneoplastic precursor of meningioma. However, future studies will be needed to rigorously test this hypothesis.

Causes of meningothelial hyperplasia. The cellular mechanisms underlying meningothelial hyperplasia remain poorly understood, though a few predisposing factors have been reported. Bellur and colleagues found statistically significant associations with both advanced patient age and chronic renal disease (3). Both of these features were common in our cases as well, although related disorders, such as hypertension and cardiac ventricular hypertrophy were also seen in most of the same cases. The association with renal disease suggests that uremia might incite meningothelial cells to proliferate, although this is unproven. The potential association with hypertension is also intriguing, since meningothelial cells are normally involved in maintaining intracranial pressure via CSF drainage into venous sinuses. One could envision that bouts of increased intracranial pressure might therefore, provide a potential stimulus for cap cells to proliferate. Again though, this is speculative. An association with patient age was also supported by our data, in that 5 (45%) of our cases occurred in patients over 70 years of age. However, there were also 3 (27%) pediatric cases in our series, indicating that meningothelial hyperplasia is not limited to the elderly. Other reported associations with meningothelial hyperplasia have included trauma, hemorrhage, neoplasia, and chronic intracranial hypotension (6, 17, 19, 24, 25, 29). The first 3 of these conditions were also seen in the current study, including one example of optic nerve glioma with florid meningothelial hyperplasia. The potential confusion of meningothelial hyperplasia with meningioma has been previously emphasized in this setting (6, 24, 29). The responsible stimuli for meningothelial hyperplasia in these conditions remain a mystery, as does the reason for a general lack of a similar reaction with other irritative CSF disorders such as meningitis, where one typically sees other reactive processes, such as inflammation, formation of granulation tissue, and fibrosis. Lastly, since so few studies have focused on meningothelial hyperplasia, it is likely that additional causes will be identified in the future.

SUMMARY

Based on our data and that of others, we conclude that meningothelial hyperplasia is a reactive process characterized by a proliferation of arachnoidal cap cells that is often non-invasive, multicentric, and at least focally reaches a thickness of 10 or more cell layers. Florid examples are often difficult to distinguish from meningioma. However, they are commonly associated with inciting factors, such as chronic renal disease, hemorrhage, trauma, intracranial hypotension, and neoplasia, particularly optic pathway

gliomas. Although meningothelial hyperplasia shares many immunohistochemical and genetic features with normal cap cells, it differs in terms of its frequent PR immunoreactivity and occasional polyploid cells. In contrast to classic meningiomas, there is no evidence for either *NF2* or *4.1B* gene deletions by FISH or merlin or protein 4.1B losses of expression by immunohistochemistry. The data suggest that meningothelial hyperplasia may represent a preneoplastic lesion in some cases, although additional studies are needed to rigorously test this hypothesis.

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