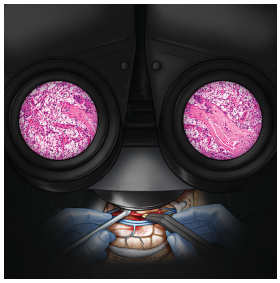

Meningioma: A Pathology Perspective

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Meningiomas are dural-based neoplasms that account for ~37% of all intracranial tumors in the adult population. They can occur anywhere within the central nervous system and have a predilection for females. The World Health Organization classifies meningiomas into 3 grades based on increased risk of recurrence and associated mortality in grade III tumors. Although most tumors are categorized as low-grade, up to ~15%-20% demonstrate more aggressive behavior. With the long-recognized association with *neurofibromatosis type 2* gene mutation, putative driver mutations can be attributed to ~80% of tumors. Several germline mutations have also been identified in some cases of familial meningiomatosis such as *SMARCE1*, *SUFU*, *PTEN*, and *BAP1*. Finally, in addition to genetic data, epigenetic alterations, specifically deoxyribonucleic acid methylation, are being increasingly recognized for their prognostic value, potentially adding objectivity to a currently subjective grading scheme.

KEY WORDS: Meningioma, WHO grade, Histologic variants, Immunohistochemistry, Molecular, Cytogenetics

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Meningiomas represent a vast and heterogeneous group of tumors. Believed to originate from arachnoid cap cells, these dural-based tumors are the most common primary neoplasms of the central nervous system (CNS).[1] Despite their frequency, each case can offer challenges from initial diagnosis to assignment to the correct World Health Organization (WHO) grade group. Now that we have moved into the molecular age of medicine, a deeper understanding of tumor biology and behavior is now possible and has already revolutionized the classification and management of other CNS tumors. In this review, we discuss the epidemiologic features and histologic patterns of meningiomas with an emphasis on the current WHO grading scheme. We then explore some of the most recent and significant discoveries in the genetics of meningiomas and how they relate to tumorigenesis and familial syndromes. We then close with a consideration of epigenetics and how deoxyribonucleic acid (DNA) methylation patterns may contribute to future grading schemes.

ABBREVIATIONS: CEA, carcinoembryonic antigen; **CNS,** central nervous system; **EMA,** epithelial membrane antigen; **HPF,** high-power fields; **KLF4,** Krupple-like factor 4; **MC,** mal methylation class malignant; **NF2,** neurofibromatosis type 2; **PAS,** periodic acid schiff; **PR,** progesterone receptor; **SSTR2A,** omatostatin receptor 2A; **SWI/SNF,** switching defective/non-sucrose fermenting; **TERT,** telomerase reverse transcriptase; **TIL,** tumor-infiltrating lymphocyte; **WHO,** World Health Organization

CLINICAL AND EPIDEMIOLOGY

Meningiomas are the most frequently encountered primary CNS tumor in adults, accounting for ~37% of intracranial lesions with an annual incidence of 8.83 per 100 000.[1] By contrast, they are quite rare in individuals under the age of 18 yr, making up just 1% to 2% of intracranial tumors in this population.[2,3] Most meningiomas occur over the age of 65 yr, with frequency continuously increasing in subsequent years.[4] They have a female:male ratio of 2 to 3:1, except in children, for whom slightly more males are affected (female:male ratio of 1:1.3).[3,4] Of note, males generally tend to have higher-grade tumors as compared to females.[5-7] The majority of tumors are supratentorial, mostly localizing to parasagittal, falcine, and skull base.[8] Spinal meningiomas are less frequent but have a higher predilection for the thoracic spine and younger females.[9] Uncommon sites include intraventricular, orbit, intraosseous, and subcutis/dermis of the scalp.[10-13] Meningiomas outside the CNS are rare, with case reports describing meningiomas within the mediastinum, lung, and neck.[14-17]

There are well-recognized genetic risk factors with multiple tumors being frequent in familial examples. Predisposing genetic syndromes include neurofibromatosis type 2 (NF2), nevoid basal cell carcinoma (Gorlin) syndrome, PTEN (Cowden) syndrome, and syndromes of familial meningiomatosis characterized by mutations in *SMARCB1* or *SMARCE1*.[18,19] The primary exposure risk factor for the development of meningioma is radiation, typically for treatment of prior CNS malignancy, though a variety of exposures, including treatment for tinea capitis and nuclear explosions, are well-recognized, albeit historical, etiologies.[20] Previous studies also reported trauma as a potential risk factor, though with less support for this association.[21,22]

HISTOLOGY

Meningiomas have a variety of histologic subtypes, and overlap between 2 or more patterns is not uncommon. The 2016 edition of the WHO Classification of Tumors of the Central Nervous System divides meningiomas into 3 grades based solely on histologic features, with ~80% of tumors being grade I, 18% to 20% grade II, and 1% to 2% grade III.[23] The current WHO grading scheme is summarized in Table.

There are 9 histologic subtypes of grade I tumors: meningothelial, psammomatous, microcystic, fibrous, lymphoplasmacyte-rich, transitional, secretory, metaplastic, and angiomatous.[23] Of note, few of these variants such as secretory and angiomatous are particularly significant from a clinical stand-point as they can elicit marked brain edema.[24-26] Meningothelial meningiomas are characterized by whorls and streams of meningothelial cells with eosinophilic cytoplasm and indistinct cytoplasmic borders. The nuclei are typically ovoid, often demonstrating nuclear grooves, clearing, and pseudoinclusions (Figure 1A). Nuclear pleomorphism in meningioma is insignificant for grading. Variable presence of psammoma bodies is a frequent finding in all the histologic variants.[27] Fibrous meningiomas demonstrate cells with a spindled morphology with fascicular and storiform architecture predominating (Figure 1B). On gross examination, these tumors are often firm to palpation, reflecting the collagen-rich nature of this variant.[28] Transitional encompasses meningiomas exhibiting both meningothelial and fibrous features.[27] Psammomatous meningiomas show diffuse psammoma body formation. The cells are often marginated between clusters of psammoma bodies and are similar in appearance to fibrous or transitional meningiomas (Figure 1C). This variant is most often found in the thoracic spine of middle-aged or elderly women, with the sex ratio reaching 9:1 (F:M).[24,29] Microcystic meningiomas have clear, microcystic spaces between cells bridged by wisps of cytoplasm, forming a "cobweb-like" appearance (Figure 1D). The angiomatous variant shows numerous, often hyalinized, blood vessels of varying caliber occupying >50% of the tumor volume (Figure 1E). The angiomatous and microcystic variants often coincide.[30]

Lymphoplasmacyte-rich meningiomas demonstrate a dense lymphoplasmacytic infiltrate in a meningothelial background (Figure 1F). These tumors are often softer than typical meningiomas on gross examination.[31] Secretory meningiomas show intracellular lumina containing eosinophilic Periodic Acid Schiff (PAS)- and Carcinoembryonic Antigen (CEA)-positive secretions and may have concomitant increase in serum CEA (Figure 1G). Finally, metaplastic meningiomas are those displaying heterotopic mesenchymal differentiation in the form of adipose tissue, cartilage (Figure 1H), bone (Figure 1I), and/or myxoid matrix.[32]

Grade II meningiomas comprise ~15% to 20% of tumors and are characterized by increased risk of recurrence.[27] Atypical meningiomas have a higher prevalence in males than grade I tumors.[7] Currently, there are 4 possible routes to the grade II category. The first is through demonstration of 3 of the following 5 "soft" features: (1) hypercellularity, (2) spontaneous necrosis, (3) sheeting architecture (patternless pattern), (4) prominent nucleoli, and (5) small cell change (Figures 2A-2E). The second is through identifying increased mitotic activity, with ≥4 and <20 mitotic figures in 10 high-power fields (HPF) (400X).[33] Brain parenchymal invasion by meningiomas is also associated with increased risk of recurrence and is considered sufficient for grade II (Figure 2F).[23] Meningiomas meeting any of the prior 3 criteria are designated as atypical meningiomas. The final criterion for grade II meningiomas is demonstration of chordoid or clear cell histology. The current WHO classification recommends designation of a special histologic type when it is "predominant and well-developed."[23] There is a lack of an objective cut-off for predominant histology with a consensus being around or more than 50%. Clear cell meningiomas are more frequently encountered in younger individuals

TABLE. Summary of Current WHO Grading Guidelines

WHO Grade I	
Meningothelial	Angiomatous
Fibrous	Microcystic
Transitional	Secretory
Psammomatous	Metaplastic
	Lymphoplasmacyte-rich
WHO Grade II	
Histologic features	Histologic subtype
≥4 and <20 mitoses in 10 HPF	Clear cell
Brain parenchyma invasion	Chordoid
At least 3 of 5 following histologic features:	
Sheeting architecture	
Small cell change	
Hypercellularity	
Spontaneous necrosis	
Prominent nucleoli	
WHO Grade III	
Histologic features	Histologic subtype
≥20 mitoses in 10 HPF	Rhabdoid
Frank anaplasia (sarcoma, carcinoma, or melanoma-like) histology	Papillary

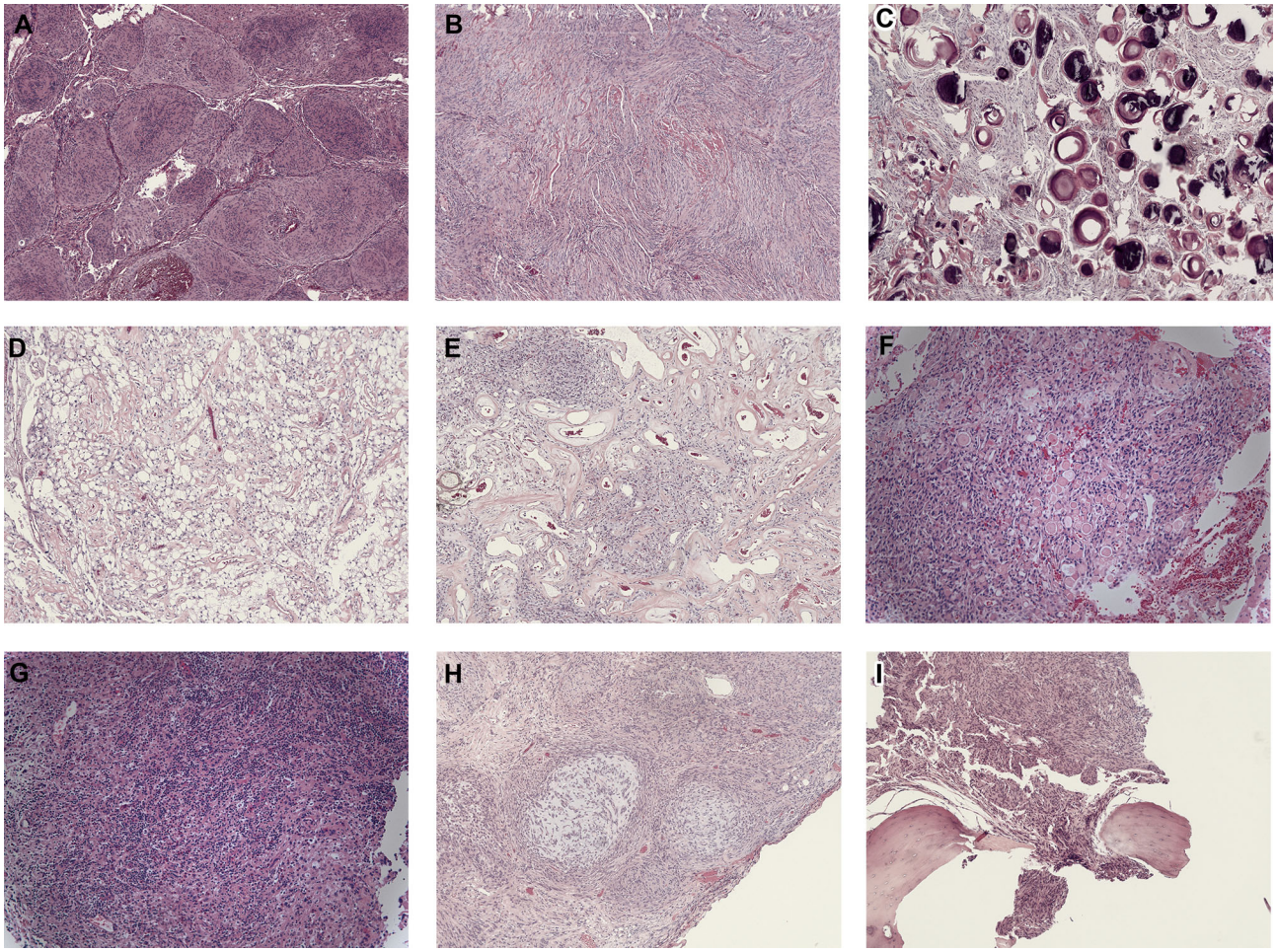

FIGURE 1. *Histologic patterns of grade I meningiomas.* **A**, *Meningothelial meningioma demonstrating whorls of meningothelial cells with eosinophilic syncytium-like cytoplasm.* **B**, *Fibrous meningioma composed of elongated spindle cells with intermixed collagen bundles.* **C**, *Psammomatous meningioma showing abundant psammoma bodies with intervening tumor cells.* **D**, *Microcystic meningioma.* **E**, *Angiomatous variant showing a high density of vessels, many of which show hyalinization in this example.* **F**, *Secretory meningiomas are characterized by eosinophilic secretions, sometimes termed "pseudopsammoma bodies."* **G**, *Lymphoplasmacyte-rich meningiomas show abundant intermixed lymphocytes and plasma cells with variable macrophages. Metaplastic meningiomas show components of mesenchymal tissue such as adipocytes, cartilage* **H**, *and bone* **I**.

and have a predilection for the spinal cord and cerebellopontine angle.[34,35] Tumors are characterized by sheets of meningothelial cells with clear cytoplasm (Figure 2G) and round nuclei. The clear cytoplasm is imparted by glycogen content and can be confirmed with PAS (Figure 2H) and PAS-diastase staining.[36] Chordoid meningiomas are so-called because of their histologic similarity to chordomas, demonstrating cells with bubbly cytoplasm and abundant extracellular mucin arranged in chords or trabeculae (Figure 2I).[37,38]

Grade III meningiomas are the least frequently encountered (~1%-2% of meningiomas) and the most aggressive with higher rates of recurrence and mortality.[27] Additionally, the predilection for females observed in grades I and II tumors is not present in higher-grade meningiomas.[6] Tumors qualifying as grade III are categorized as anaplastic or display a special variant. Tumors with ≥20 mitotic figures in 10 HPF (Figure 3A) or frank anaplasia (demonstrating sarcoma-like, carcinoma-like, or melanoma-like areas) are designated anaplastic meningiomas (Figure 3B).[39] Two special types also exist under the grade III umbrella: rhabdoid and papillary. Like grade II tumors, the WHO recommends the histology to be the predominant pattern. Rhabdoid meningiomas show meningothelial cells with eosinophilic bellies and eccentric nuclei with macronucleoli (Figure 3C). Nuclear atypia, necrosis, and a high mitotic count are also frequently identified.[40,41]

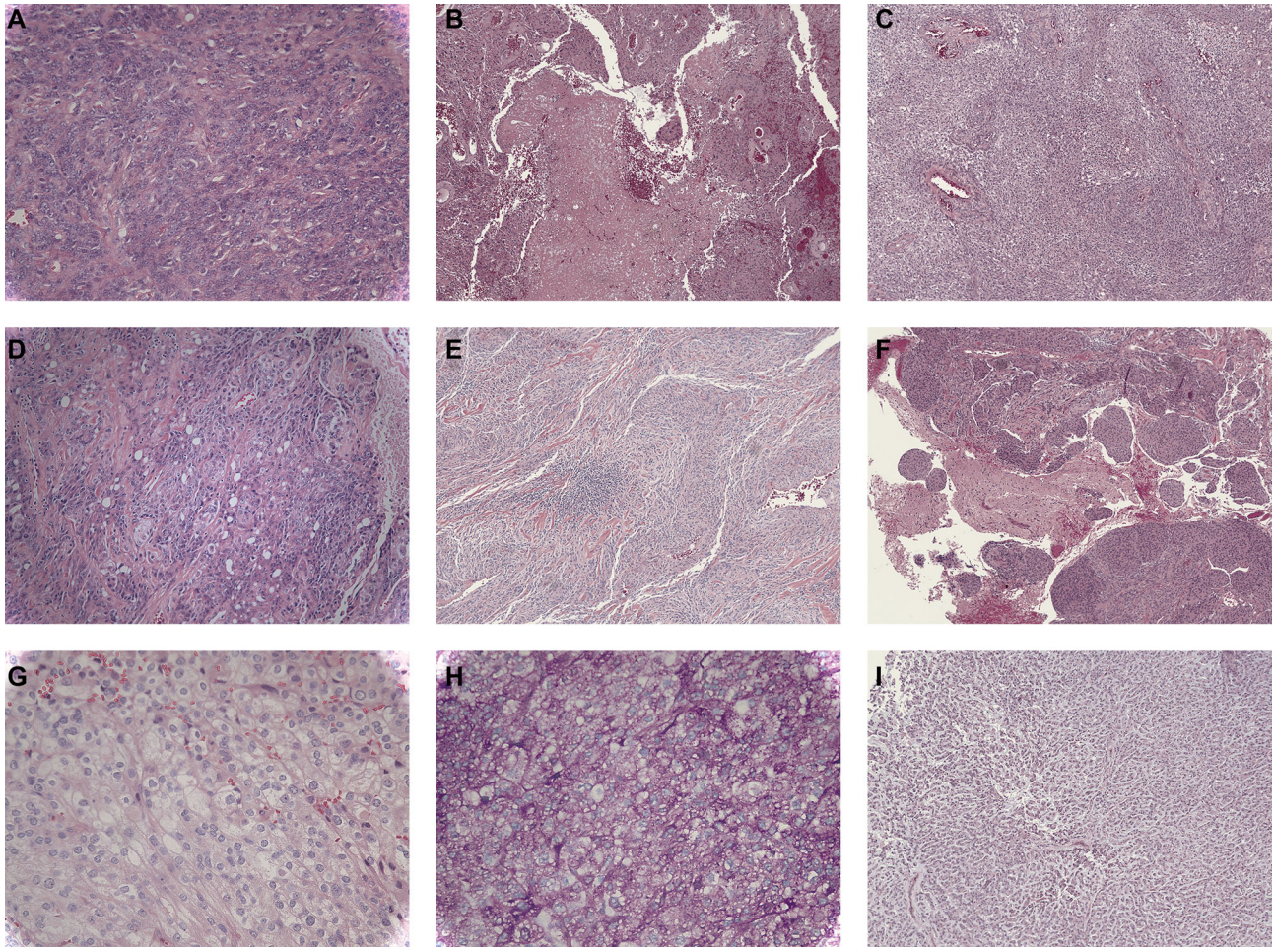

FIGURE 2. *Histologic features of grade II meningiomas. A diagnosis of atypical meningioma can be made by several standalone criteria. One of which is the presence of 3 or more of the 5 "subjective" features: hypercellularity* **A**, *spontaneous necrosis* **B**, *sheeting architecture* **C**, *prominent nucleoli* **D**, *and small cell change* **E**. **F**, *The presence of brain parenchyma invasion is sufficient for this diagnosis as well. Clear cell meningioma shows cytoplasmic clearing* **G** *due to glycogen deposition, as demonstrated on PAS staining* **H**, *which is diastase sensitive.* **I**, *Chordoid meningiomas show epithelioid cells with intervening myxoid material. Mitotic count of 4 or more per 10 HPFs also qualifies a meningioma for an atypical designation.*

Papillary meningiomas are more frequently identified in younger patients and show meningothelial cells surrounding fibrovascular cores in a papillary or solid pseudopapillary pattern (Figure 3D).[42] Histologic progression of meningiomas to higher grades is relatively rare, and most high-grade tumors are believed to be primary lesions.[43,44]

IMMUNOHISTOCHEMISTRY

Meningiomas are characterized by a mixed epithelioid and mesenchymal phenotype with expression of epithelial membrane antigen (EMA) and vimentin. Meningiomas are generally negative or show only focal cytoplasmic positivity for cytokeratins (except for the secretory subtype) and S100. Anaplastic meningiomas often show aberrant expression of cytokeratins, which may raise the differential of metastatic carcinoma.[45] Expression of markers of myocyte differentiation is generally absent except in some grade III meningioma harboring sarcomatous appearance.[46] An often-exploited characteristic of meningiomas is the nuclear expression of progesterone receptor (PR). Though PR expression is inversely proportional to grade, it is difficult to draw meaningful prognostic conclusions from immunohistochemical results.[47,48] Given the female predilection, perceived growth during pregnancy, and PR expression, a role for hormones in the development and growth of meningiomas has long been suspected.[49] However, a study of 17 meningiomas obtained from pregnant patients showed that the increase in tumor size was primarily due to increased vascularity and edema rather than tumor cell proliferation.[50-52] Rare cases of meningioma development in male-to-female transgender patients

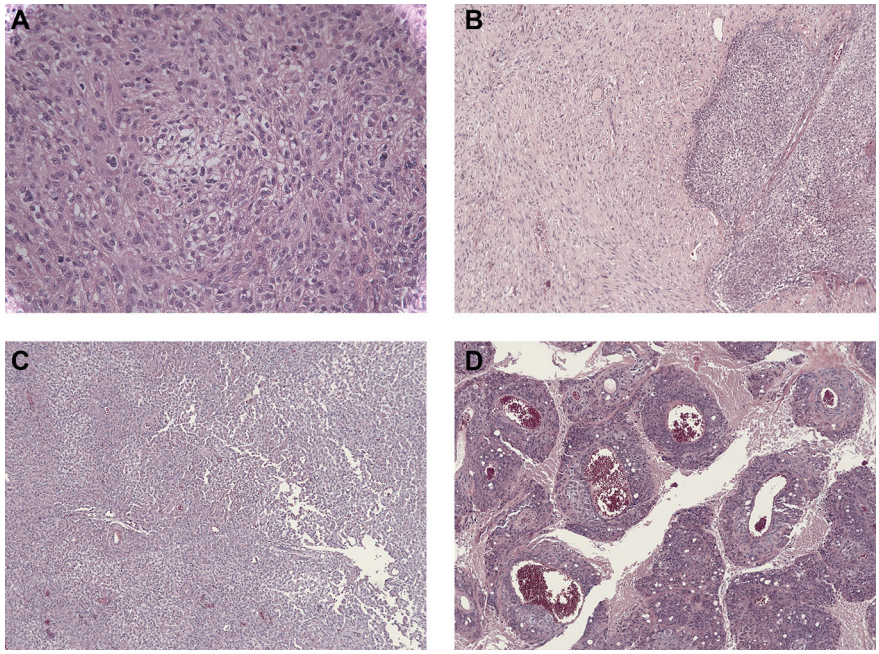

FIGURE 3. *Histologic features of grade III meningiomas. Anaplastic meningiomas show markedly increased mitotic activity* **A** *meeting or exceeding 20 figures in 10 HPFs. "Frank" anaplasia in the form of carcinomatous, sarcomatous* **B**, *or melanomatous appearance is also sufficient for diagnosis.* **C**, *Rhabdoid meningiomas show eosinophilic cytoplasmic bellies with peripheral displacement of the nucleus.* **D**, *Papillary meningioma is characterized by tumor cells lining central fibrovascular cores.*

have also been reported following initiation of hormonal therapy, though the number of patients is currently insufficient to draw conclusions.[53-55] Somatostatin receptor 2A is a recently described antigen that is expressed in meningiomas and has higher sensitivity than EMA and PR. Utilization of somatostatin receptor 2A (SSTR2A) as a marker has led to greater confidence when ruling out mimics of meningioma such as solitary fibrous tumor and malignant peripheral nerve sheath tumor.[56] The routine use of Ki-67 (MIB-1) in meningiomas is not currently recommended by the WHO, though there is some suggestion regarding its prognostic implications.[57]

DIFFERENTIAL DIAGNOSES

Perhaps the most critical reason to recognize the histologic features and immunohistochemical profiles of meningiomas is to distinguish them from other lesions, particularly metastatic tumors and other mesenchymal tumors, which may mimic meningiomas.

The fibrous and angiomatous variants of meningiomas share histological similarities to solitary fibrous tumor. However, nuclear immunoreactivity for STAT6 in solitary fibrous tumor is sufficient to confirm the diagnosis as both fibrous and angiomatous meningiomas are negative.[23,58]

Metaplastic meningioma may mimic a variety of sarcomas depending on the specific differentiation present including osteosarcoma, chondrosarcoma, liposarcoma, and fibromyxoid sarcoma. However, metaplastic meningiomas typically do not show malignant features, including lack of increased mitotic activity as would be expected for sarcomas. Once again, expression of typical meningioma markers such as EMA and SSTR2A are not typical of a sarcoma.[56,59] The myxoid background of chordoid meningiomas may also mimic the stroma of various sarcomas and is worth considering.[37]

A lymphoplasmacyte-rich meningioma may raise the differential of inflammatory processes or lymphoid neoplasms. IgG4-related disease is an autoimmune disease characterized by abundant plasma cells expressing IgG4 and "storiform" fibrosis.[60] In the CNS, IgG4-related disease may present as pachymeningitis and/or dural-based mass lesions. A diagnosis of IgG4-related disease requires demonstration of a significant increase in IgG4 plasma cells. A ratio of >10% IgG4:IgG on immunohistochemistry has been suggested for establishing a diagnosis in the dura.[60,61] Systemic lymphoma may also present as dural-based masses and should be considered in lymphocyte-rich lesions. Immunohistochemical studies are typically sufficient to prove the neoplastic nature of these lesions.[62,63]

Clear cell renal cell carcinomas are potential mimics of clear cell meningioma. Although the two share protein expression of EMA, immunohistochemical staining for PAX8, CD10, and carbonic anhydrase IX typically shows expression in clear cell carcinoma, whereas meningiomas are expected to be negative.[64,65]

Chordoid meningioma shares many characteristics with chordomas. Though most chordomas occur in the sacrum, intracranial (eg, clival) tumors are not uncommon.[37] Chordomas characteristically express S100 and brachyury, which aid in the differential. EMA expression is often present in chordomas and is not likely useful in this differential.[66,67]

The histologic appearance of papillary meningioma may raise the differential of a metastatic papillary carcinoma, such as renal cell carcinoma, papillary thyroid carcinoma, and/or adenocarcinoma of the lung, although the probability of thyroid carcinoma metastasizing to brain is rare.[68] Meningiomas do not typically express nuclear transcription factors characteristic of these tumors, such as PAX8 for renal neoplasms and thyroid transcription factor-1 in the case of lung adenocarcinoma and papillary thyroid carcinoma.[46]

Rhabdoid meningiomas can mimic a variety of tumors that show rhabdoid morphology, such as metastatic rhabdomyosarcoma or melanoma. Rhabdomyosarcoma, by definition, demonstrates some degree of skeletal muscle phenotype and nuclear expression of MyoD1 and myogenin as well as cytoplasmic expression of desmin are expected in rhabdomyosarcoma, though these may only be focally positive in some sarcomas.[69] Metastatic melanoma can readily be distinguished on immunohistochemistry through expression of melanocytic and neural crest markers (S100, HMB45, etc).[70]

When considering a dural-based mass, it is important to recognize the propensity for tumors to metastasize into meningiomas. Clinically, this may present as neurologic changes, whereas other cases show interval growth of a known meningioma on imaging follow-up. Histologically there is a biphasic appearance to the tumor with the meningioma component often marginalized and the metastatic tumor present in a more central region.[71,72] There is no definite explanation for this phenomenon, though authors have suggested hypervascularity, tumor microenvironment, and hormonal factors as possibilities.[71]

GENETIC FEATURES

Meningiomas have a diverse and incompletely understood genetic background that varies with tumor location, phenotype, and biologic behavior. The following is a discussion of many of the notable findings to date from molecular and genetic studies.

NF2 Mutant Tumors

Approximately 40% to 60% of meningiomas, regardless of grade, harbor nonfunctional copies of the *NF2* gene in the form of point mutations, insertions/deletions, and loss of 22q. The *NF2* gene, located on the long arm of chromosome 22, encodes a protein, merlin (schwannomin), which functions as a scaffold protein with a variety of roles including signal transduction in cellular proliferation and survival pathways.[73] Merlin functions as an inhibitor for PI3K through disruption of its interaction with the enhancer phosphatidylinositol 3-kinase enhancer-L.[73] Merlin also appears to function in the hippo kinase cascade pathway through inhibition of YAP expression, a transcriptional co-activator protein that promotes the transcription of multiple proliferation and survival-related genes.[74] Merlin thus functions as a tumor suppressor though interaction with a variety of pathways, though its role is still incompletely understood. A genomics study comparing mutations and chromosomal alterations between low-grade (grade I) and high-grade (grade II-III) meningiomas showed a higher frequency of chromosome 22q deletions amongst high-grade tumors when compared to low-grade, possibly suggesting that loss of other genes on 22q may contribute to tumor progression.[75]

NF2 Wild-Type Tumors

A variety of mutations have been identified in predominately low-grade tumors that are mutually exclusive of *NF2* alterations, some of which have recurrent phenotypic and clinical characteristics.

Mutations in *TRAF7* are the most frequently reported single-gene mutations in *NF2* wild-type meningiomas, present in nearly 25% of all such tumors.[76] These mutations are enriched in the skull base and often accompany a mutation in either Kruppel-like factor 4 (*KLF4*) or *AKT1*. The recurrent *KLF4* mutation, K409Q, associates with the secretory subtype of meningioma and frequently demonstrates peritumoral edema.[76,77] KLF4 is a zinc finger-containing transcription factor that is involved in the regulation and promotion of reprogramming somatic cells into pluripotent stem cells.[78,79] *AKT1* E17K is a mutation identified in ~9% of non-*NF2* mutant meningiomas and generally displays a meningothelial subtype. AKT1 is a protein involved in the mTOR signaling cascade that is involved in the regulation of cell growth and proliferation.[76,80,81] Mutations in another member of the mTOR pathway, *PIK3CA*, are present in ~7% of *NF2* wild-type meningiomas, once again frequently co-occurring with *TRAF7* mutations and showing a predilection for growth in the skull base. One tumor demonstrated a *PIK3CA* mutation with a concurrent *KLF4* K409Q mutation.[82] Recurrent point mutations in *SMO*, L412F, and W535L have been identified in ~5% of meningiomas and tend to occur in the skull base as well as the olfactory groove.[83,84] Finally, a recent genomic analysis demonstrated recurrent L438H and Q403K mutations in the gene *POLR2A*, which encodes the catalytic subunit protein RPB1 of ribonucleic acid polymerase II amongst grade I meningiomas. These tumors had a predilection for the tuberculum sellae and were exclusively grade I.[85] Angiomatous meningioma has notably been shown to harbor unique multiple polysomies, including polysomy 5.[86]

High-Grade Meningiomas

High-grade meningiomas often have multiple genomic alterations, resulting in a more complex genotype. As mentioned above, these tumors more frequently demonstrate *NF2* alterations with 22q loss and monosomy. Loss of chromosomes 1p, 6q, 10, and 14q have been associated with higher grade with the number of alterations increasing with grade.[75,87,88] Loss of 14q in particular has been identified in otherwise grade I meningiomas, which later recur and demonstrate aggressive behavior.[87] Generalized genomic disruption, specifically the copy number variation and mutations in multiple genes, has also been observed not only in high-grade tumors but also low-grade tumors, which later recur.[75] One study also found increased copy number variation in tumors with loss of 1p.[88] *SMARCE1* mutations are frequently encountered in spinal clear cell meningiomas and are present in a subset of hereditary meningiomatosis cases.[89] Mutations and homozygous deletions of *CDKN2A* and *CDKN2B*, in addition to loss of chromosome arm 9p, have been identified in recurrent meningiomas with 1 study showing as many as 76% of high-grade tumors harboring alterations. The majority of these tumors were classified as anaplastic on histologic review.[90,91] *CDKN2A* and *CDKN2B* are tumor suppressors encoding the cell cycle regulator proteins p16 (as well as p14 with alternative splicing) and p15, respectively.[92-94]

Mutations in *SMARCB1*, which encodes a component of the Switching defective/non-sucrose fermenting (SWI/SNF) chromatin remodeling complex, have been identified in a subset of meningiomas. These tumors are frequently associated with concurrent mutations in *NF2* and have increased mitotic indices on Ki-67 staining (>5%). Additionally, *SMARCB1* mutations are found in all grades of meningiomas, but are enriched in higher-grade tumors.[75,95] *SMARCB1* is located on chromosome 22, which may explain the association with *NF2* alterations (particularly chromosome 22 loss/deletions). The SWI/SNF chromatin remodeling complex is responsible for localization and function of nucleosome remodeling, which in turn affects DNA repair and transcriptional activity.[96-101]

Studies have also demonstrated *BAP1* mutations in high-grade meningiomas with a predilection for the rhabdoid subtype.[102,103] The *BAP1* gene encodes a deubiquitinase protein and is believed to function in cell cycle progression and growth. Though the exact mechanism is yet to be elucidated, inactivating mutations have been identified in a variety of malignancies including melanoma, mesothelioma, and renal cell carcinoma.[104-106]

Mutations in the telomerase reverse transcriptase (TERT) gene promoter have been well established as drivers of neoplasia in many tumors and have prognostic significance in gliomas amongst other malignancies.[107,108] The *TERT* gene encodes the reverse transcriptase subunit of telomerase that is responsible for telomere elongation and maintenance. Activating mutations in the upstream promoter allow overexpression of this enzyme and are responsible for immortalization of tumor cells in many cancers. *TERT* promoter mutations (specifically C228T and C250T) have been identified in a subset of high-grade meningiomas with progression from grade I. *TERT* promoter-mutated meningiomas have been found to have a worse progression-free and overall survival, though not many cases have been reported.[109] Other studies have shown decreased time to progression among *TERT* promoter-mutated tumors as well as decreased time to recurrence of grade III tumors.[110,111]

Radiation-Induced Meningiomas

Radiation-induced meningiomas have also been found to harbor recurrent genetic alterations, typically in the form of structural abnormalities.[112-114] Rearrangements within chromosome 22 affecting an intronic region of the *NF2* gene as well as the previously reported loss of 1p have been identified. Insufficient double-strand DNA break repair mechanisms secondary to radiation is a proposed mechanism that could contribute to the abnormalities identified.[115]

Pediatric Meningiomas

Meningiomas are rare in the pediatric population, accounting for ~1% of intracranial tumors before age 18 with a slight male predominance. As many as 40% of pediatric meningiomas are associated with NF2 with other syndromic associations responsible for a subset of cases.[116] Though convexity and falx are still the most likely locations for tumor growth, children more frequently present with tumors in unusual sites, including the spine, orbit, and ventricles.[2] As leukemia/lymphoma and medulloblastoma are amongst the most common tumors in this age group, meningiomas developing secondary to radiation therapy also contribute to a subset of meningiomas in children.[113,115] However, radiation-associated meningiomas develop following a lag period and more frequently present outside the pediatric age group.[117] There is conflicting evidence regarding the behavior of meningiomas in children, though most studies suggest a more aggressive phenotype. The biology of these tumors is not well-defined owing to their rarity, and it is not clear that current grading metrics established in adults translate well to children.[118] Additionally, the higher rate of NF2 in this population may also contribute to poor outcomes.[119]

DNA METHYLATION PROFILING: A NEW APPROACH TO TUMOR GRADING

In a study regarding DNA methylation profiling of meningiomas, approximately 500 meningiomas were clustered into 6 subgroups: methylation classes benign 1 to 3 (MC ben-1, MC ben-2, and MC ben-3), methylation class intermediate A, methylation class intermediate B, and methylation class malignant (MC mal) based on the available clinical and molecular data from each tumor.[120] Histologically, WHO grade I tumors were most prevalent in MC ben-1, MC ben-2, and MC ben-3, whereas WHO grade III tumors were most frequently identified in MC mal. WHO grade II tumors were scattered throughout all methylation classes. For 37 tumors with recurrences, analysis on the recurrent tissue demonstrated stability of the methylation class

over time. This group later developed nomograms for predicting 5-yr outcomes based on methylome data in addition to WHO grade and other clinical factors.[121] The authors argue that this information may be useful in determining which patients would benefit from adjuvant radiation therapy. Other similar studies also support a DNA methylation-based grading scheme over the current histology standard.[122,123]

MENINGIOMAS AND THE IMMUNE SYSTEM

Advances in tumor-immune system interactions have led to remarkable breakthroughs in cancer immunotherapy. As a result, new techniques are being utilized by pathologists to better predict outcomes based on histologic and immunohistochemical features of tissue specimens. For instance, scoring systems are currently in place for tumor-infiltrating lymphocytes (TILs) in melanoma, which have been shown to have prognostic value in predicting nodal metastasis.[124] Newer therapeutics target different aspects of the immune system to elicit a cytotoxic response directed toward tumor cells. These immunotherapy drugs and their targets include pembrolizumab (antiprogrammed death receptor 1), nivolumab (antiprogrammed death ligand 1), and ipilimumab (anti-CTLA4).[125-127] Immunohistochemical staining for programmed death receptor 1 and programmed death ligand 1 expression on tumor cell membranes is now frequently used by pathologists to predict response to these therapies.[128] Interest in tumor microenvironments and use of checkpoint inhibitors has also extended to a variety of primary CNS neoplasms, including gliomas and ependymomas.[129,130] Meningiomas frequently display varied amounts of immune cell infiltration, most often composed of lymphocytes and macrophages.[131,132] One study showed that meningiomas contain a relative abundance of M2 macrophages when compared to M1-type cells. Though a correlation with grade was not identified, a higher proportion of M2 macrophages were present in recurrent tumors.[131] M2 macrophages have been shown to impart a protumoral microenvironment in some cancers and tend to associate with an overall worse prognosis whereas the opposite is true for M1 macrophages.[133,134] Tumor mutational burden also appears to associate with increased TILs, particularly in *NF2* altered tumors.[135,136] One study demonstrated that higher numbers of cytotoxic T-cell in the immune microenvironment of aggressive meningiomas were associated with a favorable prognosis. Additionally, recurrent tumors tended to harbor fewer TILs overall.[137]

So far, the evidence for checkpoint inhibitors is limited in meningiomas. The expression of PD-L1 by meningiomas has been associated with higher-grade histology and worse outcomes, suggesting that immune evasion may play a significant prognostic role.[138,139] Another study showed increased CTLA4 expression in high-grade meningiomas.[140] Three clinical trials are currently underway to assess the efficacy of nivolumab (NCT02648997), pembrolizumab (NCT03016091), and avelumab (NCT03267836) in the treatment of meningiomas that are high grade and/or refractory to adjuvant radiation therapy. Immune checkpoint inhibitors may prove to be effective therapeutic options for recurrent and high-grade meningiomas in the future and may even be used as a first-line alternative to surgical resection.

CONCLUSION

In summary, meningiomas are common histologically and genetically diverse tumors. The clinical outcome depends largely on the location, histologic grade, and treatment method with extent of surgical resection being the major determinant. Though the current pathologic grading system is reliable, further genetic and molecular classification schema are likely to enhance prognostic precision.

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