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Multiple meningiomas of different variants in a single patient: illustrative cases

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BACKGROUND Meningiomas are the most common primary intracranial tumors, accounting for approximately one-third of all primary brain neoplasms, typically characterized by a single histological variant. Multiple meningiomas are a relatively rare occurrence in a single patient, particularly when exhibiting different histopathological variants.

OBSERVATIONS The authors present the cases of three patients, each with two separate intracranial meningiomas of different variants. One patient had secretory and angiomatous meningiomas, while two patients had transitional and psammomatous meningiomas.

LESSONS Studies of multiple meningiomas, especially cases like those in this report with different subtypes, will highlight how genetic mutations correlate with tumor location, histology, and possible clonal origins. Certain mutations, such as TRAF7 and KLF4, are linked to secretory meningiomas, while others like neurofibromatosis type 2 are associated with specific locations and fibrous histology. The presence of mutually exclusive mutations suggests that different meningiomas can either arise independently or share a common progenitor cell with divergent mutations. Comparing genetic profiles of multiple meningiomas in a single patient can clarify tumor pathogenesis and support the development of targeted therapies, aiding in personalized treatment strategies and improving outcomes.

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KEYWORDS multiple meningiomas; secretory meningioma; angiomatous meningioma; transitional meningioma; psammomatous meningioma; molecular genetics of meningioma

Meningiomas arise from the arachnoid cap cells of the arachnoid membrane, which envelops the brain and spinal cord. The clinical course and prognosis of meningiomas vary, depending on several factors, including histological subtype, size, location, and genetic profile. While most individuals harbor a single meningioma, the presence of multiple synchronous or metachronous tumors of different histological types represents a rare, intriguing phenomenon. Understanding the genetic underpinnings of these diverse meningiomas is crucial for elucidating their pathogenesis and biological behavior and informing treatment decisions.

Meningiomas are the most common type of benign brain tumor, accounting for one-third of brain tumors overall, exhibiting female predominance (female/male ratio 3.15:1), and presenting with diverse histopathological subtypes. Fifteen subtypes are currently codified in the World Health Organization classification.[1]Multiple meningiomas occurring within a single patient, especially displaying distinct histological variants, are exceedingly rare. Multiple meningiomas are characterized by the presence of more than one synchronous or metachronous meningioma in different regions without germline mutations associated with neurofibromatosis type 2 (NF2) or SMARCB1 mutation.[2,3] Meningiomas that are close to each other or that demonstrate regional multicentricity leading to recurrences are excluded from this definition.[4,5]

In the past, multiple meningiomas were diagnosed only rarely, but due to ongoing improvements in imaging technology, today they are seen with more regularity.[2]Histologically, a patient's multiple meningiomas are typically identical.[6–8] However, there are rare cases of multiple meningiomas with different histological subtypes.[8–11]

Herein, we describe three patients with multiple meningiomas: one patient had secretory and angiomatous meningiomas and two had transitional and psammomatous meningiomas. We focus on the genetic underpinnings and implications for diagnosis and management.

Illustrative Cases

Case 1

After a fall at home, an 82-year-old female patient's imaging revealed two extra-axial masses: one on the anterior left frontal convexity measuring 3.9 × 3.3 × 2.8 cm and the other along the lateral left frontal convexity measuring 2.2 × 1.3 × 2.3 cm (Fig. 1A). The left

ABBREVIATIONS NF2 = neurofibromatosis type 2; PAS = periodic acid–Schiff.

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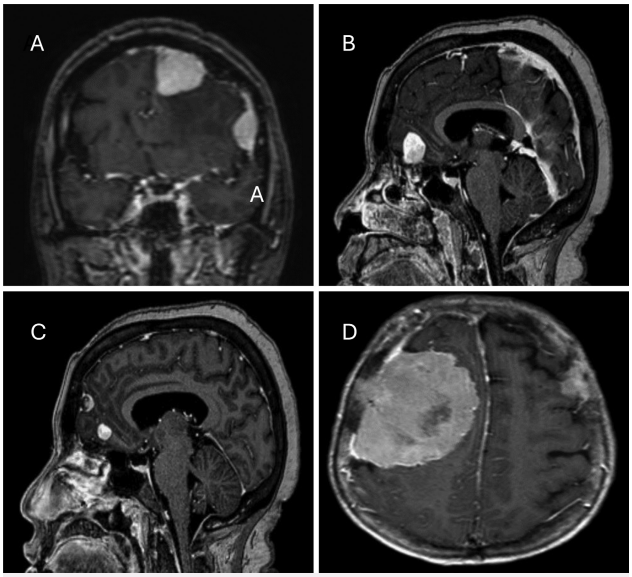

FIG. 1. A: Case 1. Preoperative coronal postcontrast MRI scan. **B and C:** Case 2. Preoperative sagittal postcontrast MRI scans. **D:** Case 3. Preoperative axial postcontrast MRI scan.

falcine tumor was a secretory meningioma displaying eosinophilic secretions (Fig. 2A), highlighted by periodic acid–Schiff (PAS) stain (Fig. 2B). The left temporal falcine tumor was an angiomatous meningioma displaying vascular components in more than 50% of the tissue (Fig. 2C).

Case 2

A 77-year-old female patient with chronic migraine headache had slowly growing extra-axial masses. At the time of surgery, there was a mass in the right olfactory groove measuring 2.8 × 2.4 × 2.1 cm and a left anterior parafalcine mass with a diameter of 0.9 cm in greatest dimension (Fig. 1B and C). The olfactory groove mass displayed a mix of fibroblastic and meningothelial features consistent with a transitional meningioma (Fig. 3A). The parafalcine mass showed numerous psammoma bodies that are typical of a psammomatous meningioma (Fig. 3B).

Case 3

A 49-year-old female patient presented with headache. Imaging revealed a 7.4 × 7.0 × 5.4–cm right frontotemporal mass and a left frontotemporal mass measuring up to 2.2 cm in greatest dimension (Fig. 1D). The right-sided mass displayed the mixture of fibroblastic and meningothelial cells that typify a transitional meningioma (Fig. 3A), and the left-sided mass showed numerous psammoma bodies that are associated with a psammomatous meningioma (Fig. 3B).

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

The cell of origin for meningiomas is believed to be the arachnoid cap cell type, based on morphology.[2] Cases of multiple meningiomas are rare in the absence of germline mutations of NF2 or SMARCB1, but the incidence of this unusual situation is increasing with improved imaging techniques.[2,3]

The relationship between genetic pathways and variant morphology in meningiomas is complex and still being actively researched. Although a single genetic alteration might not always directly determine the specific morphology of a meningioma, there are clear associations between certain pathways and the appearance and behavior of different subtypes. For example, clonality in multiple meningiomas has been demonstrated through genetic studies that incorporate X chromosome inactivation analysis or the sequencing of NF2 mutations.[6,7] These findings suggest a migratory process involving a single progenitor cell. However, Stangl et al. also demonstrate cases of multiple meningiomas without detectable mutations, which may represent co-occurring but different genetic processes.[6] The techniques available at the time of these studies limited the analysis. It now appears that multiple mutations can result in meningiomas and that specific mutations are associated with histological subtypes.[12–14]

We are beginning to understand how they are associated. Somatic mutations of the NF2 gene, including point mutations and deletions of chromosome arm 22q, are the most commonly seen in meningiomas.[12–14] This gene encodes the Merlin protein, which links plasma membrane receptors to the cytoskeleton. Mutations affect the contact-mediated inhibition of cell proliferation and modulation of multiple signal pathways including the Pi3K-AKT-mTOR pathways.[13] Psammomatous meningiomas frequently have NF2 mutations, and some transitional meningiomas do as well.[12,13] Other mutations are associated with meningiomas, but they usually do not coexist with NF2 mutations.

The Pi3K-AKT-mTOR pathway is another target of mutations. Pi3K mutations result in uncontrolled cell growth and are frequently associated with meningothelial and transitional histology. Pi3K mutations are

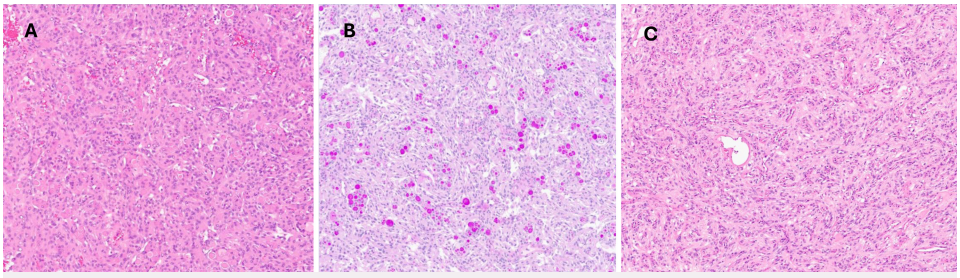

FIG. 2. Case 1. **A:** Secretory meningioma. **B:** Secretory meningioma. **C:** Angiomatous meningioma. Hematoxylin and eosin (H&E) (A and C) and PAS (B), original magnification ×100.

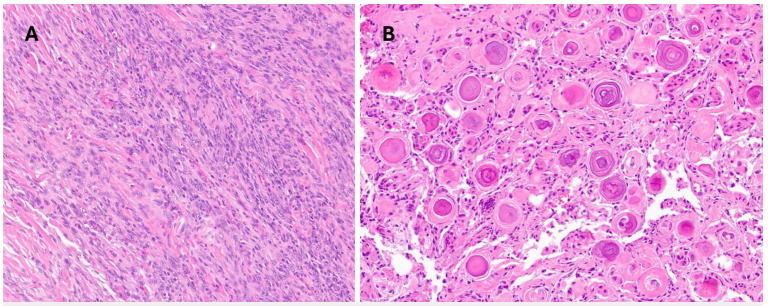

FIG. 3. Cases 2 and 3. **A:** Transitional meningioma. **B:** Psammomatous meningioma. H&E, original magnification ×200.

never seen in conjunction with NF2 or AKT mutations. AKT mutations are found in 30% of skull base meningiomas and are associated with meningothelial histology. They are not seen in conjunction with NF2 or KLF4 mutations.[12–14]

Secretory meningiomas, on the other hand, have shown mutations in both TRAF7 and KLF4.[12–14] TRAF7 is a proapoptotic E3 ubiquitin ligase associated with tumor genesis, and its mutations are considered mutually exclusive with NF2 mutations in meningiomas. KLF4 mutations occur in 50% of non–NF2-mutated meningiomas. They induce pluripotency and are also considered mutually exclusive with NF2 mutations.[13]

Angiomatous meningiomas show a distinct cytogenetic profile: polysomy of at least one chromosome, most commonly chromosome 5, 13, or 20.[15,16] It was hypothesized by Abedalthagafi et al. that the overall growth and proliferation signals outweigh the stress of being aneuploidy.[16] Although correlation has not been determined, several vascular development genes are located on chromosome 5 (PDGFR, FGFR4, and FGF10). While TERT, the telomerase reverse transcriptase, is located at 5p15.33, its expression is not increased.[15] This genotype and TERT expression pattern have also been detected in the microcytic histological subtype.[15]

Mutation type appears to be correlated with spatial location, as reviewed by Fountain et al.[12] Mutations in NF2 are associated with fibrous, psammomatous, transitional, atypical, and anapestic meningiomas, which constitute the majority of histological subtypes in the flax cerebri, tentorium cerebelli, and cerebral and cerebellar convexities. Studies with animal models suggest that these meninges derive from neural crest cells. Interestingly, meningiomas located at the skull base can involve the Pi3K-AKT-mTOR pathway, which is downstream from NF2. Animal models of skull base meningiomas suggest a mesodermal origin. Additionally, TRAF7 mutations frequently develop in the skull base. Isolated TRAF7 mutations are associated with microcytic histology.[12,13] KLF4 mutations tend to occur in lesions at the skull base, away from the midline.[12]

Epigenetic alterations, such as DNA methylation and histone modifications, can influence gene expression and contribute to the development of specific morphologies. Other factors like the tumor microenvironment can influence cell differentiation and contribute to variant morphology. Hormonal influences, particularly progesterone and estrogen, might play a role in the morphology of some meningiomas.

Lessons

When we review studies of multiple meningiomas that feature different subtypes, we must think about both the genotypic spatial correlations. In Sheng et al., a right frontal convexity meningioma showed secretory histology and had mutations in TRAF7 and KLF4.[11] While these mutations occur more frequently at the skull base, the genotype and phenotype do correlate.[12] The second tumor was in the right parietal convexity and showed fibrous histology and mutations in NF2 and elsewhere. This location is in keeping with the NF2 mutations. Interestingly, the two meningiomas have mutations that are believed to be mutually exclusive. In Klein et al., the first case presented had two secretory meningiomas: one was in the left frontal convexity and the other was a left tectorial mass.[10] A third left frontal mass, discovered 2 years after the original resection, showed meningothelial patterns with focal microcystic areas. This case might represent a clonal process with the first two lesions. The third lesion could represent a local recurrence, as microcystic and secretory meningiomas have TRAF7 mutations in common. The second case presented by Klein et al. involves a cavernous sinus lesion with meningothelial histology and a right frontal convexity lesion with secretory and meningothelial histology.[10] Skull base lesions can have mutations in the Pi3K-AKT-mTOR pathway. Since AKT mutations are considered mutually exclusive with the KLF4 mutations seen in secretory meningiomas, these lesions might be independent or possibly share a common KLF4 mutation with an additional PI3K mutation in the meningothelial subtype.

The first case we present showed secretory and angiomatous histology. These phenotypes are associated with very different genotypes, arguing against a common progenitor cell. The second case involved a mass of the olfactory groove with fibroblastic and meningothelial histology, both of which can be associated with mutations of the Pi3K-AKT-mTOR pathway. The second falcine mass in this case showed psammomatous histology, which could be associated with an NF2 mutation. The NF2 and Pi3K-AKT-mTOR pathway mutations are considered mutually exclusive. The third case presented involved a right frontotemporal transitional meningioma and left frontotemporal psammomatous meningiomas, which could represent a clonal process involving NF2 mutations. Further studies on such rare cases, contrasting cases likely involving different pathways (case 1) against cases involving the same or similar pathways (cases 2 and 3), will help us elucidate the genetic pathogenesis of meningiomas and the relation between morphology and genetics.

Modern pathology increasingly requires histopathological and molecular criteria for diagnosis and prognosis. While many meningiomas could be resected without recurrence, skull base lesions are more difficult to resect. Multiple meningiomas can add to the difficulty of treatment. The development of targeted therapy, such as alpelisib, a Pi3k inhibitor, will necessitate molecular analysis for the treatment of tumors.[14] However, with careful histological analysis, pathologists

will be able to guide genetic analysis and prognostic testing. By comparing the genetic profiles of different variants from the same patient, researchers can identify specific mutations that are unique to each variant and potentially contribute to its distinct morphology and behavior. This information can be used to develop targeted therapies tailored to the specific genetic makeup of each variant, improving treatment efficacy and reducing side effects.

The most significant limitation of our mini-series/case report is the lack of genetic testing on these cases. In publishing our rare cases, we seek an opportunity for collaboration and hope to contribute to the genetic pathogenesis and underpinning of morphological variants of meningioma.

The lessons learned or our take-home message would be that further study of multiple meningiomas, especially cases like ours with different subtypes, will highlight how genetic mutations correlate with tumor location, histology, and possible clonal origins. Certain mutations, such as TRAF7 and KLF4, are linked to secretory meningiomas, while others like NF2 are associated with specific locations and fibrous histology. Comparing genetic profiles of multiple meningiomas in a single patient can clarify tumor pathogenesis and support the development of targeted therapies, aiding in personalized treatment strategies and improving outcomes.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Cai, Reddy. Acquisition of data: Cai, Reddy. Analysis and interpretation of data: Cai. Drafting the article: Cai, Olson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Cai. Study supervision: Cai.

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