

A case series of multiple meningiomas with different histology



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ABSTRACT

Multiple meningiomas (MMs) tend to be benign with uniform histology. It is uncommon to find sporadic MMs having different histological features in the same patient. In this case series, of the four patients diagnosed with MM, two patients had different histopathology. An updated review of literature was then performed, providing the different histopathology in those cases. The first case was unique as the patient had an intradiploic meningioma with an intraparenchymal meningioma. Histology found in these cases represented WHO Grade I meningioma. After performing a literature search, it is likely that these tumors do not arise from clonal expansion, but rather have an independent origin.

Key words: Multiple meningiomas; Different histology; Intra-diploic; Meningioma; WHO grading

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INTRODUCTION

In 1938, Cushing and Eisenhardt first coined the term “meningioma.” Although many arise singly, an entity known as “multiple meningiomas (MMs)” also exists. In the same year, the duo defined MM as “at least two spatially separated meningiomas in a patient without signs of neurofibromatosis.” The concept of spatial separation is more important than the time interval between the tumor appearances or their simultaneous existence. MM occurs in 1–9% of patients.¹ Most MM has a benign nature with uniform histology.² It is much less common to find sporadic MM having different histological features in the same patient.³ Due to its unclear etiology, relative rarity, and problems-related to management strategy, the multiple histopathology feature of the meningioma attracts much interest among neurosurgeons. Herein, four patients diagnosed with MM, out of which two patients had

different histopathology, are presented. An updated review of literature regarding MM and the probable pathogenesis of the different histopathology in MM was performed.

CASE DESCRIPTION

This study did not require ethics approval. In this case series, two patients were found to have MM of different histology (Table 1). The first case was unique as it had an intradiploic meningioma at a site different from the other lesion. All of the four cases had a benign histopathology. A literature search was conducted to see the outcomes of patients with cranial MM and compare them with what was presented in this report. The results of the same are presented as shown in Table 2. The articles included did not include MM arising in the setting of prior irradiation or NF2. The cumulative diversity of the 47 tumors identified is shown in Table 3. Fibrous/fibroblastic histology

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Table 1: Patient demographics, presentation, and histopathological findings of the four cases included in the present study

Patient Details	Clinical Presentation	Number of Tumors	Location	Histopathology (respectively)	Intervention	Patient Outcome
Case 1: 50-year-old female	Headache, right-sided weakness	2	1. Left frontoparietal convexity 2. Left parietal bone	1. Meningothelial 2. Fibroblastic	Left frontoparietal craniotomy and excision	Symptomatic improvement reported.
Case 2: 65-year-old male	Disorientation, headache, seizures	2	1. Left parieto-occipital convexity 2. Right parietal convexity	1. Meningothelial 2. Transitional	1. Left parieto-occipital craniotomy and excision 2. Right parietal craniotomy and excision	The patient had seizures after the first procedure warranting a second procedure to remove the other meningioma. The patient was put on anti-epileptic drugs after the second procedure and showed symptomatic improvement.
Case 3: 45-year-old female	Headaches	3	1. Right parietal convexity 2. Frontal region, neighboring the falx cerebri. 3. Parietal region, neighboring the falx cerebri.	—	—	No surgical intervention was taken.
Case 4: 45-year-old female	Headaches, Behavioural disturbances	2	1. Right frontal region 2. Right parietal, parasagittal region	—	—	The patient was not willing for surgery.

was recorded the most,⁴ followed by meningothelial/meningotheliomatous histology.⁵ Secretory and chordoid variants were recorded the least.⁶

CLINICAL CASES

Case 1

A 50-year-old female presented with complaints of headache over the previous year and right-sided weakness for 1 month. Clinical examination revealed right-sided hemiparesis. Magnetic resonance imaging (MRI) of the brain demonstrated a well-defined, homogeneously enhancing extra-axial mass located in the left frontoparietal convexity, and an intradiploic mass in the left parietal bone abutting the parietal lobe. The imaging findings are shown in Figure 1a. She underwent a large left frontoparietal craniotomy with excision of both the masses (Simpson's Grade 1) with mesh cranioplasty. Histopathologic section of the frontoparietal mass showed, predominantly, a meningothelial pattern, and the intradiploic lesion showed sheets of fibroblastic cells separated by collagen bundles consistent with a fibroblastic variety. Both tumors were of WHO grade I, and their microscopic features are shown in Figure 1b and c. In the post-operative period, the patient showed improvement in the weakness of the right side.

Case 2

A 65-year-old male initially presented with disorientation, a history of headaches and seizures. Examination revealed a

Glasgow Coma Scale score of 14 and Grade 2 papilledema. MRI brain demonstrated a large well-defined, homogeneously enhancing extra-axial mass in the left parieto-occipital convexity and a small, well-defined, and homogeneously enhancing extra-axial mass in the right parietal convexity. The imaging finding is shown in Figure 2a. The patient underwent a left parieto-occipital craniotomy and excision of the larger mass (Simpson's grade 2). The histopathologic section of the lesion is shown in Figure 2b, had a meningothelial pattern (WHO grade 1). The patient had multiple seizures 3 months after the surgery, and he was operated on the right parietal mass through a right parietal craniotomy with excision (Simpson's Grade 1). The histopathology of this lesion is shown in Figure 2c, revealed transitional meningioma (WHO Grade I). The patient showed seizure control after the surgery with anti-epileptic drugs.

Case 3

A 45-year-old female with a history of occasional mild headaches presented to the neurosurgery clinic. She had no neurological deficit on examination. An MRI of the brain revealed three well-defined extra-axial masses, which enhanced homogeneously with the dural tail sign, suggestive of meningioma. One lesion was in the right parietal convexity, and the other two lesions were abutting the falx cerebri in the frontal and parietal region. Figure 3 shows the imaging findings. As the patient had no neurological deficit and the lesions were of small size, the patient was kept under follow-up.

Table 2: Summary of previous cases of multiple meningiomas with different histology

Author (Publication date)	Patient details	Clinical features	Number of tumors resected (in each case)	Location	Intervention	Histopathology (respectively)	Patient Outcome
Sheng et al., ¹⁴ (2019)	52-year-old male	Headaches	2	1. Right frontal region 2. Right parietal convexity	Single stage surgery-removal of two bone flaps (Simpson grade I) Surgery	Secretory Fibrous	Symptomatic improvement noted.
Liu et al., ³ (2017)	66-year-old male	Headache, scalp protrusion, left-sided weakness	2	1. Right parietal lobe 2. Right parietal lobe (both tumors were adjacent to each other)	Surgery	Fibrous Atypical	Good outcomes were noted.
Yudoyono et al., ²⁰ (2015)	28-year-old male	Headache	3	1. Left frontal region 2. Left cerebellopontine angle	Surgery	1a. Fibrous 1b. Transitional 2. Meningotheliomatous	Improvement of neurological deficits was noted.
Yang et al., ² (2013)	67-year-old male	Right-sided hemiparesis, urinary disturbances, fever, vomiting	2	1. Left frontal lobe 2. Left insular lobe	Bifrontal craniotomy	Anaplastic Fibrous	Post-operatively, the patient had no neurological deficits.
Sriram ¹⁹ (2013)	38-year-old female	Headache	2	1. Right sphenoid wing 2. Left fronto-parasagittal area	1. Craniotomy and debulking 2. Craniotomy and resection	1. Chordoid 2. Meningotheliomatous	Due to complaints of headache and seizures, a second surgery was planned for the patient. The patient reports satisfaction with life, despite having visual disturbances and slight ataxia.
Mocker et al., ¹⁷ (2011) *	36-year-old female	Headache, Hyperacusis	8 (spread over a total of 11 years) 1. 1996-one tumor 2. 1997- two tumors 3. 2005- three tumors 4. 2007- two tumors	1. 1996- right petrous bone 2. 1997- bilateral tentorium and median cerebellar convexity 3. 2005- medial cerebellar convexity (2) and left petrous bone 4. 2007- left-sided falcine meningioma in the parietal region and left-sided falcine meningioma in the occipital region	1. Simpson grade II 2. Tentorium- Simpson grade II; Cerebellar convexity- Simpson grade I 2. Cerebellar convexity (2)- Simpson grade I; Petrous bone- Simpson grade II; Parietal region- Simpson grade I; Occipital region- Simpson grade II	1. Fibroblastic 2. Fibroblastic (both) 3. Fibroblastic (all three) 4a. Transitional- atypical 4b. Transitional- psammomatous	
Ge et al., ¹⁶ (2010)	42-year-old male	Headaches	2	1. Left sphenoid ridge (2)	Single-staged left frontotemporal craniotomy	1a. Exterior- Fibrous 1b. Interior- Psammomatous	—

(Contd...)

Table 2: (Continued)

Author (Publication date)	Patient details	Clinical features	Number of tumors resected (in each case)	Location	Intervention	Histopathology (respectively)	Patient Outcome
Emmez et al., ¹⁵ (2010)	56-year-old female	Speech and balance difficulties	2	1. Frontal lobe, parafalxian 2. Right frontotemporal convexity	Single-staged bicoronal craniotomy	1. Meningothelial 2. Atypical	The patient was discharged with no further neurological deficit.
Tomita et al., ⁹ (2003)	61-year-old female	Dementia, decrease in activity, disorientation	2	1. Left sphenoid ridge 2. Left parasagittal region	Preoperative embolization with single-staged fronto-parieto-temporal craniotomy; Simpson grade 2	1. Anaplastic 2. Fibrous	There was an improvement in the patient's dementia and no tumor recurrence was noted after 3 years of follow-up. The patient's weakness gradually improved.
Koh et al., ¹² (2001)	65-year-old male	Headache, left leg weakness	2	1. Right frontal paramedian region 2. Left parietal convexity	Two-staged surgery resulting in complete resection of both tumors. 1. Adjuvant radiotherapy for right frontal meningioma.	1. Atypical 2. Psammomatous	The patient's weakness gradually improved.
Zhu et al., ²³ (1999)	57-year-old female	Diplopia, bilateral leg weakness	8	1. Parasagittal, attached to the dura (6) 2. Falx cerebri 3. Frontal convexity	1. Surgery (details not known)	1. T1-5, T8- Meningothelial 2. T6, T7- Transitional	—
Butti et al., ⁶ (1989) *	P1. 70-year-old male P2. 56-year-old female P3. 39-year-old female P4. 46-year-old female	P1- Bone bulging P2a. Visual deficits P2b. Paraparesis P3a. Visual deficits P3b. Hypoesthesia P3c. Anosmia P4a. Behavioral disturbances P4b. Behavioral disturbances P4c. None P4d. None	P1. 2 P2. 2 P3. 3 P4. 4	P1a. Left anterior falx P1b. Left frontal convexity P2a. Left sphenoid wing P2b. D4/D5 P3a. Left occipital convexity P3b. Right parietal convexity P3c. Olfactory groove P4a. Anterior falx P4b. Anterior falx P4c. Falx, tentorial P4d. Right occipital convexity	P1a. Simpson grade 1 P1b. Simpson grade 2 P2a. Simpson grade 2 P2b. Simpson grade 1 P3a. Simpson grade 1 P3b. Simpson grade 1 P3c. Simpson grade 2 P4a. Simpson grade 2 P4b. Simpson grade 1 P4c. Simpson grade 2 P4d. Simpson grade 1	P1a. Fibroblastic P1b. Meningothelial P2a. Meningothelial P2b. Psammomatous P3a. Meningothelial P3b. Meningothelial P3c. Fibroblastic P4a. Fibroblastic P4b. Fibroblastic P4c. Fibroblastic P4d. Meningothelial	No operative mortality was recorded.
Yamashita et al., ¹¹ (1989)	65-year-old female	1a. Cold sensation and tingling in both lower limbs, weakness in right leg 1b. Muscle weakness, hypesthesia	2	1a. Right ventral side of spinal cord at T2-3 1b. Left posterior fossa	1a. T1-4 laminectomy 1b. Left suboccipital craniotomy (enucleation with CO2 laser)	1a. Meningotheliomatous 1b. Fibroblastic	No neurological deficits were recorded postoperatively.

(Contd...)

Table 2: (Continued)

Author (Publication date)	Patient details	Clinical features	Number of tumors resected (in each case)	Location	Intervention	Histopathology (respectively)	Patient Outcome
Neuss et al., ¹⁰ (1988)	P1. 49-year-old female P2. 61-year-old female	—	P1. 3 P2. 2	P1a. Pre-sellar P1b. Left olfactory bulb P1c. Frontal falx P2a. Right cavernous sinus P2b. Right convexity	P1. Single stage surgery P2. Single stage surgery	P1a. Psammomatous P1b. Meningotheliomatous P1c. Meningotheliomatous P2a. Meningotheliomatous, P2b. Fibrous	—

The age of first tumor resection is mentioned (*) for some studies. P: Patient, T: Tumor

Table 3: Frequency of MM histopathology as per the published literature included in the present review. Respective WHO grade of meningioma enclosed in parentheses

WHO meningioma histopathology	Number of tumors
Fibrous/Fibroblastic (I)	19
Meningothelial/Meningotheliomatous (I)	13
Transitional (I)	4
Psammomatous (I)	4
Secretory (I)	1
Atypical (II)	3
Chordoid (II)	1
Anaplastic (III)	2

Case 4

A 45-year-old female with a history of headache and irrelevant behavior presented to the neurosurgery clinic. The patient showed deficits in her frontal lobar examination with bilateral Grade I papilledema and right-sided hemiparesis. An MRI of the brain revealed two, multilobulated and separate masses in the right frontal and parietal parasagittal region with dural-tail sign, suggestive of meningioma. Figure 4 shows the MM. Despite being advised for surgery, the patient was not willing for the same.

DISCUSSION

The incidence of MM is estimated to be 1–10%.⁴ Its rising incidence has been attributed to the abilities of the computed tomography scan to detect smaller tumor nodules.⁶ A common association of MM is neurofibromatosis Type 2, caused by mutation of the NF2 gene. NF2 is a tumor suppressor gene that requires both alleles to be lost to express disease (two-hit hypothesis). NF2 produces the gene product known as Merlin, also called schwannomin. Neurofibromatosis Type 2 causes a neurological tumor phenotype of meningiomas, acoustic neuromas, and ependymomas. In those with NF2 mutations, 50% will develop at least one intracranial meningioma in their life.⁷ Although neurofibromatosis Type 2 is an important autosomal disorder causing MM, this relationship may be overemphasized. MM arising due to the influence of the NF2 allele accounts for only 1% of all cases, whereas 4% of cases occur independently of NF2 allelic aberrations.⁸ Nonetheless, non-NF2 originated that MM is still a rare phenomenon. It is estimated that slightly more than one-third of MM have different histology.⁹

There are two distinct hypotheses for MMs. The first suggests that the tumors arise independently from each other. This theory is backed by histological and cytogenetic examinations, which revealed microscopic and karyotypic differences in multiple tumors in the same patient. The

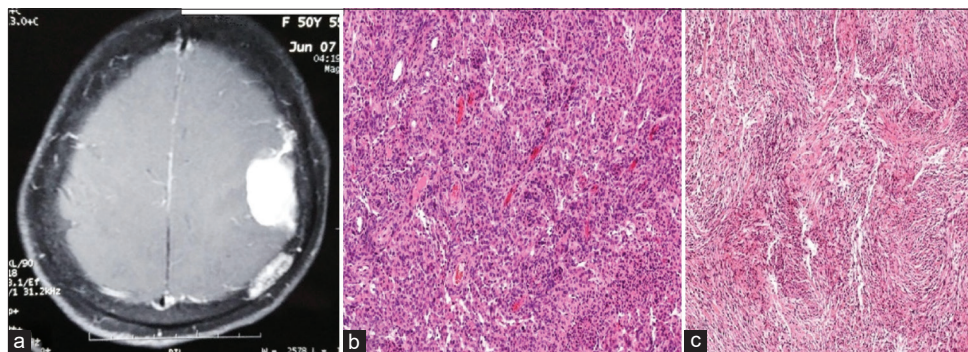


Figure 1: (a) A T1-weighted MRI image with contrast showing a homogeneously enhancing extra-axial mass located in the left frontoparietal convexity and an intradiploic mass in the left parietal bone abutting the parietal lobe. (b) Histopathologic section of the frontoparietal mass showing predominantly meningothelial pattern (WHO Grade I). (c) Intradiploic lesion showing sheets of fibroblastic cells separated by collagen bundles, consistent with the fibroblastic type of meningioma (WHO Grade I)

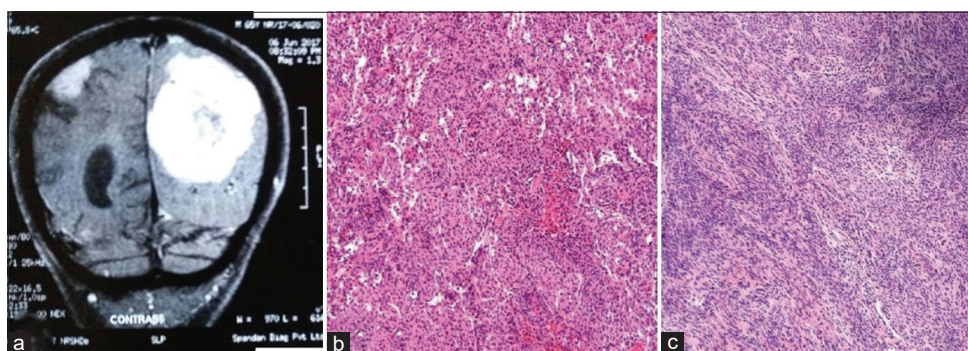


Figure 2: (a) A T1-weighted MRI image with contrast showing large well-defined, homogeneously enhancing extra-axial mass in the left parieto-occipital convexity and a small, well-defined, and homogeneously enhancing extra-axial mass in the right parietal convexity. (b) Histopathologic section of the left parieto-occipital lesion showing a meningothelial pattern (WHO Grade I). (c) The histopathology of the right parietal convexity lesion revealing a transitional meningioma (WHO Grade I)

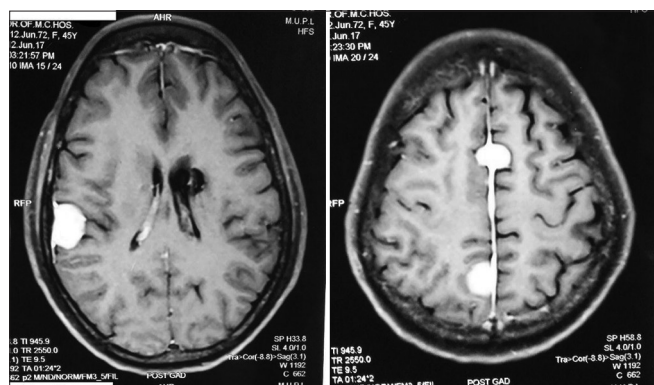


Figure 3: A T1-weighted contrast MRI scan showing a homogeneously enhancing extra-axial lesion in the right parietal convexity and two other lesions abutting the falx cerebri in the frontal and parietal region with the dural-tail sign

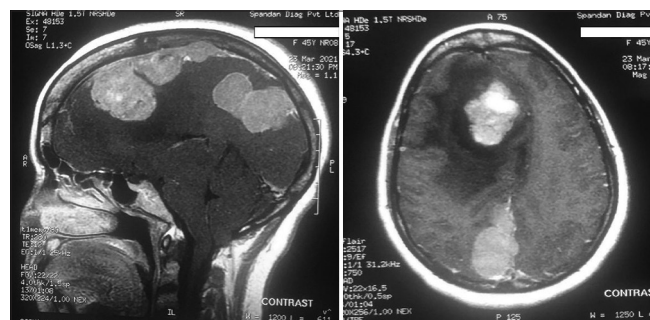


Figure 4: A T1-weighted contrast MRI image showing multiple meningioma. The left frontal parasagittal mass shows significant perilesional edema

second hypothesis suggests that a single triggering event causes the original clone of cells to spread throughout the meninges, resulting in multiple and clonally-related tumors.⁹

The earliest case of MM with different histology dates to 1988 when Neuss et al.,¹⁰ found that two out of their eight cases had this unique feature. A year later, the report by Yamashita et al.,¹¹ described a case of MM present in the

thoracic spinal cord and the posterior fossa. Their work illustrated only the fourth case of that unique combination.¹¹

Butti et al.,⁶ reported four cases of different histology out of their case series of eight patients. Three cases were operated on a tumor of different histology (TDH) after at least a year in those four cases. P1 (patient 1) had a time gap of 3 years before operating on the second TDH. One-year after her first tumor resection, P2 underwent surgery for the TDH. P3 was operated on a TDH 16 years after

her initial tumor surgery. There was a lapse of 7 years between the initial operation for P4 and the operation for the TDH. Only three patients had multiple tumors detected on initial imaging. After performing cytogenetic studies for five patients, eight neoplastic specimens were identified. No specific abnormality for MMs was found compared to single meningiomas (SMs), but they found a different origin for each tumor and excluded cellular migration through the subarachnoid space as a causative factor in MMs.

In 2001, Koh *et al.*,¹² published a report of a patient with MM having both benign and malignant pathology. Pathological diagnosis showed that the patient had a psammomatous meningioma in the left parietal region and an atypical meningioma in the right frontal falx region. The authors claimed it to be the first case reported where two tumors existed concurrently, with each having different histology (benign versus malignant).

Two years later, Tomita *et al.*,⁹ reported a case of a 61-year-old female with two mass lesions at the left sphenoid ridge and the left parasagittal region. The tumor in the sphenoid ridge was suggestive of anaplastic meningioma, and the parasagittal tumor corroborated to fibrous meningioma histologically. After using anti-schwannomin immunohistochemistry, both tumors did not express schwannomin, ruling out a mutation of the NF2 gene.⁹ The sphenoidal ridge tumor did not express neurofibromin after performing the same examination with anti-neurofibromin immunohistochemistry. However, the parasagittal tumor did. This meant that a mutation of the NF1 gene existed within the sphenoid ridge meningioma.

By far, Huang *et al.*,¹³ described the most significant number of cases of MM with different histology. In 2005, the team reported 39 cases of MM, out of which 29 patients had two meningiomas, five patients had three, and five patients had more than three meningiomas. Of the patients described, some had six meningiomas at most. There were no associated spinal meningiomas. They excised more than two meningiomas in 19 patients. None of the patients had neurofibromatosis Type 2. The excised tumors showed an identical histological pattern in 12 patients and different histological features in seven. The study did not go into the specifics of histology for the seven patients. They compared SM with MMs and concluded that progesterone receptor expressivity is higher in MM than in SM. They also showed that there is a female predilection for MM when compared to SM. Concerning SM; males have a slightly higher risk of developing the malignant subtypes.^{3,14}

In 2010, Emmez *et al.*,¹⁵ reported a case of a giant right frontal parasagittal meningioma with a smaller mass in the right frontotemporal convexity. Both the masses were

excised in a single sitting. Histology of the giant mass was suggestive of meningothelial meningioma (WHO Grade I), and the histology of the smaller mass was an atypical meningioma (WHO Grade II). In the same year, Ge *et al.*,¹⁶ put out a report describing a male patient with MM located at the sphenoid ridge. Histopathologic examination revealed one fibrous and one psammomatous meningioma.

One year later, Mocker *et al.*,¹⁷ carried out a thorough genetic analysis in a 36-year-old female with MMs. They reported both WHO Grade I and II meningiomas concurrently, sharing terminal deletions on chromosome 1p. In addition, the higher-grade meningioma also showed a paracentric inversion within 1p36. They were the first to describe low-frequency dicentric chromosome 4. This was identified in both tumor nodules. They concluded that the paracentric inversion and dicentric chromosome 4 has to be further explored in a larger group of meningiomas. Three out of the four operations they performed ended with resection of at least two tumors. This patient had a total of eight tumors distributed across a bit more than a decade. Butti *et al.*,⁶ proposed that multiplicity of meningiomas were partly due to aging. However, the middle-aged patient described by Mocker *et al.*,¹⁷ did not follow this convention.

After reporting different histology of meningioma in the same patient, many authors have negated the hypothesis of a single transforming event causing tumorigenesis and are currently giving more credence to independent occurrence for these tumors.^{9,12,15}

Recently, Sheng *et al.*,¹⁴ published a study elucidating the clonal relationship between two sporadic meningiomas of different histology from the same patient using a next-generation sequencing platform. The 52-year-old male patient underwent tumor excision frontally and another one parietally. Pathological examinations, whole-exome sequencing, and sanger sequencing were performed on the samples. The masses were diagnosed as secretory and fibrous subtypes on histology (WHO Grade I). The tumor DNA exhibited unique somatic mutation patterns. This strongly suggested that the two tumors have developed independently in this patient. Their team demonstrated that molecular subtyping is valuable to standard cellular diagnostic methods.

The optimal management of each WHO grade of meningioma is beyond the scope of this literature review. However, what is certain is that MM themselves can pose significant challenges to the surgeon. MM may cause difficulties when surgery is indicated due to their large size or proximity to major vasculature. The latter feature may only permit subtotal resection of the tumor. The grading for meningioma tumor resection was eponymously named

after Dr. Simpson as he was the first to identify that radical resection was the antidote for limiting tumor recurrence.¹⁸ Incomplete resection, as a result of intraoperative obstacles, may inevitably lead to the growth of the tumor, causing reappearance or worsening of the patients' symptoms. Surgeons may have to deal with this by performing multi-staged surgeries, as were the circumstances in three of the mentioned studies.^{12,19,20} Beyond this, the post-operative course from the initial surgery may be tumultuous and characterized by complications, malignant transformations, the requirement for supplementary therapy to address resistant tumors, and additional surgeries to address the sporadic tumors as they arise.

Specific histological variants are accompanied by their troublesome characteristics. In the 42-case experience of chordoid meningiomas put forth by Couce et al.,²¹ 42% of their follow-up patients experienced a recurrence. Their team concluded that chordoid meningiomas have a notorious predilection for recurrence, especially if subtotal resection is performed as all but one of their sub-totally resected tumors recurred. WHO Grade I meningiomas have a recurrence rate of approximately 47% with extended follow-up.²² One retrospective study found that 64% of their patients with atypical meningioma had a recurrence or progression.⁵ Four articles in this review described tumor recurrences.^{6,19,20,23} Considering the histopathological variant of the meningioma may warrant the need for pre-emptive supplemental therapy and close follow-up.

CONCLUSION

Although meningiomas are a common tumor, non-NF2-associated MM is still an uncommon entity, and those having different histologic characteristics are even rarer. A literature search suggested that MM have an independent origin, and its genesis is not related to clonal expansion. This conclusion is supported by the histological and cytogenetic examinations, which revealed microscopic and karyotypic differences in multiple tumors in the same patient.

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