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Somatic SMARCB1 mutation in spinal meningioma represents branched evolution in a patient with multiple sporadic meningiomas

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Multiple meningiomas (MMs) are defined in this manuscript by the presence of at least 2 lesions without associated neurofibromatosis (NF) or Schwannomatosis. MMs in spatially separated neuraxial compartments (brain and spine) are extremely rare. MMs occurring without NF type 2 (NF2) still frequently harbor somatic mutations in the *NF2* locus, along with mutations in *AKT1, TRAF7, SMO, PIK3CA*, and *SMARCB1*. While the origin of MMs can be multiclonal, monoclonally originating tumors often go through branched evolution introducing intertumoral variation in histology, grade, and mutational landscape. We conducted whole exome sequencing on tumors and matched blood samples from a non-NF2 64-year-old female with 3 cranial meningiomas and one spinal meningioma. While chr22 loss was shared among all tumor samples, the cerebral and spinal meningiomas harbored different unique *NF2* mutations, and the spinal meningioma acquired a new *SMARCB1* mutation, indicating a monoclonal origin followed by a branched evolution. This is the first report highlighting the intertumoral heterogeneity and branched evolution of a non-NF2 patient harboring MMs in separate neuraxial compartments.

Meningiomas can occur in the brain or spine as solitary or multiple lesions. Multiple meningiomas (MMs) can be either synchronous (occurring at the same time) or metachronous (arising sequentially over time).[1] Multiple meningiomas can occur sporadically, in association with radiation, or in the context of a genetic tumor syndrome. They constitute approximately 1–10% of all meningiomas, increasing in incidence with age.[1,2]

MMs may have distinct (multiclonal) or shared (monoclonal) genomic profiles. Multiclonal MMs harbor distinct somatic mutation profiles pointing to their independent origin. Monoclonal tumors are thought to arise from a single clonal transformation and subsequent spread of the transformed cells through the cerebrospinal fluid to seed multiple loci.[3] However, not all monoclonal tumors share the same mutation profile, tumor grade, or histopathologic subtype. This genetic heterogeneity and morphologic variation could be explained by branched evolution, where additional somatic alterations emerge forming new subclones and seeding additional lesions.[4] We report a case of sporadic MMs involving both cranial and spinal lesions.

Case

A 64-year-old female was found to have multiple lesions suspicious of meningiomas after MRI scans were performed after a fall (Figure 1). These included 3 cranial masses (CM) in the left frontal and parietal regions, as well as an intradural, extramedullary spinal lesion (spinal mass, SM) at the thoracic 2–3 level. Medical history was notable for ductal carcinoma in situ of the breast for which she underwent a right mastectomy and sentinel node biopsy, and then completed tamoxifen therapy. She had no significant prior radiation exposure. There was no known family history of neurological or neurocutaneous disorders. The patient was initially neurologically intact and elected to maintain active surveillance over a 2-year period, during which she had stable intermittent headaches and progressive growth of the intracranial masses. At 2-year follow-up, she developed symptoms consistent with thoracic myelopathy.

Staged microsurgical resection of the cranial and spinal masses was performed. The thoracic lesion was resected first due to the symptomatic spinal cord compression and the anticipated need for a lumbar drain during craniotomy. Six weeks after resection of the spinal meningioma, the 3 intracranial masses were resected via a single craniotomy. The patient recovered uneventfully.

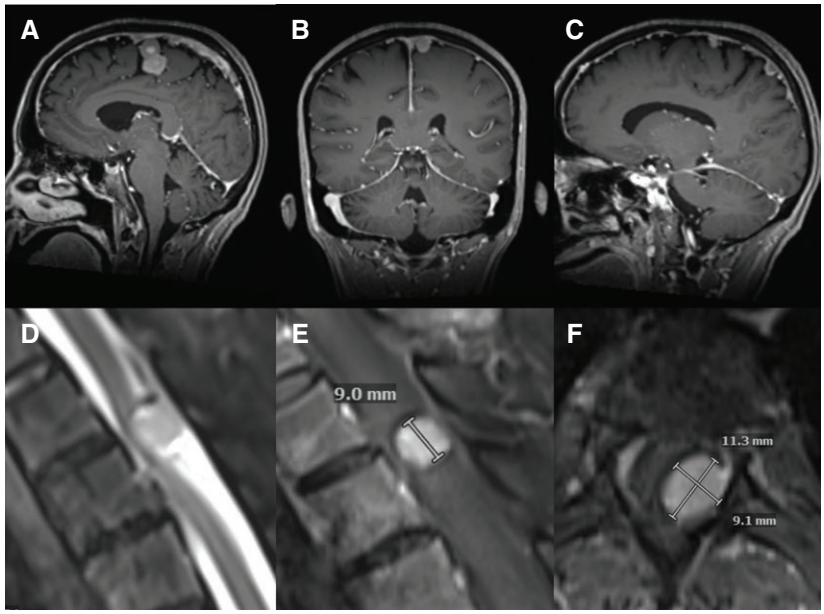

Figure 1. Radiographic findings. MRI brain—T1 contrast showing—axial, coronal, and sagittal sections of the Tumor 1 (A), Tumor 2 (B), and Tumor 3 (C) noted along the falx and parasagittal region. All lesions were resected through a single left parasagittal craniotomy and interhemispheric approach. MRI of the thoracic spine—Sagittal T2W (D), Sagittal T1W-Post Contrast (E), Axial T1-Post contrast (F) showing dural based intradural extramedullary mass extending from T2 to T3. The spinal cord is compressed by the tumor and displaced to the right as noted in the axial images.

All tumors were classified according to the 5th edition of the CNS WHO classification system[5] and reviewed by a board-certified neuropathologist (D.M.). Meningothelial lineage (CNS WHO grade 1) was confirmed through immunohistochemistry (IHC) staining for EMA and PgR. Histopathologic analysis revealed that the spinal tumor exhibited higher cellular density compared to the cranial tumors (Figure 2). Ki-67 expression positivity was similar across the lesions (CM1: 1–2%, CM: 3–4%, CM3: < 1%, SM: < 3–4%) (Supplementary Table S1).

Genomics Findings

Whole exome sequencing (WES) was performed on genomic DNA derived from each of the 4 tumors and matched peripheral blood. The genomic findings from the 3 cranial meningiomas (CM1, CM2, and CM3) and one spinal meningioma (SM) are displayed in Figure 3A–D. Analysis of the cranial meningiomas revealed 17, 9, and 17 total somatic alterations, reflecting both single-nucleotide variants (SNVs) and insertions/deletions (INDELs) in CM1, CM2, and CM3, respectively (Supplementary Tables S2–S5). Notably, all 3 cranial meningiomas shared a stop-gain mutation in *NF2* (p.K20X) with variant allele frequencies (VAF) of 45.9%, 49.8%, and 44.4% in CM1, CM2, and CM3, respectively, suggestive of clonal events, and were absent in the matched normal blood sample. Somatic copy number variation (CNV) analysis indicated that only a minimal portion of the genome was altered by somatic CNV events in all 3 cranial meningiomas, specifically of interest a single-copy deletion of chromosome 22q, likely representing the second hit (Figure 3).

Although the spinal meningioma displayed a similar CNV profile to the cranial tumors, including the chromosome 22q deletion, WES identified a distinct *NF2* stop-gain mutation (NM_000268, p.W191X) along with a *SMARCB1* mutation (NM_001007468, p.R365Q). *SMARCB1* mutations have been previously reported in meningiomas, often co-occurring with *NF2* somatic alterations. The identified missense mutation (p.R365Q), which is classified as "Pathogenic" in ClinVar and predicted to be "deleterious" by impact prediction tools such as SIFT, PolyPhen-2, and MetaSVM, resides in exon 9, a known hotspot region for *SMARCB1* mutations in meningiomas. The VAFs of the *NF2* p.W191X and *SMARCB1* p.R365Q mutations were found to be 71.1% and 61.7%, respectively, resulting in bi-allelic loss caused by a co-occurring chromosome 22q deletion encompassing both *NF2* and *SMARCB1*.

Phylogenetic analysis of all somatic alterations, including SNVs, INDELs, and CNVs, revealed a monoclonal branched evolution originating from a founding clone with a chromosome 22q deletion. While the cranial branch acquired an *NF2* mutation (p.K20X), the spinal branch acquired both a distinct *NF2* mutation (p.W191X) and a *SMARCB1* mutation (Figure 3E).

No germline data revealed any pathogenic or likely pathogenic mutations related to a predisposition for meningiomas.

Methods

Genomic Analysis

Whole exome sequencing (WES) was conducted on both the tumor and blood samples from the index patient. DNA

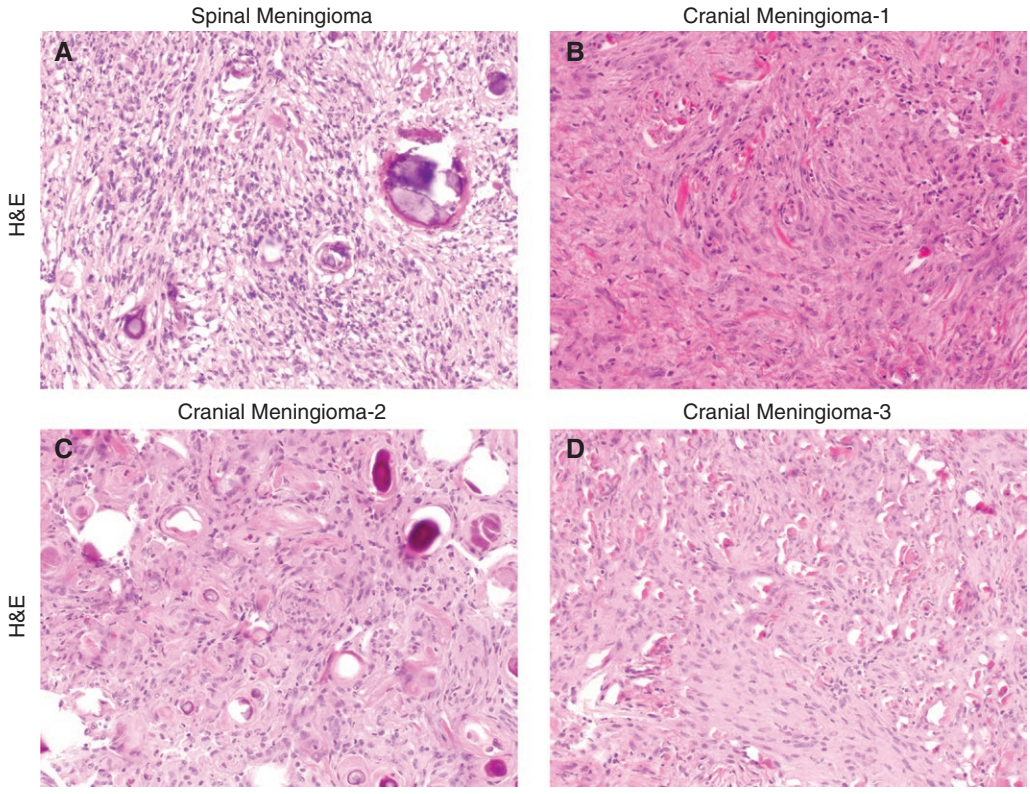

Figure 2. Histopathology. Meningiomas stained with hematoxylin and eosin (H&E) stain, showed strong diffuse nuclear hematoxylin staining in the spinal tumor (A) and cranial tumors (B–D). All images are at 200× magnification. Scale bars represent 250 μm distance.

extraction and exome capture were performed using the IDT xGen Research Panel Version 1 with additional spike-ins, and sequencing was executed at the Yale Center for Genome Analysis (YCGA) on the Illumina NovaSeq 600 WES systems, producing 2 × 101-bp reads. This process yielded a high mean coverage of 433.45× for the tumor and 111.4× for the blood samples. Downstream analysis included alignment to the reference genome (GRCh37), duplicate marking, and local realignment, all performed using the Genome Analysis Toolkit (GATK) (v3.4, GRCh37). Germline single-nucleotide variations (SNVs) and insertions/deletions (INDELs) were identified with GATK Haplotype Caller (v3.4). Variant annotations were conducted using ANNOVAR (version 2019-10-24) and VEP (v95). Rare germline variants were identified by filtering out variants with an allele frequency greater than 1% in control databases such as gnomAD-genome and gnomAD-exome (release 170,228) across all subpopulations. For somatic variant discovery, GATK Mutect2 (v4.4.0.0) was employed to call somatic SNVs and INDELs under default parameters in the tumor-matched normal mode using gnomAD as the germline reference. Post-variant calling, FilterMutectCalls was applied to exclude variants with a variant allele frequency (VAF) lower than the estimated contamination rate. Following the variant annotation with VEP, variants were kept if they exhibited a minor allele frequency (MAF) of ≥ 10%, passed quality assessments of Mutect2, had "Medium" or "High" impact classification per VEP, or were categorized as "Pathogenic" or "Pathogenic/Likely pathogenic" by ClinVar. This filtration approach was designed to select clinically and biologically significant SNVs suitable for further analysis. Copy number variations (CNVs) were assessed using GATK version 4.4.0.0, following the GATK Best Practices guidelines with the following modifications: the smoothing iterations per fit were adjusted to 10 from the default value of 0, the number of changepoints penalty factor was increased to 10 from the default setting of 1, smoothing credible interval threshold allele fraction, and smoothing credible interval threshold copy ratio to 4 from the default setting of 2. These adjustments were made to mitigate noise.

Phylogenetic Analysis

To investigate the branching evolution among samples, we generated a phylogenetic tree based on the somatic SNV/INDELs and CNVs using the R "ape" package (version 5.8).[6] A binary presence-absence matrix was constructed, where rows corresponded to samples and columns to unique somatic SNV/INDEL/CNVs. Pairwise distances between samples were calculated using the Manhattan distance metric. The resulting distance matrix was used to construct a phylogenetic tree employing the neighbor-joining (NJ) method. The phylogenetic tree was created using a radial layout to visualize the branching evolution among the samples.

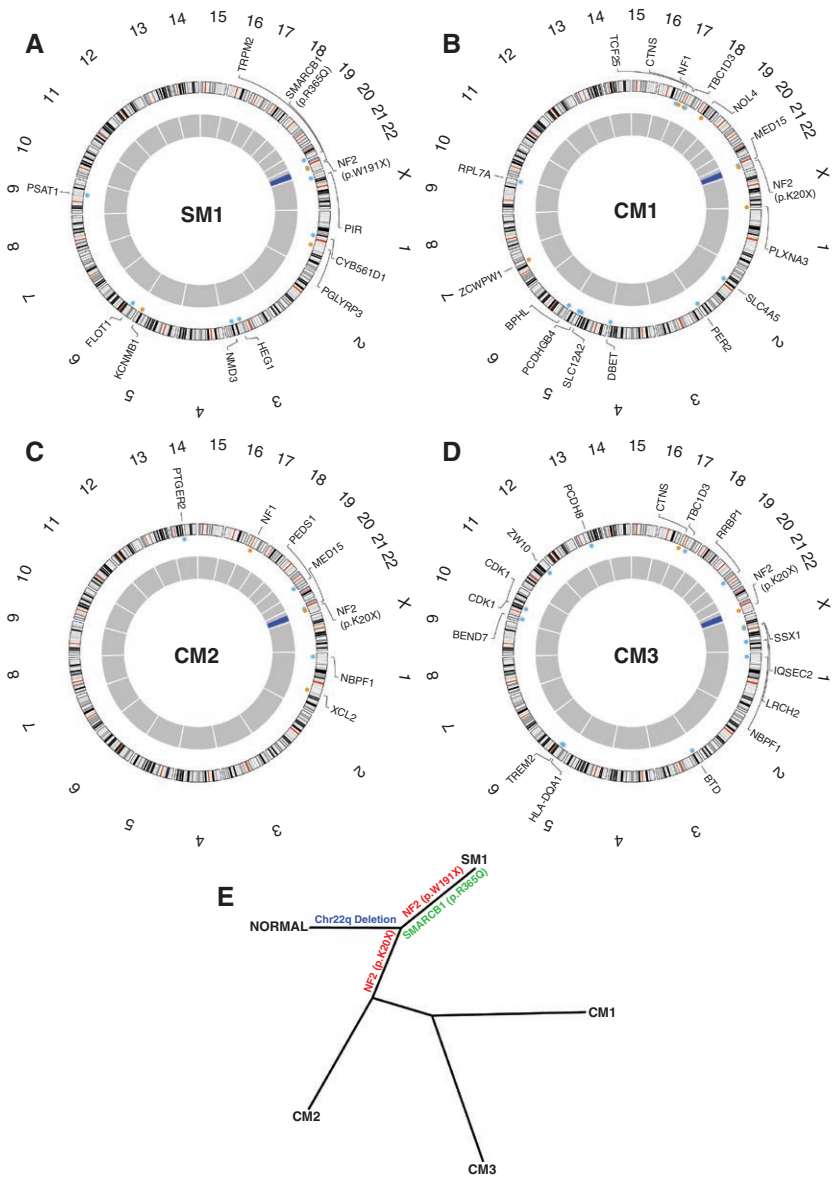

Figure 3. Genomic findings. Circos plot of all 4 cases with outer tracks indicating chromosomes, labels pointing to genes with somatic SNV/INDELs identified. Inner track shows somatic CNV events, with blue bars indicating deletion, such as chr22q deletion on all 4 tumors, ie (A) spinal meningioma, (B)–(D) cranial meningiomas. (E) Phylogenic tree depicting the branched evolution of meningiomas originating from the same clone carrying chr22q deletion. In addition, somatic alterations relevant to meningioma tumorigenesis and acquired during the evolution of the tumors are labelled on tree branches.

Study Protocol

Appropriate institutional review board approval was obtained for the project (HIC Protocol #9406007680). The authors confirm that written consent for submission and publication of this case report, including the images and associated text, have been obtained from the patient(s) in line with COPE guidance.

Discussion

MMs commonly present in the sixth decade in life.[7] Although the majority are small (< 2 cm), 2 thirds of MMs require treatment compared to one-third of solitary meningiomas.[2,7] MMs in separate neuraxial compartments are extremely rare and their current standard of care is surgical resection and/or radiation of growing and/or symptomatic tumors.[2,4] Radiation can be considered for small/medium-sized tumors or tumors in the skull base with possible increased surgical morbidity.[2] Tumors in separate neuraxial compartments pose unique clinical challenges including identification of symptomatic masses, selection of therapeutic approaches, and determination of appropriate treatment timing.

Multiple meningiomas, despite mostly originating from a monoclonal source, do not always display a homogenous genomic profile. Instead, they exhibit significant

heterogeneity, which we hypothesized can be attributed to branched evolutionary trajectories. This variation underscores the complexity of tumorigenesis and progression, suggesting that individual tumor clones evolve and adapt independently, potentially impacting therapeutic outcomes.[4,7]

Sporadic MMs have mutations in *NF2*, *AKT1*, *TRAF7*, *SMO, PIK3CA*, and *SMARCB1* mutations.[7,8] Somatic *NF2* mutations are the most common genetic alterations in sporadic MMs. Juralti et al. described 17 sporadic cranial meningiomas from 8 patients. The most common driver mutations were *TRAF7* (present in 5/17 lesions) followed by *PIK3CA* (4/17 lesions) and *AKT1* (3/17 lesions).[7] *NF2* mutations were low in frequency (2/17 lesions) compared to studies including familial meningiomas. The same mutation was not present in separate tumors of the same patient, supporting their independent origin. All tumors from the same patient had different histopathological subtypes except for one patient.

Our group previously described monoclonal MMs with *NF2* and non-*NF2* (primarily *TRAF7*) mutations,[4] where somatic mutations acquired through branched evolution in monoclonal MMs within multiple patients explained the observed intertumoral genetic heterogeneity. Of note, our definition of MMs in this manuscript is the presence of at least 2 meningiomas in the absence of associated NF or schwannomatosis. The physical distance between tumors did not relate to clonality, where some physically distant MMs harbored genomic profiles pointing toward their monoclonal origin. Dural specimens taken from uninvolved regions, that are anatomically closely located to 5 MMs, were negative for any genetic abnormality, pointing against the dural spread theory.

Familial disorders with MMs are caused by predisposing germline mutations in *NF2*, *SMARCB1*, *SMARCE1* (SWI/SNF complex), or *SUFU* genes. These include neurofibromatosis type 2 disorder and familial multiple meningiomas,[2] and typically display autosomal dominant inheritance. *SMARCE1* mutations have been described in familial multiple spinal meningiomas associated with clear cell subtypes.[9] Germline *SMARCB1* mutations with somatically acquired *NF2* co-mutation have been described in a family with a history of multiple meningiomas.[10]

The genetic landscape of solitary spinal meningiomas is different from cranial meningiomas. Hua et al. described 2 groups of sporadic spinal meningioma (SM) with mutually exclusive *NF2* and *AKT1* mutations.[11] The *NF2* mutation group had a significantly lower mean age of onset (65.5 years), female preponderance, thoracic spinal dorsal/dorsolateral location, and meningothelial subtypes. On the other hand, the *AKT1* subgroup had a higher mean age (71 years), balanced gender distribution, cervical spine anteriorly location, and meningothelial, psammomatous, and transitional fibrous subtypes.

SMARCB1 (SWI/SNF related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1) is a tumor suppressor gene that encodes INI1, a core component of the SWI/SNF chromatin remodeling complex. Loss of *SMARCB1* leads to epigenetic dysregulation, affecting chromatin remodeling and gene expression. This results in enhanced cell proliferation and reduced differentiation.[12]

SMARCB1-deficient meningiomas tend to be more aggressive, higher-grade (CNS WHO grade 2/3), and recurrent, often showing features of rhabdoid or atypical histology. Loss of *SMARCB1* leads to oncogenic enhancers activation, which reshapes the regulatory landscape specifically in malignant rhabdoid tumors.[13,14] *SMARCB1* somatic mutations frequently co-occur with other genetic abnormalities, such as those in *NF2*, across various mesenchymal neoplasms including meningiomas,[4,14] as may arise in the setting of Schwannomatosis.[15,16] Immunotherapy strategies are under investigation for other tumor types, as SMARCB1-deficient tumors often exhibit altered immune microenvironments.[17] However, further research is needed to completely elucidate the impact of SMARCB1 deficiency on tumor microenvironment, especially in meningiomas.

The presented case, with multiple cranial and spinal meningiomas, displayed a branched evolution with shared chr22q deletion. While the 3 CMs shared the same genomic profile, with *NF2*: p.R20X mutation in addition to the chr22q deletion, the SM displayed evolution by acquiring *NF2*: p.R191X and *SMARCB1*: p.R365Q mutations. While we did not have the somatic genomic profiling of the uninvolved dura for the presented case, we previously showed that uninvolved dura from the MM cases did not carry any of the somatic alterations the tumor harbored,[4] strongly suggesting the founding clone and branched evolution pattern.

Behling et al. noted overall S100 positivity in 13.1% of meningioma samples with higher rates in spinal meningiomas (23.8%).[18] Though univariate analysis displayed favorable progression-free survival for S100-positive meningiomas, the authors concluded that positive prognosis may be attributed to confounding clinical factors such as enrichment of patients with female gender or those with neurofibromatosis type 2 in the S100-positive group, tumor location, and lower CNS WHO grade.

Our findings contribute to the growing understanding of the genomic complexity underlying multiple meningiomas. This represents the first report of multiple meningiomas involving a spinal tumor, highlighting branched evolution as a feature of their progression. A comprehensive approach to genetic analysis in meningiomas is required and must consider both high and low-impact mutations for their potential roles in tumor development and therapy response.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

branching evolution | cranial and spinal meningioma | multiple meningioma | spinal meningioma | SMARCB1

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Author Contributions

Conception and study design: E.M., E.Z.E.O., S.P.S.S., Mi.G., and J.M.G. Acquisition of data: E.M., E.Z.E.O., S.P.S.S., Mi.G., D.M., and J.M.G. Analysis and interpretation of data: E.M., E.Z.E.O., S.P.S.S., Mi.G., and D.M. Drafting of the first manuscript: Mi.G., S.P.S.S., E.Z.E.O., and E.M. Critical revisions and writing: all authors. All authors read and approved the final manuscript.

Data Availability

Supporting data for the manuscript will be made available upon reasonable request to the communicating author.

Affiliations

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