Case Report

Multiple meningiomas arising within the same hemisphere associated with Li-Fraumeni syndrome

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ABSTRACT

Background: While meningiomas are some of the most common intracranial tumors, the presence of multiple ones at the time of presentation is rare and can most commonly be observed in patients with well-described syndromes (i.e., neurofibromatosis type 2) or those with prior cranial radiation history. In others, however, the pathophysiology remains unclear.

Case Description: A 49-year-old female with no significant personal or familial oncologic medical history presented with a generalized seizure and was found to have ten meningiomas arising within the right hemisphere. She underwent a two-staged resection of all tumors, with pathology revealing the World Health Organization Grade I meningioma. Whole-exome sequencing revealed somatic NF2 mutations and heterozygous deletion of chromosome 22 overlapping with NF2, and analysis of the germline uncovered mutations of TP53, rendering a diagnosis of Li-Fraumeni Syndrome.

Conclusions: This case represents a novel presentation of multiple meningiomas in a patient with newly diagnosed Li-Fraumeni syndrome, suggesting meningioma may be considered as part of this tumor-predisposed patient population.

Keywords: Li-Fraumeni, Meningioma, TP53

INTRODUCTION

While meningioma is one of the most common types of intracranial tumor, the presence of multiple meningiomas occurs in approximately 10% of these patients at the time of diagnosis.[24] In a majority of these cases, patients have a prior history of cranial irradiation or are genetically predisposed with an underlying syndrome such as neurofibromatosis type 2.[25] Indeed these tumors may have a propensity to behave more aggressively than typical World Health Organization (WHO) Grade I meningiomas with higher rates of radiographic recurrence.[12,24] While the genetic landscape of sporadic meningiomas has been elucidated in recent years,[4] the pathogenesis of multiple meningioma formation is not well understood.

CASE DESCRIPTION

A 49-year-old female presented with a new-onset generalized seizure and was found to have multiple hyperdense masses with calcifications in the right hemisphere on computed
However, unlike nonsense 
mutations and somatic 
mutations unique to each sample were discovered, 


tumor, targeted through surgical resection. 

While multiple meningiomas have not been previously described in the setting of Li-Fraumeni syndrome, a single case of a patient with a solitary benign meningioma in the context of a medical history of numerous other malignancies has been reported. Aside from the history of a basal cell carcinoma, the patient presented had no other significant relevant history, making her presentation of multiple meningiomas in the setting of newly-diagnosed Li-Fraumeni syndrome previously undescribed.

The pathogenesis of multiple meningioma formation remains poorly understood. Early theories hypothesized spread of original clonal tumor cells through the cerebrospinal fluid. However, this has not garnered support as cerebrospinal fluid dissemination is infrequent and rarely seen in cases of aggressively behaving sarcoma-like meningiomas often with extracranial metastasis. A more plausible explanation relates to an inherent multicentricity of tumor foci, perhaps secondary to intrinsic genetic changes in the dura itself, leading to tumor growth under the influence of local oncogenic factors. This could indeed offer insight into the reports of multiple tumors confined to one hemisphere.

In the patient presented, the relevance of the germline TP53 mutations remains unclear. While TP53 mutations have been frequently described in other brain tumors, such as gliomas, there have been more limited reports in meningioma. They have typically been reported in higher grade meningiomas but have also been found in the WHO Grade I tumors as, similar to this patient. However, unlike the TP53 mutation in the presented patient, which had a known association with Li-Fraumeni syndrome, less than half of the reported mutations were predicted to be deleterious, and correlations with clinical outcomes remain unclear. The somatic NF2 mutation detected in this patient's tumors,
on the other hand, along with the heterozygous deletion of chromosome 22 overlapping with NF2, likely represents the major driver mutation leading to meningioma formation in this case based on recent discoveries of mutually exclusive meningioma genomic subgroups. Clinically, NF2 mutated meningiomas can be associated with more aggressive features, such as atypical (i.e., WHO Grade II) histology, as well as others, leading to more malignant behavior and higher rates of recurrence. While the pathogenic contribution of the germline TP53 mutations found in the current patient remains unclear, particularly in regard to the development of multiple tumors with the more aggressive NF2 mutated subgroup, multiple meningiomas remains a novel clinical presentation of Li-Fraumeni syndrome.

Management of multiple meningiomas, such as solitary tumors, remains maximal surgical resection when tumors become symptomatic or reach significant size with associated mass effect. While there is currently no effective chemotherapy for meningiomas, adjuvant radiotherapy can often times be used in patients with multiple meningiomas, particularly for residual tumors or those with growing tumors that may pose a high surgical risk due to wound considerations. In addition, it is frequently used postoperatively for higher grades (i.e., WHO Grade II or III) tumors. In this particular case, however, the discovery of Li-Fraumeni syndrome precluded the potential use of radiation, given the well-established increased risk for development of further radiation-induced malignancies in these patients. Thus, the presented patient continues to undergo periodic surveillance imaging of her tumors with the understanding that additional surgery will likely be necessary as the only effective and safe modality to control her disease.

CONCLUSION

Although the role of germline TP53 mutations in the formation of multiple meningiomas remains unclear, this case is a novel presentation of multiple meningiomas in a patient with newly-diagnosed Li-Fraumeni syndrome, in the absence of more common predisposing risk factors. Multiple meningiomas may be considered as part of the spectrum of tumors that can develop in patients with Li-Fraumeni syndrome and given its implications in the overall treatment, seemingly important to recognize and consider.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Declaration of patient consent

Patient's consent not obtained as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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### SUPPLEMENTARY TABLE

**Supplementary Table 1:** Whole-exome sequencing data of tumor samples from both surgeries of index patient.

| Gene       | Chromosome | Position     | Ref | Alt | VAF: surgery 1 - sample 1 | VAF: surgery 1 - sample 2 | VAF: surgery 2 - sample 1 | VAF: surgery 2 - sample 2 |
|------------|------------|--------------|-----|-----|---------------------------|---------------------------|---------------------------|---------------------------|
| NF2        | 22         | 30067836     | C   | T   | 0.535                     | 0.549                     | 0.383                     | 0.648                     |
| STAP2      | 19         | 4328792      | AC  | A   | 0.293                     | 0                         | 0                         | 0                         |
| ANKRD30B1  | 2          | 132912299    | C   | T   | 0.262                     | 0                         | 0                         | 0                         |
| ARHGAP35   | 19         | 47440657     | A   | C   | 0.094                     | 0                         | 0                         | 0                         |
| DARS2      | 1          | 173795839    | G   | T   | 0.129                     | 0                         | 0                         | 0                         |
| F10        | 13         | 113803412    | G   | A   | 0.26                      | 0                         | 0                         | 0                         |
| FLG        | 1          | 152284319    | C   | A   | 0.352                     | 0                         | 0                         | 0                         |
| GLUT8D2    | 12         | 104383191    | T   | C   | 0.301                     | 0                         | 0                         | 0                         |
| ILRA3      | 19         | 54802629     | C   | T   | 0.039                     | 0.053                     | 0                         | 0                         |
| RUVBL1     | 3          | 127800998    | T   | G   | 0.123                     | 0                         | 0                         | 0                         |
| TRHR       | 8          | 110099966    | G   | T   | 0.041                     | 0                         | 0                         | 0                         |
| SLC22A18AS | 11         | 29099513     | C   | CG  | 0                         | 0.206                     | 0                         | 0                         |
| ACSM3      | 16         | 20797521     | T   | A   | 0                         | 0.115                     | 0                         | 0                         |
| C8orf44-SGK3,SGK3 | 8 | 67759438 | T   | A   | 0                         | 0.12                      | 0                         | 0                         |
| FHOD3      | 18         | 3498626      | A   | T   | 0                         | 0.122                     | 0                         | 0                         |
| GLIPR2     | 9          | 36147796     | T   | G   | 0                         | 0.049                     | 0                         | 0                         |
| LMTK3      | 19         | 49002806     | T   | G   | 0                         | 0.126                     | 0                         | 0                         |
| POPDC2     | 3          | 119367264    | C   | A   | 0                         | 0.058                     | 0                         | 0                         |
| PRKAA1     | 5          | 40765291     | C   | A   | 0                         | 0.05                      | 0                         | 0                         |
| TNN        | 1          | 175116080    | A   | G   | 0                         | 0.133                     | 0                         | 0                         |
| USP32      | 17         | 58286792     | T   | G   | 0                         | 0.096                     | 0                         | 0                         |
| XKR4       | 8          | 56436473     | G   | A   | 0                         | 0.037                     | 0                         | 0                         |
| NFATC2     | 20         | 50007992     | C   | A   | 0                         | 0.159                     | 0                         | 0                         |
| CACNB1     | 17         | 37340644     | T   | G   | 0                         | 0.238                     | 0                         | 0                         |
| CCND2-AS1  | 12         | 4385164      | A   | C   | 0                         | 0.105                     | 0                         | 0                         |
| DDX60      | 4          | 169194553    | A   | C   | 0                         | 0.059                     | 0                         | 0                         |
| NEB        | 2          | 152552202    | A   | C   | 0                         | 0.098                     | 0                         | 0                         |
| OCM2       | 7          | 97619351     | T   | C   | 0                         | 0.104                     | 0                         | 0                         |
| PPHLN1     | 12         | 42768660     | C   | T   | 0                         | 0.153                     | 0                         | 0                         |
| SCN8A      | 12         | 52139683     | A   | T   | 0                         | 0.053                     | 0                         | 0                         |
| TRPC1      | 3          | 14246232     | G   | T   | 0                         | 0.167                     | 0                         | 0                         |
| NCOR2      | 12         | 124862917    | T   | G   | 0                         | 0                         | 0.186                     | 0                         |
| CAMSAP5    | 19         | 7606849      | A   | C   | 0                         | 0                         | 0.02                      | 0                         |
| ENTPD2     | 9          | 139944734    | A   | G   | 0                         | 0                         | 0.032                     | 0                         |
| LIMK1      | 7          | 73498322     | T   | G   | 0                         | 0.148                     | 0                         | 0                         |
| ACRC       | X          | 70824010     | T   | C   | 0                         | 0                         | 0.077                     | 0.09                     |
| AHNAK2     | 14         | 105405086    | G   | T   | 0                         | 0                         | 0.21                      | 0                         |
| C17orf97   | 17         | 263652       | G   | C   | 0                         | 0                         | 0.104                     | 0                         |
| C17orf97   | 17         | 263682       | G   | C   | 0                         | 0                         | 0.116                     | 0.098                     |
### Supplementary Table 1 (Continued):

| Gene         | Chromosome | Position   | Ref | Alt | VAF: surgery 1 - sample 1 | VAF: surgery 1 - sample 2 | VAF: surgery 2 - sample 1 | VAF: surgery 2 - sample 2 |
|--------------|------------|------------|-----|-----|---------------------------|---------------------------|---------------------------|---------------------------|
| CHD8         | 14         | 21867864   | A   | C   | 0                         | 0                         | 0.131                     | 0                         |
| CLEC18C      | 16         | 70208251   | G   | A   | 0                         | 0                         | 0.034                     | 0                         |
| ENTPD1       | 10         | 97602203   | A   | C   | 0                         | 0                         | 0.037                     | 0                         |
| FTH1         | 11         | 61734852   | C   | A   | 0                         | 0                         | 0.039                     | 0.058                     |
| GGT1         | 22         | 25016911   | C   | T   | 0                         | 0                         | 0.054                     | 0                         |
| KCNH2        | 7          | 150647252  | A   | C   | 0                         | 0                         | 0.082                     | 0                         |
| KDELRC2      | 11         | 108361915  | A   | C   | 0                         | 0                         | 0.131                     | 0                         |
| KRTAP5-2     | 11         | 1619378    | G   | C   | 0                         | 0                         | 0.081                     | 0                         |
| MEIS1        | 2          | 6666784    | T   | G   | 0                         | 0                         | 0.244                     | 0.289                     |
| MRPL21       | 11         | 68660120   | C   | T   | 0                         | 0                         | 0.067                     | 0.075                     |
| MUC2         | 11         | 1093342    | A   | C   | 0                         | 0                         | 0.07                      | 0                         |
| NBPF1        | 1          | 16892148   | C   | T   | 0                         | 0                         | 0.036                     | 0.041                     |
| PRB4         | 12         | 11461616   | T   | C   | 0                         | 0                         | 0.058                     | 0                         |
| PRG4         | 1          | 18626739   | T   | G   | 0                         | 0                         | 0.073                     | 0                         |
| PRG4         | 1          | 18626782   | A   | C   | 0                         | 0                         | 0.095                     | 0                         |
| PRG4         | 1          | 18626782   | A   | C   | 0                         | 0                         | 0.064                     | 0                         |
| PRR36        | 19         | 7935318    | T   | G   | 0                         | 0                         | 0.117                     | 0                         |
| SKAP2        | 7          | 26779515   | G   | A   | 0                         | 0                         | 0.038                     | 0                         |
| SNX29        | 16         | 12155432   | C   | G   | 0                         | 0                         | 0.183                     | 0                         |
| TCHH         | 1          | 152082257  | C   | G   | 0                         | 0                         | 0.048                     | 0.055                     |
| TROAP        | 12         | 49724819   | A   | C   | 0                         | 0                         | 0.07                      | 0                         |
| SPEN         | 1          | 16248740   | A   | T   | 0                         | 0                         | 0.044                     | 0                         |
| CCDC18       | 1          | 93691885   | C   | G   | 0                         | 0                         | 0.216                     | 0                         |
| DARS2        | 1          | 17379582   | A   | T   | 0                         | 0                         | 0.045                     | 0                         |
| ZPB2         | 17         | 38028519   | A   | T   | 0                         | 0                         | 0.036                     | 0                         |
| NCO2         | 12         | 124848227  | T   | G   | 0                         | 0                         | 0                         | 0                         |
| IQCD         | 12         | 113638325  | T   | TG  | 0                         | 0                         | 0                         | 0                         |
| RERE         | 1          | 8420527    | G   | GC  | 0                         | 0                         | 0                         | 0                         |
| C1orf97      | 17         | 263532     | A   | C   | 0                         | 0                         | 0                         | 0                         |
| C1orf97      | 17         | 263622     | A   | C   | 0                         | 0                         | 0                         | 0                         |
| CCDC183      | 9          | 13969495   | A   | C   | 0                         | 0                         | 0                         | 0                         |
| CCDC183      | 9          | 13969500   | C   | G   | 0                         | 0                         | 0                         | 0                         |
| CD320        | 19         | 836785     | A   | C   | 0                         | 0                         | 0                         | 0                         |
| CPSF1        | 8          | 145622130  | T   | G   | 0                         | 0                         | 0                         | 0                         |
| LAMB1        | 7          | 107642244  | A   | C   | 0                         | 0                         | 0                         | 0                         |
| MUC4         | 3          | 195511294  | T   | G   | 0                         | 0                         | 0                         | 0                         |
| NANOS1       | 10         | 120789908  | T   | G   | 0                         | 0                         | 0                         | 0.19                      |
| OR7D4        | 19         | 9324835    | C   | T   | 0                         | 0                         | 0                         | 0                         |
| PRB2         | 12         | 11546811   | C   | G   | 0                         | 0                         | 0                         | 0                         |
**Supplementary Table 1: (Continued).**

| Gene          | Chromosome | Position     | Ref        | Alt | VAF: surgery 1 - sample 1 | VAF: surgery 1 - sample 2 | VAF: surgery 2 - sample 1 | VAF: surgery 2 - sample 2 |
|---------------|------------|--------------|------------|-----|---------------------------|---------------------------|---------------------------|---------------------------|
| PRRT2         | 16         | 29825010     | A          | C   | 0                         | 0                         | 0                         | 0                         |
| RIMBP3,ZNF74  | 22         | 20710961     | G          | T   | 0                         | 0                         | 0                         | 0                         |
| SARM1,SLC46A1| 17         | 26726570     | A          | C   | 0                         | 0                         | 0                         | 0                         |
| SETD1B        | 12         | 122252343    | T          | A   | 0                         | 0                         | 0                         | 0                         |
| SETD1B        | 12         | 122252355    | T          | A   | 0                         | 0                         | 0                         | 0                         |
| TLE3          | 15         | 70389199     | C          | G   | 0                         | 0                         | 0                         | 0                         |
| GEMIN2        | 14         | 39591627     | C          | G   | 0                         | 0                         | 0                         | 0                         |
| RARG          | 12         | 53607489     | A          | T   | 0                         | 0                         | 0                         | 0                         |
| ST6GALNAC4    | 9          | 13067084     | C          | G   | 0                         | 0                         | 0                         | 0                         |
| AR            | X          | 66766356     | TGGCGGCGGC | T   | 0                         | 0                         | 0                         | 0.877                     |
| SMC1A         | X          | 53421734     | A          | C   | 0                         | 0                         | 0                         | 0.078                     |
| ARHGD1A       | 17         | 79826693     | G          | GC  | 0                         | 0                         | 0                         | 0.212                     |
| RAB36         | 22         | 23498333     | A          | AAAACCACACTGAGAAAAC | 0                        | 0                         | 0                         | 0.667                     |
| DMTF1         | 7          | 86813934     | A          | C   | 0                         | 0                         | 0                         | 0.085                     |
| ESX1          | X          | 103495090    | A          | C   | 0                         | 0                         | 0                         | 0.069                     |
| GOLGA6L1,GOLGA6L22 | 15    | 22743221     | G          | A   | 0                         | 0                         | 0                         | 0.038                     |
| IFT140        | 16         | 1576630      | A          | C   | 0                         | 0                         | 0                         | 0.131                     |
| IQCD          | 12         | 113638342    | A          | C   | 0                         | 0                         | 0                         | 0.244                     |
| MUC15         | 11         | 26587436     | T          | A   | 0                         | 0                         | 0                         | 0.056                     |
| NPIPA5        | 16         | 15457676     | A          | G   | 0                         | 0                         | 0                         | 0.034                     |
| PDP1          | 16         | 70176575     | A          | G   | 0                         | 0                         | 0                         | 0.044                     |
| PRDM6         | 5          | 12424299     | A          | C   | 0                         | 0                         | 0                         | 0.085                     |
| PRDM9         | 5          | 23527335     | C          | G   | 0                         | 0                         | 0                         | 0.038                     |
| RIMBP3,ZNF74  | 22         | 20709323     | T          | C   | 0                         | 0                         | 0                         | 0.154                     |
| RIMBP3,ZNF74  | 22         | 20709620     | C          | T   | 0                         | 0                         | 0                         | 0.12                      |
| TCHH          | 1          | 15208349     | T          | C   | 0                         | 0                         | 0                         | 0.06                      |
| TCHH          | 1          | 15208484     | G          | T   | 0                         | 0                         | 0                         | 0.046                     |
| UBXN11        | 1          | 26608811     | TCCAGGACAGGACTGGGGCGGGA | T   | 0                        | 0                         | 0                         | 0.336                     |
| UNC93B1       | 11         | 67763138     | T          | C   | 0                         | 0                         | 0                         | 0.028                     |
| ZNF729        | 19         | 22498678     | G          | C   | 0                         | 0                         | 0                         | 0.025                     |
| IRF8          | 16         | 85935387     | A          | T   | 0                         | 0                         | 0                         | 0.152                     |
| CABIN1        | 22         | 24439588     | G          | T   | 0                         | 0                         | 0                         | 0.068                     |
| FAM122C       | X          | 133948793    | C          | G   | 0                         | 0                         | 0                         | 0.09                      |
| GFG16         | X          | 7670956      | G          | T   | 0                         | 0                         | 0                         | 0.133                     |
| GBP7          | 1          | 89618466     | G          | T   | 0                         | 0                         | 0                         | 0.117                     |
| GNA12         | 3          | 50293617     | A          | T   | 0                         | 0                         | 0                         | 0.083                     |
| TUBB4B        | 9          | 140136170    | T          | G   | 0                         | 0                         | 0                         | 0.1                       |