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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

tomography. A brain magnetic resonance imaging with and without contrast demonstrated ten distinct dural-based, homogeneously enhancing lesions within the right hemisphere (Figure 1a-c), the largest measuring 5 × 8 cm (arrow, Figure 1c) and effacing the lateral ventricles. On examination, she was neurologically intact. Her medical history was significant for basal cell carcinoma of the face excised four years earlier. Family history was unremarkable.

She was taken to the operating room for resection of the dominant right parafalcine mass (arrow, Figure 1c) and four other (arrow, Figure 1b) lesions that were amenable to the same incision and craniotomy access. Although the tumors all displayed a mildly elevated Ki-67 index of 5–10% on histologic examination, they did not meet criteria for an atypical meningioma diagnosis and thus the final diagnosis was the WHO Grade I meningioma. Whole exome sequencing (WES) of the resected tumors and matching blood was performed and identified the presence of the same clonal somatic *NF2* nonsense mutation and somatic heterozygous deletion of chromosome 22 overlapping with *NF2*. Germline mutations in *NF2* were not found. However, a germline missense mutation in *TP53* (c.542G >A, p.Arg181His) was revealed, previously described as deleterious.[7] Subsequently, the patient was referred for formal genetic testing, which confirmed this finding, and she was diagnosed with Li-Fraumeni syndrome. Postoperatively, the patient underwent periodic surveillance imaging to monitor for growth of her tumors. Twenty-eight months after surgery, she underwent the second stage of resection of the progressively enlarging, although asymptomatic tumors that remained, which similarly demonstrated WHO Grade I pathology and a mildly elevated Ki-67 index of 4–6%.

WES of all tumors revealed the same somatic *NF2* nonsense mutation and chromosome 22 deletions with otherwise normal copy numbers of all other chromosomes. Additional somatic mutations unique to each sample were discovered, but likely non-pathogenic as none were previously characterized as oncogenic [Supplementary Table]. Together, these findings suggested that all tumors originated from the same founding clone.

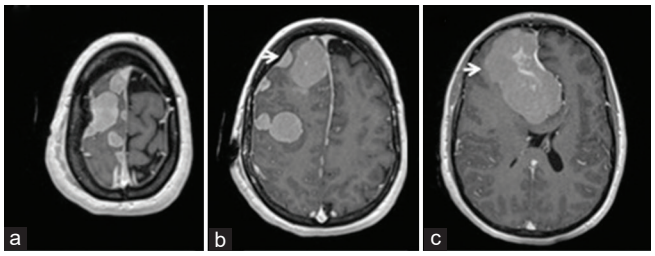

Figure 1: Magnetic resonance imaging of multiple meningiomas arising within the same hemisphere. (a-c) Representative axial slices of T1-weighted magnetic resonance images after gadolinium contrast administration are shown. The arrows point to the (b) smaller frontal convexity tumor (c) and dominant parafalcine tumor, targeted through surgical resection.

DISCUSSION

The differential diagnosis for multiple dural-based lesions includes meningioma and metastasis, but the appearance and lack of vasogenic edema typically favors the former. Among the approximate 10% of meningioma patients harboring multiple tumors at the time of diagnosis,[15,17] a subset exhibit known risk factors, such as a history of prior cranial irradiation or an underlying diagnosis of genetic syndromes such as Neurofibromatosis 2 or Cowden Syndrome.[22,24] However, in most instances, multiple meningiomas arise sporadically and are typically driven by somatic mutations of *NF2*, followed by a second-hit characterized by loss of chromosome 22.[4,21,23] Interestingly, multiple meningiomas in patients without previous risk factors may anecdotally occur on just one side in some patients.[18] 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.[6] 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.[14,26] 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.[3] 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.[2,13] 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[16,19] but have also been found in the WHO Grade I tumors as, similar to this patient.[1,20] 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.[4,5,9] 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.[25] 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.[8,24] 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.[10,11] 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
ANKRD30BL	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	T	0.352	0	0	0
GLT8D2	12	104383191	T	C	0.301	0	0	0
LILRA3	19	54802629	C	T	0.039	0.053	0	0
RUVBL1	3	127800098	T	G	0.123	0	0	0
TRHR	8	110099966	G	T	0.041	0	0	0
SLC22A18AS	11	2909513	C	CG	0	0.206	0	0
ACSM3	16	20797521	T	A	0	0.115	0	0
C8orf44-SGK3,SGK3	8	67759438	A	T	0	0.12	0	0
FHOD3	18	34298626	C	A	0	0.123	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	142462323	G	T	0	0.167	0	0
NCOR2	12	124862917	T	G	0	0	0.186	0
CAMSAP3	19	7660889	A	C	0	0	0.2	0
ENTPD2	9	139944734	A	G	0	0	0.032	0
LIMK1	7	73498322	T	G	0	0	0.148	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

(Contd...)

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
KDELC2	11	108361915	A	C	0	0	0.131	0
KRTAP5-2	11	1619378	G	C	0	0	0.081	0
MEIS1	2	66667848	T	G	0	0	0.244	0.289
MRPL21	11	68660120	C	G	0	0	0.067	0.075
MUC2	11	1093342	C	A	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	186276394	T	G	0	0	0.073	0
PRG4	1	186276739	G	C	0	0	0.095	0
PRG4	1	186276820	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	173795821	A	T	0	0	0.045	0
ZPBP2	17	38028519	A	T	0	0	0.036	0
NCOR2	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
C17orf97	17	263532	A	C	0	0	0	0
C17orf97	17	263622	A	C	0	0	0	0
CCDC183	9	139694995	A	C	0	0	0	0
CCDC183	9	139695000	C	G	0	0	0	0
CD320	19	8367857	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	G	T	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

(Contd...)

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	130670864	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
ARHGDIA	17	79826693	G	GC	0	0	0	0.212
RAB36	22	23498333	A	AAAACCACTGAGAAAAC	0	0	0	0.667
DMTF1	7	86813934	A	C	0	0	0	0.085
ESX1	X	103495090	G	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	A	T	0	0	0	0.056
NPIPA5	16	15457676	A	G	0	0	0	0.036
PDPR	16	70176575	A	G	0	0	0	0.044
PRDM6	5	122426299	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	152082449	T	C	0	0	0	0.06
TCHH	1	152082484	G	T	0	0	0	0.046
UBXN11	1	26608811	TCCAGGACAGGGACTGGGGCCGGGA	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	85953837	A	T	0	0	0	0.152
CABIN1	22	24439358	G	T	0	0	0	0.068
FAM122C	X	133948793	C	G	0	0	0	0.09
FGF16	X	76709756	G	T	0	0	0	0.133
GBP7	1	89618466	G	T	0	0	0	0.117
GNAI2	3	50293617	T	A	0	0	0	0.083
TUBB4B	9	140136170	T	G	0	0	0	0.1