Genetics or Coincidence: Navigating Multiple Malignancies in Neuro-Oncology Clinic

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Chief Complaint: Post-op follow up for a meningioma

History of Present Illness: 37 year old male with a past history of seizure disorder, Ewing sarcoma, right parietal PNET, and right sided chordoid meningioma presenting for management of an atypical grade II temporal meningioma. Shortly after resection, patient suffered from a subdural hematoma requiring a second surgery to drain. The hematoma was discovered after hospital admission due to multiple falls and seizures. Patient denies any drowsiness, tremors, or recent falls. Patient has been using a cane for 3 weeks to further avoid falls, and medication continues to prevent seizures. Patient will return to remove his cranial stitches, but reports positive outcomes post-op and adherence to current medication schedule. He is interested in smoking cessation, and requested a patch. Patient was offered genetic testing considering his history of multiple malignancies, and has agreed to undergo testing to identify any genetic anomalies responsible.

Past Medical History:

1. Right lower extremity ewing sarcoma, diagnosed 1986
2. Right parietal PNET, diagnosed 1991
3. Right sided grade I chordoid meningioma, diagnosed 2015
4. Left temporal atypical grade II meningioma, diagnosed June 2019
5. Left subdural Hematoma, diagnosed October 2019

Past Surgical History:

1. Right below knee amputation due to ewing sarcoma, 1986, no reported complications
2. Surgical resection of R. parietal PNET followed up with radiation, complication of post-op seizure disorder, 1991
3. Surgical resection of a right sided chordoid meningioma with no reported complications, 2015
4. Surgical resection of a left sided, temporal meningioma with no reported complications, August 2019
5. Subdural hematoma drainage, October 2019

Medications:

1. Zonisamide 100 mg PO twice a day
2. Keppra/Levetiracetam 2000 mg PO every 12 hours, new medication
3. Levothyroxine 50 mcg PO daily for 30 days
4. Olanzapine 20 mg PO daily
5. Acetaminophen-Hydrocodone 325-10mg PO every 6 hours

Allergies: NKDA

Social History: 37 year old male currently living in a nursing home due to his current health post-op and a history of multiple falls. Patient has a history of tobacco dependence syndrome, substance abuse, and high risk sexual behaviors. Patient denies alcohol use, and reports cessation of other substances. He is currently working on quitting smoking. Patient was in the foster system and cannot provide a complete family history. He is currently unemployed due to his health.

Review of Systems: Negative for all systems except as in HPI

Vital Signs: Temperature: 97.2 F BP: 121/73 Pulse: 80 RR: 18

Physical Exam:

General: no acute distress, gait and station normal given BKA

Mental status: alert and orientied x3, attentive, positive 3 object recall, normal comprehension and articulation

Cranial nerves II-XII: Intact.

Motor (bilateral): Muscle strength upper extremity and left lower extremity 5/5 bilaterally; biceps, triceps, knee reflexes: +1 bilaterally; coordination (finger-to-nose) is intact; muscle tone is normal; facial, palms of hand and feet pinprick sensation is intact.

Labs/Imaging:

Date	WBC	RBC	MCV	HgB	HCT	Plat	%NEUT	%LYMPH	%MONO
10/16/19	6.5	3.78	96.1	11.7	36.3	198	61.5	24.6	9.8
08/09/19	10.2	3.00	94.8	9.5	28.4	215	67.6	18.2	13.3

Table 1. Pre and post op surgical resection of the Grade II atypical meningioma CBC values. Features consistent with cancer include anemia of chronic disease, and mild monocytosis typical of chronic conditions.

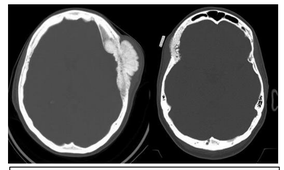


Image 1. Meningioma presentation in two different patients (Fogh, et. al 2016)

Diagnosis

- Per his history of seizures, one approach could have been to reassess current medications and whether they were effective prophylaxis.
- Given the sudden onset of falls, an MRI was indicated. The MRI revealed a mass in the left temporal area resembling meningiomas. Pathology confirmed a grade II atypical meningioma post surgical resection
- The incidence of multiple malignancies prior to the age of 40 may indicate an underlying genetic abnormality

Discussion of Disease Process/Clinical Correlations

1. Possible genetic syndromes relating meningiomas and ewing sarcoma are Li-Fraumeni Syndrome and Neurofibromatosis-2 (NF-2). NF-2 is rare, and usually presents with Schwannomas, however diagnostic criteria can include the presence of multiple meningiomas. Presentation in childhood usually involves ocular areas, unlike this patient. Li-Fraumeni Syndrome is associated with TP53 gene mutation. TP53's role is a tumor suppressor and is important as a pro-apoptotic regulator. Faulty P53 could result in tumor survival. It is the most commonly mutated gene in cancer. Another possibility is a RUNX1 gene mutation, another tumor suppressor. It has been implicated in solid tumors and blood disorders.
2. Misdiagnosis of the first meningiom should be considered a possibility, although unlikely. With history of Ewing sarcoma and a parietal PNET, the chordoid meningioma may have been a metastasis from the original cancer. This would suggest that the tumors are linked to a common source. Peripheral PNETs can present as a "local, dural based mass, mimicking meningioma" (Kumar, et.al 2017).
3. Radiation therapy serves as a risk factor for meningiomas, therefore the meningiomas may be related to his prior history of radiotherapy.

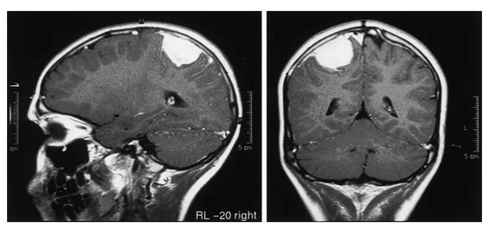


Image 2. T1 MRI of a peripheral PNET of the dura. Meningiomas are the most common brain masses, while pPNETs are very rare and may be mistaken as a meningioma (Dedeurwaerdere, et. al 2002).

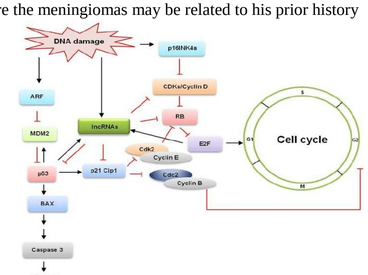
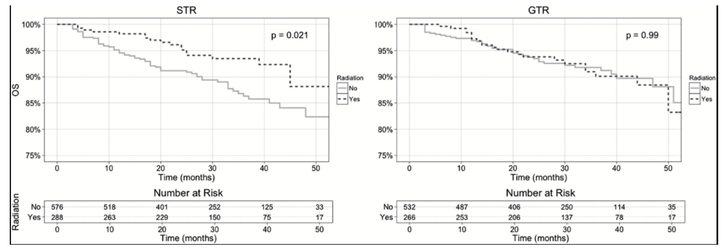


Image 3. Regulation of the cell cycle. P53 is mutated in many cancers. Patients with Li Fraumeni syndrome have an inherited mutation w/p53 predisposing them to multiple cancers (Subramanian, et. al 2013).

Treatments

Given that grade II atypical meningiomas are more pervasive and have an increased risk of local recurrence than grade I meningiomas (7), resectioning of the tumor potentially along with adjuvant radiation therapy is recommended. Depending on the location, size, and type of tumor, patients can undergo different types of tumor removal, including subtotal tumor removal (STR) and, more aggressively, gross tumor removal (GTR). GTRs have been shown to have a longer overall survival rate than STRs (6). Because of the high recurrence rate of these grade II atypical meningiomas, adjuvant radiation therapy has been recommended for STRs with a significantly higher progression-free five year survival rate (6). But adjuvant radiation therapy has not seen a significant reduction in tumor recurrence for patients who have undergone GTRs (7). Some complications from radiation therapy can include latent spontaneous brain tumors. Currently, there have been clinical trials for atypical meningiomas involving molecular targets identified by genomic sequencing (9, 10).



Graph 1. Kaplan–Meier OS plots for atypical meningioma patients who underwent STR and GTR. P-value from log-rank test is shown. (6)

Conclusions

Multigene Panel testing was negative for this patient. Given his previous history of radiation, he will not undergo radiation therapy without further counseling on the risks. Current guidelines recommend against radiation therapy, and he will be followed up with MRI every 3 months to confirm the resection was complete.

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Thank you Dr. Sushant Puri for your mentorship and time. This would not have been possible without you.