Secondary Anaplastic Medulloblastoma in a Li-Fraumeni Syndrome patient with Primary Osteosarcoma

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Abstract

Li-Fraumeni syndrome (LFS) is a cancer predisposition syndrome caused by germline TP53 mutation. Malignancies associated with LFS include osteosarcomas, leukemias, CNS, and adrenocortical tumors. While CNS tumors are common primary malignancies, we report the case of a pediatric patient with LFS who developed a never reported secondary anaplastic medulloblastoma.

Introduction

First described by Li and Fraumeni in 1969, LFS is a hereditary neoplastic predisposition syndrome[1]. It is commonly caused by germline TP53 pathogenic mutation which is a multifunctional transcription factor that serves to control cellular proliferation and plays a pivotal role in tumorigenesis[2,3].

Germline TP53 mutation confers a nearly 100 % cumulative risk of cancer in females, and about 70% cumulative risk of cancer in males by age 50[4]. There is also a significantly higher risk of childhood cancers associated with LFS, with an 18 % risk of developing cancer in females and 10% risk of developing cancer in males by age 20[4,5]. The majority of cancers in those with LFS consist of core cancers which include breast cancer, bone and soft tissue sarcomas (specifically osteosarcomas and rhabdomyosarcomas), CNS tumors, adrenocortical tumors, and leukemia[6-8].

CNS tumors such as choroid plexus carcinomas and medulloblastomas are also primary malignancies of LFS[8]. Specifically, anaplastic medulloblastoma is a known primary malignancy of LFS[8]. To our knowledge, there are no known reported cases of secondary anaplastic medulloblastomas. We hereby present the case of a pediatric patient who developed an asymptomatic secondary anaplastic medulloblastoma after undergoing successful treatment for his primary osteosarcoma.

Case Report

An 11-year old male presented after injuring his left tibia and had an abnormality on X-ray which prompted a follow-up MRI. MRI demonstrated a left tibial bony lesion, suspicious for a malignancy. Patient underwent core needle biopsy of his left tibia and pathology revealed a low grade osteosarcoma. Patient underwent surgical excision of his left tibia with allograft reconstruction. Pathology now confirmed the presence of a high-grade osteosarcoma. Patient received chemotherapy per Children's Oncology Group's AOST0331 protocol[9]. He completed the planned therapy regimen without any major complications.

He was followed up regularly every 3 months for physical exam, surveillance labs, and imaging studies that did not demonstrate any acute disease. Several months after completing therapy, his younger brother was diagnosed with high grade osteosarcoma of left ilium. Our patient was then evaluated via genetic testing that revealed a TP53 mutation, specifically TP53, c.818G>A (p.Arg273His), consistent with LFS. His mother, younger brother, and another half-brother tested positive for the same TP53 mutation. Patient underwent surveillance as per LFS Education and Early Detection Program (LEAD)[10] . The program included annual brain and whole body MRI's, annual blood and urine tests to evaluate adrenal gland function, tumor markers for common LFS associated tumors, and physical exams every 6 months[10]. The inclusion of whole body MRI and brain MRI is particularly essential as LFS has a high incidence of asymptomatic tumors[11]. Following LEAD guidelines, our patient was evaluated with MRI of brain and whole Body which showed no evidence of new tumors or other abnormalities.

He underwent a brain MRI as part of his surveillance scans (13 month interval since previous surveillance scan) that showed a well-circumscribed mass in the left lateral cerebellum measuring 1.5 X 1.1 X 0.6 cm (Fig. 1). He was clinically asymptomatic, had no abnormalities on physical exam, and had no evidence of lesions at other body sites. The patient underwent surgical resection of his cerebellar lesion. Neuropathological evaluation showed densely cellular highly mitotic neoplasm with large pleomorphic nuclei and apoptotic cells without the presence of any cerebellar tissue (Fig. 2). Next Generation Sequencing identified the following genomic alterations; SMO copy number loss, DDX3X copy number loss, TP53 mutation p.R273H, TP53 copy number loss, and MYCYN copy number gain. Testing revealed that the tumor was positive for YAP-1 and GAB-1. These results are consistent with Sonic Hedgehog (SHH)-activated large cell anaplastic medulloblastoma arising in a patient with germline TP53 mutation. Patient's medulloblastoma was located in the lateral cerebellum and most SHH tumors are known to be mainly located in the cerebellar periphery[12]. Medulloblastomas identification is enhanced via diffusion MR because they are hypercellular tumors that result in decreased Apparent Diffusion Coefficient (ADC) values[13]. Overall, SHH-activated and TP53-mutant medulloblastomas are rare and associated with a dismal prognosis[14].

Patient and his mother decided to forego any systemic chemotherapy due to the poor prognosis of secondary anaplastic medulloblastoma. Repeat MRI of brain 3 months post craniotomy showed evidence of recurrent neoplasm along the superior aspect of the left cerebellar hemisphere that measured 3.2 X 3.4 X 1.3 cm. Patient was placed on hospice as the family decided to forego any further intervention and he died at home on July 23, 2018.

Shortly after, his mother died from recurrent high grade pleomorphic sarcoma of pelvis. Patient's younger brother, who was diagnosed with osteosarcoma developed recurrent pulmonary metastatic disease of his osteosarcoma. He succumbed to his illness while under Hospice care at home. Patient's half-brother is undergoing serial evaluations according to LEAD program and remains cancer-free.

Discussion

To our knowledge, there have not been an published cases reporting the presence of secondary anaplastic medulloblastomas in the pediatric population.

There is another screening protocol for patients with LFS, which recommend annual whole body MRI and brain MRI's (at 6 months interval), but recommend blood tests every 3-4 months[15,16]. We followed the LEAD program guidelines, which recommend blood tests, urine tests, and physical exam every 6 months, since it is logistically more feasible to patients and parents[10,11]. The frequency of visits would not have led to earlier detection of our patient's secondary medulloblastoma as he was asymptomatic and the frequency of obtaining MRI of brain is similar in the two programs.

Several imaging features of medulloblastomas are helpful in diagnosing the primary tumor and determining its molecular status. Medulloblastomas result in decreased ADC values and hyperintensity on diffusion MRI images[13]. On T2-weighted images, medulloblastomas can demonstrate heterogenous intensity or isointensity to gray matter (Fig. 1)[17]. Furthermore, tumor locations are associated with molecular group as SHH tumors are primarily located in the cerebellar periphery which corresponded with a positive predictive value

of 94.7%[12].

Neuropathological evaluation showed histologic features consistent with large cell/ anaplastic medulloblastoma. Next Generation Sequencing identified genomic alterations that confirmed the diagnosis of SHH-activated anaplastic medulloblastoma[14]. Additional testing revealed that the tumor was positive for YAP-1 and GAB-1, which further confirmed the diagnosis and ruled out osteosarcoma since osteosarcomas do not express YAP-1 and GAB-1.

The purpose of presenting this case is two-fold: first, to present the previously unreported finding of secondary anaplastic medulloblastoma in a LFS patient and secondly, to emphasize the importance of appropriate cancer surveillance in LFS patients and their families.

Cancer screening for LFS is extremely delicate and complicated as imaging modalities should not include ionizing radiation as these would increase the risk of cancer in the LFS population. Per a prospective and a subsequent 11-year follow-up observational study by Villani et al, the 5 year survival rate of individuals who underwent this screening protocol was 88.8% whereas those who did not undergo screening had 5 year survival rate of 59.6%[15, 16].

Although our patient, his mother, and younger brother underwent screening as per LEAD protocol, all three succumbed to their respective malignancies in a short time while his step brother remains cancer free. It is important to emphasize genetic testing in family members of patient's with LFS and the continued use of a robust screening regimen such as the LEAD program to identify any additional cancers at the earliest stage.

Conflicts of Interest: none

Acknowledgements: none

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Figure Legends

- Figure 1. Axial MRI of the Brain demonstrating Left Lateral Cerebellar Mass from March 15, 2018. **A** . Apparent Diffusion Coefficient (ADC) Map demonstrates decreased signal confirming restricted diffusion within the mass **B** . Diffusion Weighted Image (DWI) demonstrates a rounded area of increased signal **C.**T1-Post-Contrast image demonstrates homogenous enhancement in the mass**D.** T2-weighted image shows relative hyperintense signal in the mass.
- Figure 2. Densely cellular highly mitotic neoplasm with prominent nuclear pleomorphism and apoptotic cells with no identifiable cerebellar tissue.

Supplemental Figure Legends

- Figure S1. T2-weighted MRI of Brain demonstrating L lateral cerebellar mass. June 8, 2018
- Figure S2. T1-weighted Pre-contrast MRI of Brain demonstrating L lateral cerebellar mass. June 8, 2018