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Li-Fraumeni Syndrome Cancer Surveillance Strategy Considerations for Glioblastoma Multiforme

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Abstract

Sporadic or inherited deficiencies in the production or activity of the tumor suppressor P53 lead to Li-Fraumeni Syndrome (LFS), a multi-organ tumorigenic condition. Glioblastoma multiforme (GBM), a tumor that commonly presents with a median age of 64, has a higher chance of appearing in much younger patients who have LFS [9]. Since the implementation of the 2016 Toronto Protocol to increase cancer surveillance in LFS patients, three cases of LFS-GBM have been discussed [11, 12, 13]. Here, we report a case of LFS in an 18-year-old male who had a seizure due to a GBM that had evaded a full-body MRI six months prior. Furthermore, we discuss the potential quality of life (QOL) benefits of providing patients with a shorter brain MRI screening interval: better survival outcomes and peace of mind. Though there may be a rise in the financial cost with an increase in the number of MRI scans, the prevalence of aggressive tumors that must be treated early for a better prognosis warrants more frequent screening. Furthermore, we address the importance of expanding clinical knowledge on GBM in the LFS setting as well as addressing the benefits of the protocol through statistical studies.

Keywords

Li-Fraumeni Syndrome, Glioblastoma Multiforme, Cancer Surveillance, Toronto Protocol, Brain MRI

Background

Li-Fraumeni syndrome (LFS) is a predisposed oncogenic state that catalyzes early-onset, multi-organ tumor growths [1,2], occurring at a frequency of 1 in 5,000 to 1 in 20,000 [3]. This disease is caused by an inherited or acquired autosomal dominant mutation in the tumor suppressor TP53 gene, which encodes the P53 protein that guards cell cycle regulation, DNA repairs, apoptosis, senescence, and cellular metabolism [4]. Mutant P53 and the abnormal control of these processes raise susceptibility to radiation, wherein the use of whole-body MRI (WB-MRI) is recommended for regular cancer screening [2].

Accounting for 9-14% of LFS cases, glioblastoma multiforme (GBM) is a malignant and aggressive brain tumor [5] of astrocytes [6] that has been clinically under-characterized in the LFS setting [7]. Among the studies that analyze GBM in the LFS setting, none have discussed the number needed to treat before seeing a benefit with the current screening protocol. Are we doing enough to catch these fast-growing tumors? The 2016 Toronto Protocol [8], an annual surveillance system created to catch cancers in LFS patients, may not detect every tumor promptly, especially those as rapidly expanding as GBM. To shed light on the need for increasing surveillance, we present a case involving

an 18-year-old male with LFS-GBM, who came in six months after a clean full-body MRI.

Case Presentation

An 18-year-old man with a significant medical history of Li-Fraumeni syndrome was admitted to the ED shortly after experiencing a tonic-clonic seizure in the morning that lasted 2-3 minutes. His mother noted that before the seizure episode, the patient appeared confused, heard a ringing sound, and was unable to walk. Upon examination, the patient denied any discomfort but was not oriented to place. He did not have any history of drug use or seizures prior to this incident. Given the high rate of malignancies in individuals with Li-Fraumeni syndrome, the patient received a full-body MRI annually and an abdomen/pelvis ultrasound every 4 months. His last full-body MRI, 6 months prior to this incident, showed no signs of malignancy.

Same-day lab findings showed leukocytosis, likely due to an acute leukemoid reaction to the seizure. After ruling out infection with negative results for urinalysis and chest x-ray, the patient was monitored without antibiotics. The patient's new onset of seizure was most likely related to the appearance of a brain lesion on computed tomography (CT), and brain magnetic resonance imaging (MRI) with and without contrast was recommended for further confirmation. According to radiology, brain MRI results revealed "2 adjacent posterior right temporal and right periatrial intraparenchymal masses versus a bilobed mass with hemorrhage and dense cellularity. Local mass effect was present with effacement of the right atrium and posterior right lateral ventricle." See **Fig-1**.

Further consultation of the MRI findings with neurosurgery and neurology raised concerns about a potentially high-grade infiltrative glioblastoma without midline shift. CT chest/abdomen/pelvis was also ordered to check for other potential primary tumors (all negative). As per recommended seizure control, the patient was given IV Keppra 500 mg twice daily (BID) and had no observed seizures since. The patient was discharged with a neurosurgery follow-up and DVT prophylaxis.

Discussion

Identifying malignancies in the brain through MRI may allow for increased longevity of patient survival and improved quality of life (QOL) [8][9]. While earlier detection does not equate to complete elimination of cancer mortality, previous guidelines indicate that it can lead to less aggressive treatment and, consequently, a reduction in adverse side effects [9]. However, it is worth noting that GBM often comes back and grows rapidly post-resection [10]. With more frequent screenings, there is a greater chance to detect GBM before it has grown to a size indicating resection. Although more frequent cancer screening does not necessarily improve the prognosis of individuals with LFS, it can ensure a decreased likelihood of metastases from cancers when detected early enough.

In the case of our patient, they underwent a tonic-clonic seizure likely due to GBM, which may have been prevented under a more frequent screening schedule. Oftentimes, core tumors (that may include

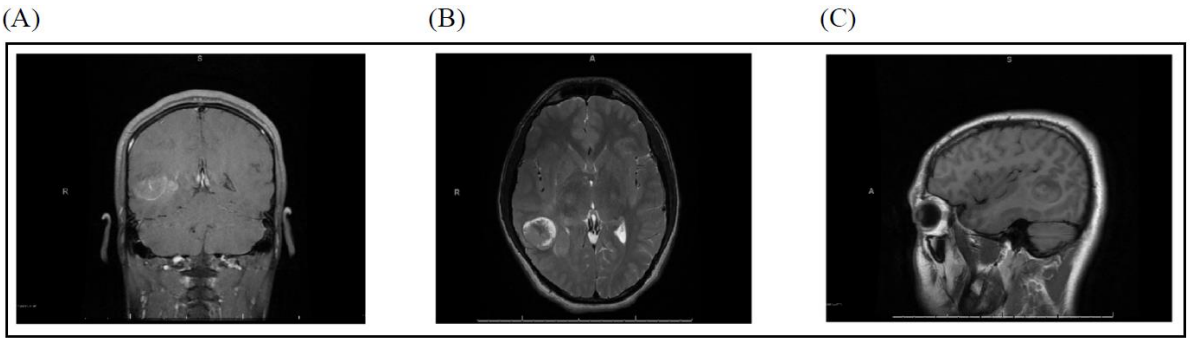

Fig-1: MRI Scans of GBM Bi-lobed Tumor in the Right Parietal Lobe

A: T1-FLAIR Coronal section;
B: T2-Weighted FSE Transverse section;
C: T1-FLAIR Sagittal section

adrenocortical cancer, brain tumor, and osteosarcoma) that appear in LFS patients tend to present more acutely in the pediatric population. Of all the cases currently published regarding GBM in LFS patients, the onset of our patient's condition was less than the age of 25. Therefore, in regard to the susceptible age range (<25 years old) of GBM onset in LFS patients, we would suggest increasing the annual brain MRI schedule recommended by the Toronto Protocol 2016 to one that is biannual.

When considering the effectiveness of cancer surveillance and its benefits, it is also essential to keep in mind the risk of false positives, potential overdiagnosis of benign growths, and complications that may arise due to procedures that require sedation. The patient's financial burden should also be taken into consideration if they increase their frequency of costly cancer screening. Alternatively, patients can consider other screening options like liquid biopsy, which may offer quicker and more accurate detection of cancer [9].

In regards to expanding our current knowledge and database on hereditary tumors such as LFS, clinical trials can be implemented and offered to these individuals to help develop a more "comprehensive medical care system." Researchers studying LFS have postulated policy recommendations to assist with the implementation of clinical trials that include the following: (1) establishing a registry for hereditary tumors; (2) training genetic counselors specialized in hereditary tumors; and most importantly, (3) providing public subsidies to help with the costs of genetic tests and cancer surveillance [9].

Moving forward, monitoring the extent of fast and evading tumors in LFS patients would allow us to estimate the public health improvement by giving patients the choice to have a more frequent screening brain MRI schedule.

Conclusion

LFS is a genetic disorder associated with a significant increase in the chance of tumor growth. Currently, the Toronto Protocol recommends annual cancer surveillance for LFS patients using full-body MRI and brain MRI, in addition to abdominal ultrasounds every 3 to 4 months. Similarly, to our case report, some LFS patients experience a more rapid expansion of malignant brain tumors, which may call for shortening the time interval between each screening to detect these growths early, treat them, and improve patient QOL and prognosis. Further insight into how GBM presents in the LFS setting may provide additional management considerations.

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Conflict of Interest

The authors have read and approved the final version of the manuscript. The authors have no conflicts of interest to declare.

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