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Long-term survival in a patient with Li-Fraumeni syndrome–associated giant cell glioblastoma treated with nivolumab: illustrative case

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BACKGROUND Li-Fraumeni syndrome (LFS) is characterized by *p53* germline mutations and a high predisposition to cancers including glioblastoma (GBM), the most common and aggressive primary malignant brain tumor in adults. Despite current therapies, the 5-year survival rate is 5%–10%. The authors report a case with a durable long-term response to immunotherapy with checkpoint inhibition in a patient with LFS-associated GBM.

OBSERVATIONS An 18-year-old female presented after a syncopal episode and left leg weakness and was found to have a right frontal tumor. She underwent gross-total resection of the tumor (grade IV giant cell GBM IDH-wildtype, MGMT unmethylated, associated with a *p53* germline mutation), radiation, and chemotherapy. On later imaging, increased enhancement was demonstrated, which raised concerns for tumor recurrence, and she underwent stereotactic radiosurgery followed by lomustine and procarbazine. These agents were later replaced with bevacizumab after a second resection, negative for recurrent glioma. Subsequently, nivolumab was added, given concerns for tumor progression, and the patient showed improvement within 5 months. The patient has continued nivolumab monotherapy and has had progression-free survival for more than 7 years.

LESSONS Despite advances in treatment, the median survival of patients with GBM is only 15 months. This case highlights the potential of immunotherapy with PD-L1 checkpoint inhibition in improving outcomes for LFS–associated GBM patients.

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KEYWORDS Li-Fraumeni syndrome; glioblastoma; giant cell glioblastoma; checkpoint immunotherapy

Li-Fraumeni syndrome (LFS) is a well-established cancer predisposition disorder associated with autosomal dominant mutations in the *p53* tumor suppressor gene. LFS increases the risk for both childhood and adult-onset malignancies, the most common of which include breast cancer, sarcoma, and brain tumors, including glioblastoma (GBM).[1] GBM is the most malignant brain tumor in adults and has a poor prognosis despite a variety of therapeutic interventions. The median survival is 15–16 months, and the 5-year survival rate is a dismal 5%–10%, with no significant difference between those with or without p53 mutations.[2] Therefore, long-term survival is a rarity, with less than 1% of patients reaching 10 years.[3] We present a patient with LFS-associated giant cell GBM who has survived 10 years from diagnosis to date with a durable, long-term response to immunotherapy. Our case emphasizes the response to immunotherapy with checkpoint inhibition in a patient with LFS, which has been largely undocumented to date.

Illustrative Case

An 18-year-old female with a history of migraines presented after a syncopal episode and was found to have weakness in her left lower extremity. Brain magnetic resonance imaging (MRI) revealed an enhancing lesion near the motor cortex of the right frontoparietal region, measuring 19 × 27 × 26 mm. The patient underwent gross-total resection of the mass, and pathology revealed a World Health Organization grade IV giant cell GBM (IDH-wildtype, MGMT unmethylated; Fig. 1). Germline analysis revealed an association with a *p53* germline mutation, suggesting LFS. The patient's family history included prostate cancer in her maternal grandfather, kidney cancer in her maternal great-aunt, and breast cancer in her maternal great-aunt's daughter. Her paternal grandmother had cancer of unknown etiology, and her grandfather was diagnosed with prostate cancer (Fig. 2). Additionally, there was a history of seizures in many maternal

ABBREVIATIONS GBM = glioblastoma; LFS = Li-Fraumeni syndrome; MRI = magnetic resonance imaging.

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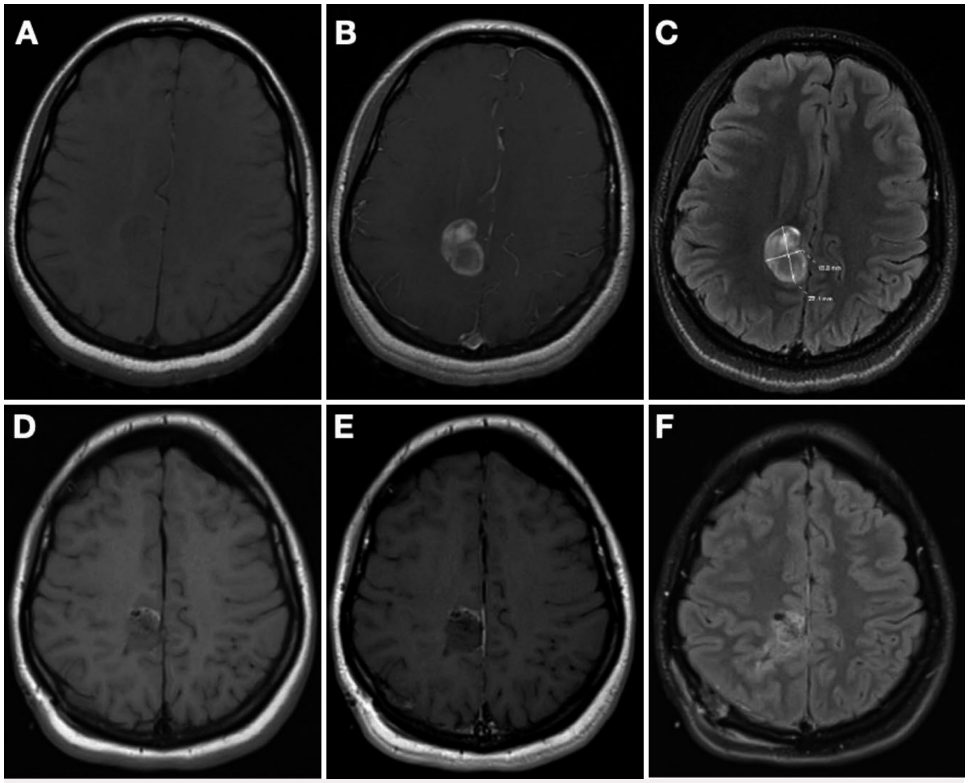

FIG. 1. Preoperative axial T1-weighted MRI without contrast (**A**) and with contrast (**B**), the latter showing enhancement. The dimensions of the tumor (18.8 × 27.1 mm) can be seen on an axial T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence (**C**). Postoperative axial T1-weighted MRI without contrast (**D**) showing no enhancement compared to imaging with contrast (**E**). Complete resection was visualized on a T2-weighted FLAIR image (**F**).

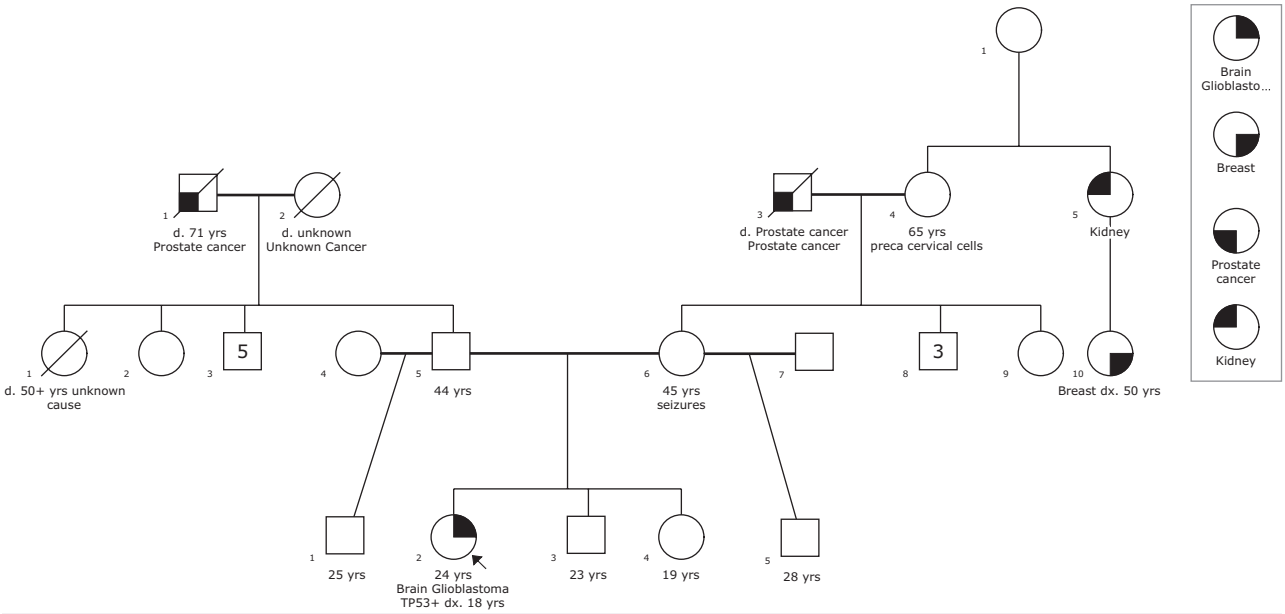

FIG. 2. A pedigree chart showing a family history of confirmed cancer diagnoses, supporting patient diagnosis of LFS. d. = died; dx. = diagnosis; preca = precancerous.

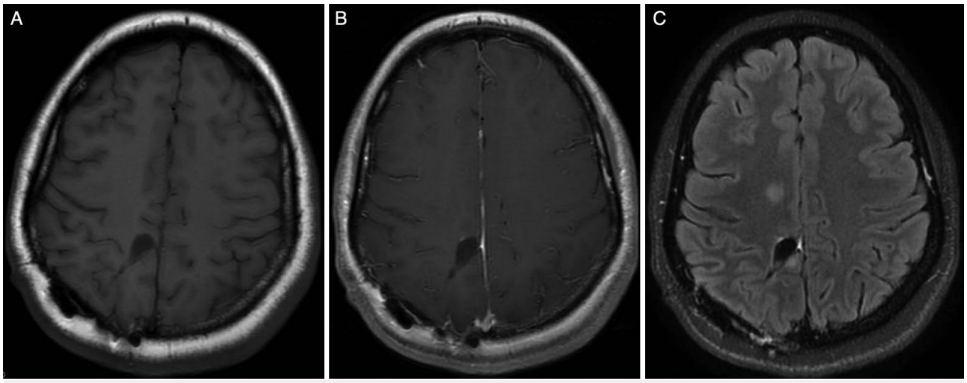

FIG. 3. Axial T1-weighted MRI without contrast, 6 months postresection, before stereotactic radiosurgery (**A**) compared to T1-weighted MRI with contrast showing slightly increased enhancement in the inferior margin of the resection cavity as well as the corpus callosum (**B**). These findings were also visualized on the T2-FLAIR sequence (**C**) before the patient underwent stereotactic radiosurgery.

family members. Accordingly, the diagnosis of LFS was confirmed in this patient.

The patient was subsequently treated with radiation and temozolomide. She underwent radiation therapy for 6 weeks with concurrent temozolomide at 140 mg/day, followed by 12 cycles of adjuvant temozolomide. Seventeen months later, the patient was having increased headaches, and routine brain MRI showed areas of increased enhancement (Fig. 3). She was started on lomustine with procarbazine and ultimately underwent stereotactic radiosurgery for the new area of recurrence. The area of enhancement continued to progress, and the patient opted for a second resection from which pathology confirmed radiation necrosis without recurrent glioma (Fig. 4). Lomustine and procarbazine were stopped, and the patient initiated biweekly bevacizumab at 10 mg/kg 4 months later. After 2 months, the patient was found to have a mass in the right parietal region that appeared consistent with tumor progression and was started on nivolumab as

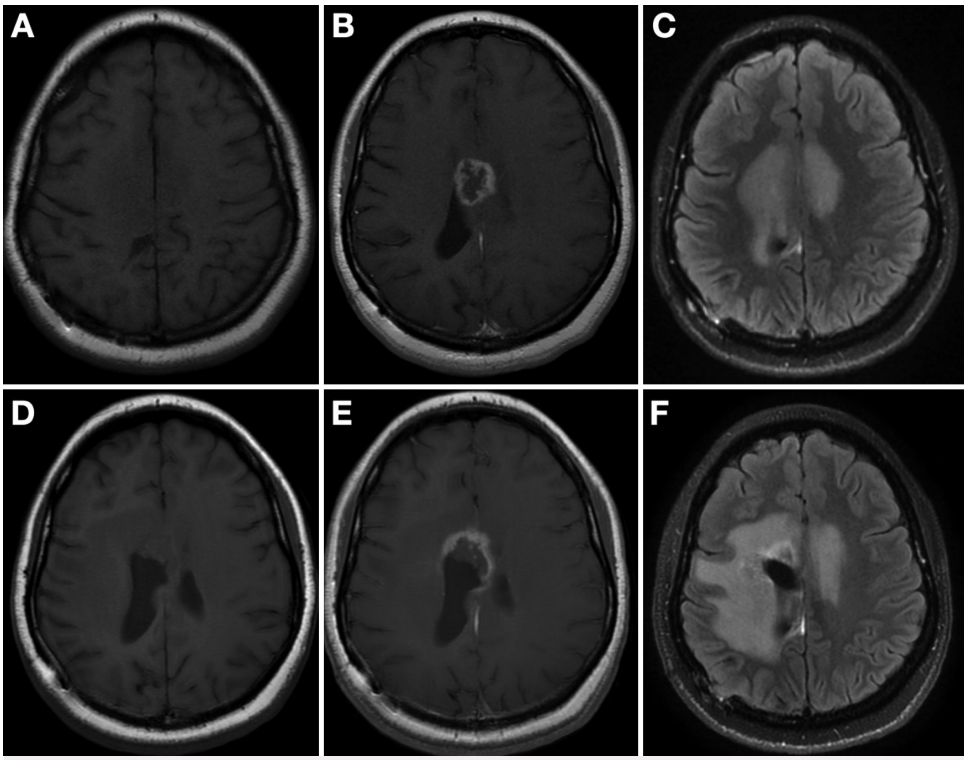

FIG. 4. Axial T1-weighted MRI without contrast, 8 months postresection, after stereotactic radiosurgery (**A**) with an increased area of enhancement on T1-weighted MRI with contrast (**B**) and tumor visualization on the T2-FLAIR sequence (**C**). Axial T1-weighted MRI without contrast after the second tumor resection (**D**) as well as T1-weighted MRI with contrast postresection (**E**). The T2-weighted FLAIR sequence demonstrates some increase in the hyperintense signal surrounding the resection cavity without new enhancement (**F**).

well at that time. MRI showed improvement after 5 months of combination therapy compared to prior imaging. After 3 years, the patient developed proteinuria secondary to bevacizumab use, and this was discontinued. The patient has continued nivolumab monotherapy via a monthly dose of 480 mg, without experiencing seizure activity or increased migraines. MRI perfusion studies have been routinely performed, radiographically confirming that there has been no tumor progression. She remains both physically and socially functional with neurologically stable left lower-extremity weakness. To date, she has had progression-free survival for more than 7 years since the initiation of nivolumab (Fig. 5).

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

The diagnostic criteria for LFS include either a confirmed germline mutation in *TP53* and/or a diagnosis of sarcoma before age 45 years in an individual with a first-degree relative who was also diagnosed with cancer before age 45 years, as well as a first- or second-degree relative with cancer before age 45 years or sarcoma at any age.[1] Although LFS is recognized as an infrequent genetic predisposition to cancer, *TP53* germline mutations occur in approximately 1 in 5000 to 1 in 20,000 individuals.[4] Furthermore, an individual's *TP53* status is highly predictive of their likelihood of developing cancer in their lifetime and is also associated with an earlier age of cancer onset. About half of those who carry *TP53* mutations will develop at least one cancer associated with LFS by age 30 years.[5] Additionally, a study by Gonzalez et al. reported that individuals with *TP53* mutations experienced a median age of cancer onset that was 35 years younger compared to those without mutations who eventually developed cancer.[6] Cancers of the central nervous system account for between 9% and 14% of LFS-associated cancers, with astrocytoma and (GBM) being the most common.[7] Despite the poor prognosis of GBM, long-term survival and quality of life remains the primary objective of treatment.

Despite treatment advancements, there remains a lack of understanding regarding the therapy of LFS–associated GBM, and long-term survival has been scarce in the literature. We conducted a thorough literature review on GBM arising in the setting of LFS. A single case from 2019 reported a 14-year-old male with LFS-associated giant cell GBM who achieved complete remission with radiotherapy, maintenance everolimus immunotherapy, and electromagnetic field therapy 33 months from diagnosis at the time of publication.[8] Aside from this instance, there exists no documented cases of long-term, progression-free survival in LFS-associated GBM, thereby rendering a 10-year survival milestone particularly noteworthy.

Observations

Currently, the mainstay of GBM treatment, regardless of *TP53* status, is maximal tumor resection followed by radiation and concurrent chemotherapy via temozolomide as well as adjuvant temozolomide.[9,10] However, even with the ideal treatment, the recurrence of the disease is universally unavoidable. The addition of bevacizumab as an additional chemotherapy has been used in clinical practice and has been

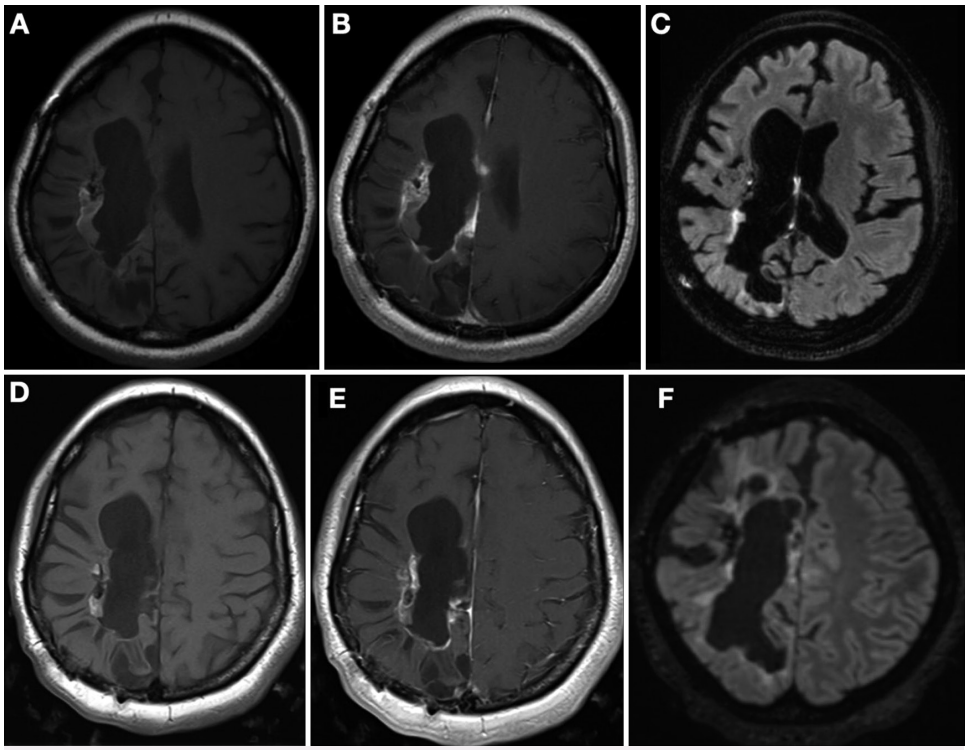

FIG. 5. Axial T1-weighted MRI after almost 6 years on nivolumab immunotherapy (**A**) as well as T1-weighted MRI with contrast (**B**) and T2-weighted FLAIR sequence showing stable disease (**C**). The patient's most recent MRI scans included T1-weighted MRI without contrast (**D**) and with contrast (**E**) and T2- weighted FLAIR sequence (**F**) showing a remarkable, stable lack of progression.

found to increase progression-free survival; however, it has not been shown to improve overall survival in patients with primary GBM91. Additionally, specific tumor pathology has been implicated in overall survival and progression-free survival. In our case, the patient's pathology indicated unmethylated MGMT. It is widely understood that unmethylated MGMT reduces the efficacy of chemotherapy agents such as temozolomide and is associated with decreased survival in many studies.[11] This is illustrated by the recurrence of disease seen in our patient, enhancing the need for further exploration of alternative treatments in patients with recurrent disease.[9]

In our case, the patient was placed on nivolumab monotherapy, an immune checkpoint inhibitor, in October 2016. The patient still receives monthly intravenous administration and has had progression-free survival for almost 8 years to date, with complete resolution of seizure activity and a significant decrease in the frequency and severity of headaches. The literature review identified another case indicating the promising effects of nivolumab therapy on LFS-associated cancers in a 48-year-old male. This patient was found to have LFS-associated gastric adenocarcinoma as well as a pancreatic neuroendocrine tumor. The patient underwent 8 cycles of chemoimmunotherapy and has been on nivolumab monotherapy for 12 months at the time of publication, with stable disease.[12]

Immunotherapy with checkpoint inhibition is of particular interest in LFS-associated GBM, given the changes in cell cycle regulation that are seen in patients with *p53* mutations. In nonmutated cells, *p53* acts as a transcription regulator to promote the arrest of the cell cycle in response to DNA damage, allowing the cell to either repair or undergo apoptosis.[13] However, variant *p53* is present in about 50% of cancers and can have numerous effects, including decreased efficacy of the intrinsic checkpoint activity. Many studies have shown that mutated *p53* is associated with increased expression of several immune checkpoints, including programmed death protein 1 (PD-1) as well as its receptor programmed death protein ligand 1 (PD-L1).[14] Therefore, targeted therapy aimed at PD-L1, such as nivolumab, may have increased efficacy in those with these *p53* mutations. While this treatment approach has shown substantial success in non–small cell lung cancer,[15] it has not been published for LFS-associated GBM, thus prompting our report.

Lessons

In summary, we present long-term, progression-free survival of 10 years in a patient with LFS-associated GBM, who was 18 years old at the time of diagnosis and has been receiving nivolumab monotherapy for almost 8 years. Our case emphasizes the response to immunotherapy with checkpoint inhibition in a patient with LFS, which has not been heavily documented and needs to be replicated in a similar patient population. While those with LFS have a notably increased lifelong cancer risk, the methods of best treating such tumors are still poorly understood with respect to GBM. As outlined, the methylation status of the tumor itself can promote resistance to temozolomide, which is included in the current standard of care. Therefore, given the variant *p53*, LFS patients have the potential to benefit from further exploration of alternate therapy such as checkpoint inhibition.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Restrepo-Orozco, Verhey, Vitaz. Acquisition of data: Mitchell, Restrepo-Orozco, Verhey. Analysis and interpretation of data: all authors. Drafting the article: Mitchell, Restrepo-Orozco. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mitchell. Administrative/technical/material support: Restrepo-Orozco. Study supervision: Restrepo-Orozco, Vitaz.

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