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A solitary case of gliosarcoma an indication for TP53 mutation analysis: a non-concordant finding. Case report

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ABSTRACT

Background: Li-Fraumeni syndrome (LFS) is a hereditary, autosomal dominant malignancy predisposition induced by a mutant TP53. Here, we describe a gliosarcoma (GS) case with a clinical family history impressive for an LFS case in the absence of inherited germline TP53 mutations.

Case description: We present a 44-year-old female with a right high parietal mass. The mass proved pathologically to be GS with an isocitrate dehydrogenase-1 (IDH1) mutation. Pedigree analysis identified five first-degree and second-degree relatives with LFS spectrum malignancies. The patient tested positive for TP53 mutation; however, her family tested negative.

Conclusion: Of all the tumours, GSs are the least described entity with LFS. We are highlighting the need to do a genetic survey in family members of the patient who has been diagnosed to have gliosarcoma and other tumours consistent with LFS.

INTRODUCTION

Gliosarcoma (GS) is an infrequent malignancy that is made up of glial and sarcomatous components (3). According to the WHO classification (2016), GS falls under the umbrella of isocitrate dehydrogenase (IDH)-wild type Glioblastoma (GBM) (8). The distinction of primary GS is given to GS tumours that arise without the presence of previous GBM (3). Despite being known for over a century, many aspects of GS remain ill-defined (7) (13). The median age for GS patients at diagnosis ranges from 55 to 61 years (3) (7). GS has a male predominance and a predilection for the temporal lobe (7).

Currently, GS tumours are treated in accordance with Stupp's trimodal regimen originally designed for GBM; the regimen entails the combination of maximum safe surgical resection, radiation therapy, plus concomitant and adjuvant temozolomide (16). Despite the absence of solid evidence to support Stupp's regimen for GS, several

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studies have reported encouraging results (3) (4) (15) (17). Even in the era of multimodality therapy, the prognosis of GS tumours remains grim, with the median survival ranging between 8.3 and 16.7 years (5-7) (17). Factors impacting GS's survival include age at presentation, the extent of surgical resection, and adjuvant radiotherapy (7).

We aim to describe a case of GS with a clinical family history impressive for a LFS case; However, no inherited germline TP53 mutations have been detected.

CASE DESCRIPTION

A previously asymptomatic 44-year-old female was introduced to our institution after experiencing a fall. She complained of progressive weakness of her left arm and leg over the course of one month, which had led to a worsening ability to walk and handle items (Figure 1). She denied any other limb weakness or paraesthesia, speech or visual disturbances, nausea, vomiting, or headache. Throughout this period, she also denied any episodes of seizures or alteration in mental status.

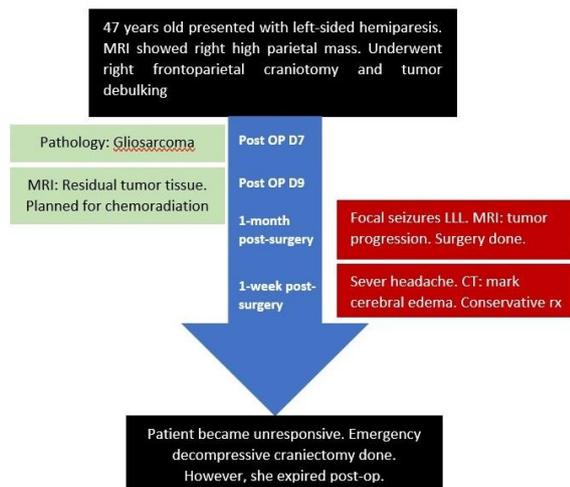


Figure 1. Timeline showing the course of the patient during the follow-up and outcome. **Keys:** OP: operative; LLL: left lower limb; Rx: treatment.

The patient was presented with left breast cancer with stage III (aT3N2M0) of invasive ductal carcinoma metastasized to the ipsilateral axillary lymph nodes, for which she had modified radical mastectomy and axillary clearance followed by adjuvant radiation therapy two years back. Pathological evaluation was negative for oestrogen

receptor, progesterone receptor, and human epidermal growth factor receptor-2 defined by immunohistochemistry and fluorescent in situ hybridization.

On physical evaluation, she was grossly intact, aside from left-sided hemiparesis (Grade II Medical Research Council) and left-sided deep tendons hyperreflexia. Cranial magnetic resonance imaging (MRI) (Figure 2) verified the presence of a 3.4×3.3 cm right high parietal mass with surrounding hyperintensity on T2-weighted sequence, representing vasogenic oedema. Postcontrast images revealed thick irregular peripheral enhancement with central hypointensity representing central necrosis.

Right frontoparietal craniotomy and brain tumour debulking with stereotactic computer-aided navigation was performed. Histopathology (Figure 3) revealed a high-grade glial neoplasm admixed with an area comprising of spindle-shaped cells arranged in fascicles. The glial area of the tumour was positive for glial fibrillary acidic protein (GFAP) immune stain and showed poor reticular network. The spindle-shaped area was negative for GFAP and showed a rich reticular network. The specimen was immunoreactive for IDH-1. Based on the presence of both glial and sarcomatous areas in the tumour, a diagnosis of GS was established.

The patient was offered genetic counseling; her family history revealed that her oldest sister was diagnosed with breast cancer at 39 years old (yo) and synovial sarcoma of the foot at 42 yo. Her other sister was diagnosed with primary spinal osteosarcoma at 40 yo and breast cancer at 44 yo. Among her maternal uncles, one developed leukaemia at 35 yo, and another one had lymphoma at 55 yo. Her paternal uncle was diagnosed with lung cancer at 50 yo. Based on the clinical family history in the context of GS, a diagnosis of LFS was highly suspected. Genetic testing revealed a presence of a mutated TP53 in our patient with an absence of germline TP53 mutations in her family. The BRCA1, BRCA2, and PTEN mutations were not identified.

Postoperative MRI (Figure 4) showed 1.3×1cm residual tumour tissue, for which she received adjuvant temozolomide and radiotherapy. At the one-month follow-up, the patient endorsed focal jerky movements in her left leg. Cranial computerized tomography (CT) scan revealed a further progression of the previously seen residual

tumour tissue with significant midline shift and surrounding vasogenic oedema. Surgical extirpation of the brain tumour was done. She had recovered from surgery with persistent left-sided hemiparesis and discharge on dexamethasone. One week later, she endorsed severe headaches and episodes of vomiting. A cranial CT scan (Figure 5) revealed marked cerebral oedema. Her family refused the

decompressive craniectomy option. She was started on mannitol and dexamethasone. However, two-day after, she became unresponsive and developed a right fixed dilated pupil for which she had an emergency decompressive craniectomy. Unfortunately, her clinical status progressively deteriorated till she expired.

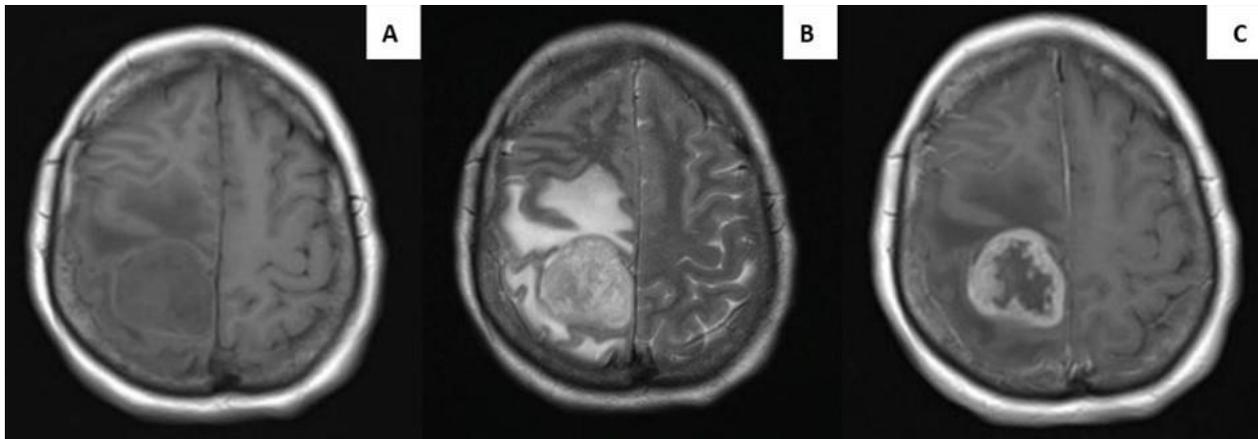


Figure 2. Brain MRI demonstrates a right high parietal lesion with surrounding vasogenic oedema. The mass shows isointensity on the sagittal T1-weighted sequence (A), heterogeneous hyperintensity on the sagittal T2-weighted sequence (B), and thick irregular peripheral enhancement in the postcontrast T1-weighted sequence (C).

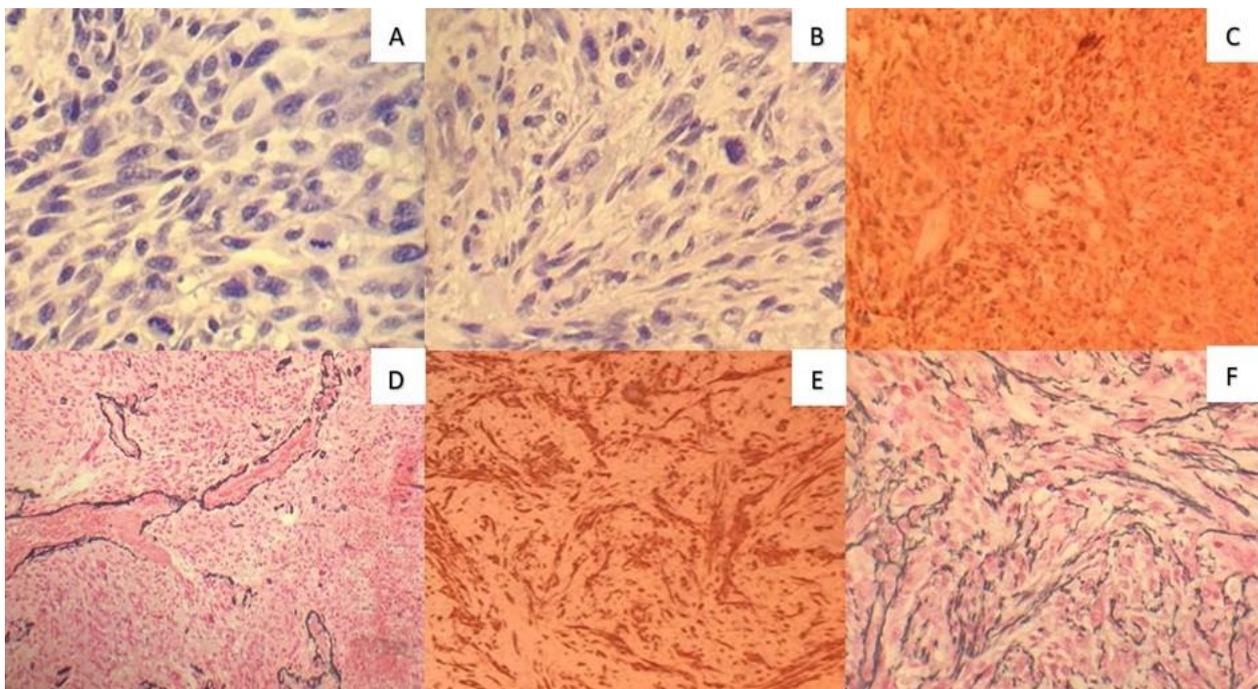


Figure 3. The histopathology revealed a brain tumour tissue comprising two cells types. Area of neoplastic glial cells depicting moderate nuclear pleomorphism and frequent mitosis (A) admixed with area comprising of spindle shaped cells arranged in fascicles (B). Glial area of tumour was positive for GFAP immunostain and showed a poor reticular network (C&D). Spindle shaped area were negative for GFAP and showed a rich reticulin network (E&F).

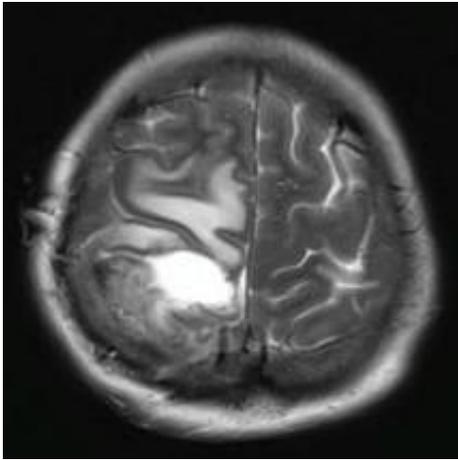


Figure 4. Postoperative Brain MRI demonstrates a 2.8×1.7×2.7 cm fluid filled cystic cavity at the operative bed with 1×1.3cm peripherally irregular enhancing lesion at its anterior-inferior border suggestive of residual tumour tissue.



Figure 5. Cranial CT scan revealed mark cerebral oedema.

DISCUSSION

LFS is an inherited autosomal dominant cancer predisposition triggered by a mutant TP53 (9). TP53 is a transcription factor located on chromosome 17 (17p13.1), which normally controls the cell cycle, genomic stability, and cell death (2) (14). Accumulation of secondary mutations over and above the mutated TP53 attributes to the fact that LFS is characterized by unusual patterns of cancer incidence (11).

The Chompret Criteria allows the clinical identification of LFS. The three clinical presentations are taken into consideration: 1. Family presentation of LFS cancers such as breast cancer, soft tissue sarcoma, central nervous system cancer, adrenocortical carcinoma, leukaemia, and bronchoalveolar lung cancer under the age of 46 and

one first or second degree relative with an LFS cancer under the age of 56. 2. Multiple primary tumours related to the LFS spectrum with the first diagnosis before the age of 46. 3. Rare cancers such as adrenocortical carcinoma or choroid plexus carcinoma irrespective of family history (1) (12).

Full-body MRI is the currently used screening modality for LFS patients with high sensitivity and specificity in detecting various tumours (10). 18F-fluorodeoxyglucose positron emission tomography and full-body CT scan as screening modalities are not recommended as they increase the risk of radiation-induced tumours (10).

Genetic testing and counseling should be offered to the LFS patient's family. Using basic Mendelian genetics, the probability of inheritance can be determined, assuming that the mutant allele is inherited in an autosomal dominant fashion. Siblings of an affected patient have a 50% chance of having LFS. If neither parent has LFS, the mutation is assumed to be de novo, and the risk to siblings is lower. However, the risk to siblings is higher than the general population due to the possibility of germline mosaicism (10).

In this specific instance, the clinical family history was impressive for a LFS case according to Chompret criteria; however, no inherited TP53 alterations have been found except for the patient. We believe that this lack of an absolute phenotype-genotype concordance could be ascribed to other, as yet unidentified mutations involved in the pathogenesis of LFS. Further genetic studies involved in cell growth regulation and proliferation may be efficient in deciphering such aggregations and addressing the genetic events involved in cancer predisposition in families suspected to have LFS.

CONCLUSION

The description of this case highlights the importance of genetic family counseling of patients diagnosed to have GS and other tumors consistent with LFS. Early identification of high-risk subjects will provide appropriate lifelong monitoring within clinical and psychological programs. Importantly, sporadic cases should not be dismissed.

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