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Case Report

Approach to Suspected Li-Fraumeni Syndrome: A Case Report in Genetic Counseling and Multidisciplinary Management

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Abstract

Background: Li-Fraumeni syndrome (LFS) is a highly penetrant hereditary cancer predisposition syndrome caused by germline *TP53* mutations. It is characterized by early-onset, diverse malignancies, including sarcomas and brain tumors. Synchronous occurrence of two primary LFS-associated tumors is extremely rare and poses significant diagnostic and therapeutic challenges, particularly in resource-limited settings where genetic testing may be inaccessible.

Case Presentation: We report a 36-year-old male presenting with two distinct primary malignancies: small-cell type glioblastoma multiforme (GM) and mandibular osteosarcoma (MO). Brain CT revealed a left paraventricular mass requiring craniotomy, with histopathology confirming GM. Shortly after, a rapidly enlarging mandibular mass was identified; biopsy and expanded immunohistochemistry confirmed MO. p53 immunohistochemistry showed strong nuclear overexpression in the majority of tumor cells nuclei, strongly suggestive of a missense *TP53* mutation. A three-generation pedigree revealed multiple LFS-associated malignancies. Although genetic testing was recommended, it was declined due to financial constraints. The patient received temozolomide-based chemoradiation for GM and cisplatin–doxorubicin chemotherapy for unresectable osteosarcoma. His condition deteriorated, and he died six months after osteosarcoma diagnosis.

Conclusion: This case illustrates an exceptionally rare presentation of Li-Fraumeni syndrome, marked by two distinct primary malignancies glioblastoma multiforme and unresectable mandibular osteosarcoma. The clinical, histopathological, and p53 IHC findings strongly suggest underlying *TP53* dysfunction, emphasizing the importance of recognizing LFS even when genetic testing is unavailable. The case further highlights the indispensable role of multidisciplinary management and specialized genetic counselling in guiding surveillance, family risk assessment, and therapeutic decision-making. In resource-limited settings where molecular testing is not accessible, structured genetic counselling and risk-adapted surveillance remain essential for optimizing care in hereditary cancer syndromes.

Keywords: *Li-Fraumeni Syndrome; TP53 mutation; genetic counseling; hereditary cancer syndromes; cancer surveillance*
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INTRODUCTION

Li-Fraumeni Syndrome (LFS), introduced by Li and Fraumeni in 1969, is a rare hereditary cancer predisposition syndrome caused by germline mutations in the *TP53* tumor suppressor gene, located at chromosome 17p13, and inherited in an autosomal dominant manner.[1,2] It significantly increases the risk of developing various cancers at a young age, including soft tissue sarcomas, osteosarcomas, brain tumors, breast cancer, leukemia, and adrenocortical carcinoma.[3]

The prevalence of LFS is 1:5000, and about 70% of affected individuals harbor a germline *TP53* mutation, making genetic counseling and molecular testing highly recommended in suspected cases.[4] However, because nearly 30% of clinically diagnosed patients do not show detectable *TP53* mutations, diagnosis often relies upon clinical evaluation using established criteria.[5] In addition to the classic LFS criteria, the Li-Fraumeni-like (LFL) and the revised Chompret criteria broaden the diagnostic framework and help identify *TP53* related cancer predisposition in families with incomplete phenotypes.[6]

Multidisciplinary care involving oncologists, neurosurgeons, geneticists, radiologists, and pathologists is crucial for accurate diagnosis and coordinated treatment.[7] Genetic counseling clarifies inheritance patterns, supports psychological readiness for testing, guides communication within families, and facilitates cascade testing among at-risk relatives.[8,9] The value of integrating multidisciplinary care with strong genetic counselling has been demonstrated not only in LFS, but also in Lynch syndrome and *BRCA*-related hereditary breast cancer, as reported by Mendes et al. and Kwong et al.[10,11]

Compared with most documented LFS cases, our patient's presentation was exceptionally rare due to the coexistence of two distinct primary malignancies glioblastoma multiforme (GM) and mandibular osteosarcoma (MO), an unusual combination only scarcely reported in the literature.

CASE REPORTS

Demographic Information and Medical History

A 36-year-old male from Murni Teguh Hospital was evaluated for suspected LFS after developing two distinct primary tumors. Written informed consent was obtained for publication of clinical data and imaging. Three months before the current presentation, the patient experienced convulsions, persistent headache, and left-sided hemiparesis. Brain CT revealed a left paraventricular space-occupying lesion, prompting urgent craniotomy. Two weeks later, he developed a rapidly enlarging right mandibular mass, raising suspicion of a second primary malignancy.

Diagnostic Process and Investigations

Brain Tumor Findings

Histopathology showed stromal fragmentation without epithelial lining, infiltrated by tumor cells with round nuclei, small size, basophilic, coarse granular chromatin, indistinct cytoplasm, and atypical mitotic cells, along with areas of necrosis. Immunohistochemistry (IHC) showed S100 positive, cytokeratin AE1/AE3 negative, and CD45 negative, consistent with small-cell type glioblastoma multiforme (see Fig.1).

Mandibular Tumor Findings

Mandibular CT showed a sunburst periosteal reaction with submandibular gland involvement and cortical erosion. Biopsy revealed pleomorphic, hyperchromatic tumor cells embedded within lace-like osteoid, consistent with a malignant bone tumor (see Fig.2). Expanded IHC (SATB2 positive; GFAP, Olig2, S100, Synaptophysin negative) confirmed that it is periosteal osteosarcoma ruling out GB metastasis.

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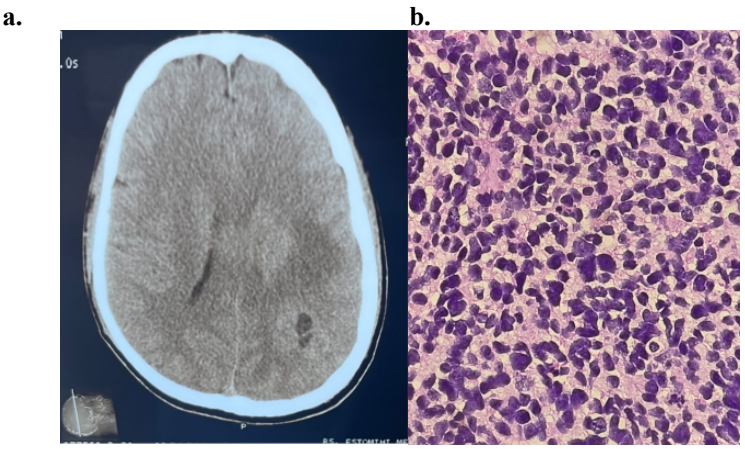

Figure 1. Brain Imaging and Brain Tumor Histopathology. **a.** Brain CT-Scan before surgery, revealed a leftsided central paraventricular space occupying lesion. **b.** Tissue preparations show stromal fragmentation without epithelial lining. Fragments of the stroma were seen infiltrated by nested structures of tumor cells, which consisted of tumor cells with round nuclei, small size, basophilic, coarse granular chromatin, unclear cytoplasm, and atypical mitotic cells were also found. The surrounding area consists of cerebral tissue and areas of necrosis. (H&E staining, magnifications: 400 x)

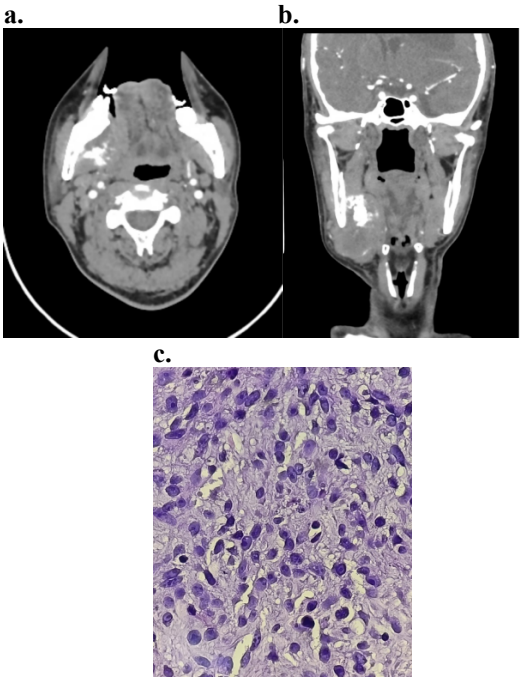

Figure 2. Mandible Imaging and Histopathology of Mandible Osteosarcoma. a. Sunburst periosteal reaction. b. Malignant mass in the right submandibular area, involving the right submandibular gland, extending to the floor of mouth muscles on the right side. **c.** Tissue preparations contain a tumor mass consisting of a proliferation of neoplastic cells that form irregular fasciculus and diffuse structures. The neoplastic cells had round ovoid-spindle morphology, eosinophilic cytoplasm, increased N/C ratio, ovoid nuclei, moderate nuclear pleonorphia, irregular nuclear membrane, vesicular chromatin with conspicous-insconspicous nuclei. Between these cells, there is an osteoid matrix that weaves together (lace like pattern). (H&E staining, magnifications: 400 x)

p53 Immunohistochemistry

p53 IHC demonstrated strong nuclear overexpression in the majority of tumor cells nuclei (see Fig.3), characteristic of missense *TP53* mutations in which mutant p53 protein accumulates due to impaired degradation. This finding aligns with an 80% concordance between p53 overexpression and *TP53* pathogenic variants noted by Ogi et al.[12]

Genetic Counseling

A pre-test counselling session included construction of a three-generation pedigree, revealing breast cancer in the patient's mother (age 49), early-onset colorectal cancer in a sibling, and colorectal and thyroid cancers in cousins (see Fig. 4). The proband's asymptomatic younger sister also participated, reflecting a family-centered approach essential for hereditary cancer syndromes. The counsellor explained autosomal dominant. inheritance, the 50% transmission risk to first-degree relatives, and the implications of potential *TP53* test outcomes (pathogenic variant, negative result, or VUS). Counselling also addressed psychological readiness, surveillance implications, and communication of results to at-risk relatives. Although the patient understood the importance of testing, he and his family declined germline *TP53* analysis due to financial constraints. The counsellor emphasized lifestyle modification, symptom awareness, risk-reducing strategies, and the importance of routine early-detection protocols for relatives.

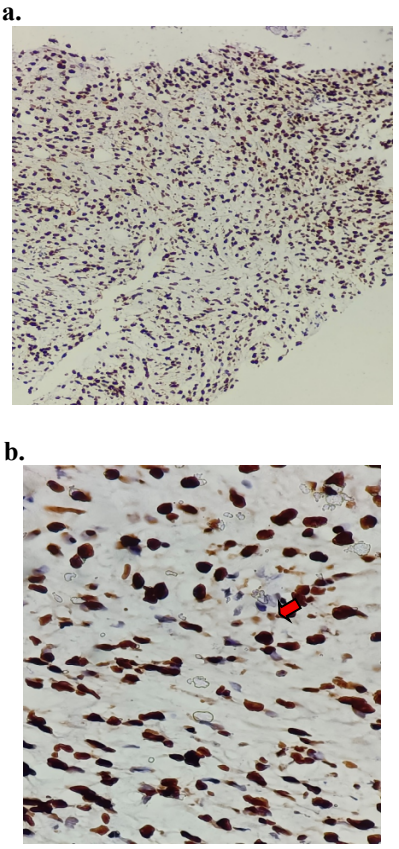

Figure 3. Right Manibullar Mass Immunohistochemistry of p53. **a & b.** Immunohistochemistry shows overexpression of p53 (arrows) in the right submandibular tumor mass, p53 stains in the majority of tumor cells nuclei with strong intensity. Magnifications: 100 x and 400 x

Management and Outcomes

GB was treated with standard chemoradiation consisting of oral temozolomide 75 mg/m² daily during intensity-modulated radiotherapy (IMRT) delivered at 60 Gy in 30 fractions. MO was deemed unresectable; he therefore received systemic chemotherapy with cisplatin 50 mg/m² and doxorubicin 35 mg/m². Despite multimodal supportive management, the proband's clinical condition progressively deteriorated, and he died six months after the diagnosis of MO.

DISCUSSION

LFS Pathogenesis and Tumor Biology

GM and MO are both aggressive malignancies within the LFS spectrum and tend to occur earlier than in the general population due to severe disruption of p53-dependent tumor suppression. MO represents only

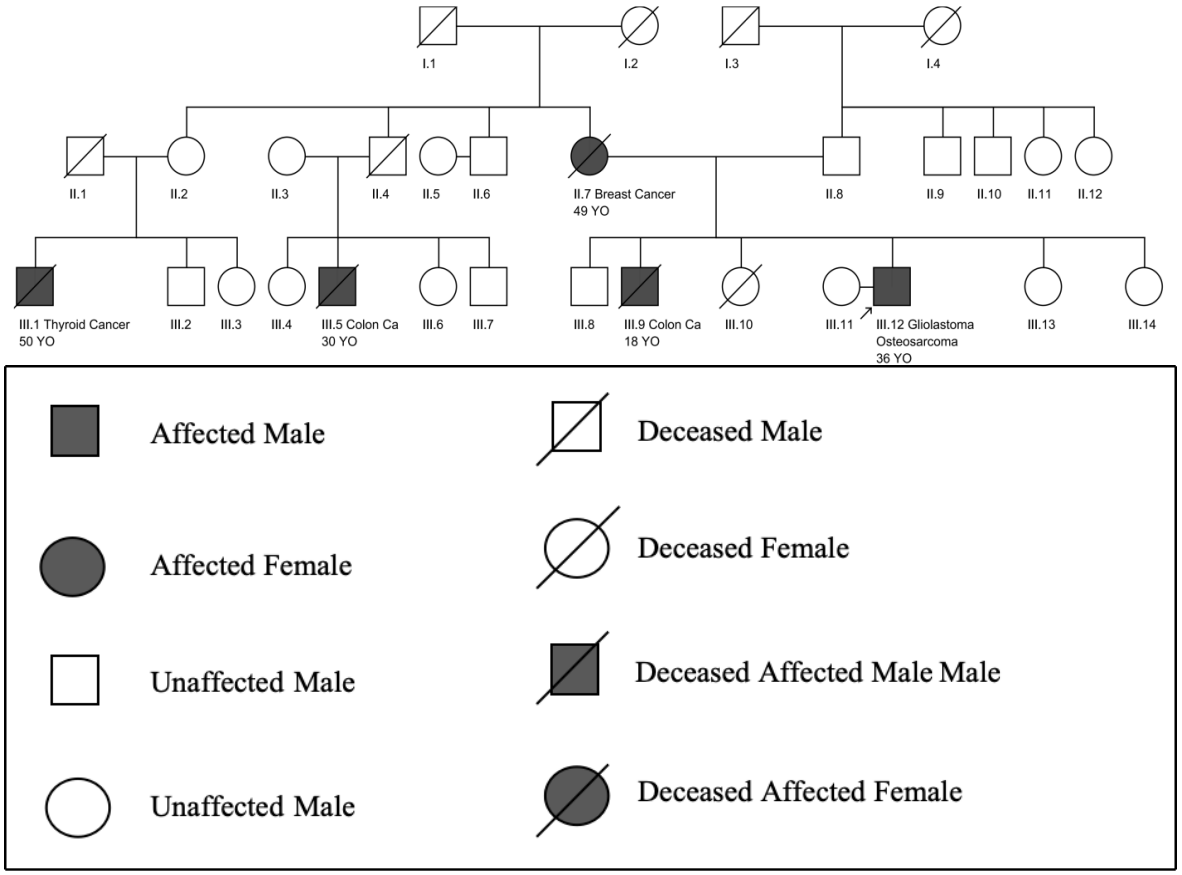

Figure 4. Three Generation Pedigree
Generation I : Unaffected parents (paternal & maternal)
Generation II : Mother with breast cancer at 49 Years Old
Generation III :

- Proband (black arrow) with Glioblastoma and Osteosarcoma at 36 Years Old
- One sibling with early-onset colorectal cancer at 18 Years Old
- Cousins with colorectal cancer at 30 Years Old and thyroid cancer at 50 Years Old

6–10% of all osteosarcomas, making its occurrence particularly rare.[13-15] LFS arises from germline *TP53* mutations that impair p53 regulation of cell-cycle arrest, apoptosis, and genomic stability. Wild-type p53 is rapidly degraded and minimally detectable on IHC, whereas many missense mutations produce structurally abnormal protein that accumulates in nuclei, leading to the strong mutant-type staining seen in this case.[12,16] As described by Baliakas et al., mutant p53 accumulation may reflect loss-of-function changes, dominant-negative inhibition, or gain-of-function (GOF) oncogenic properties.[17] Additional dysregulation of the *TP53–MDM2–RB1–CDKN2A* pathway further promotes uncontrolled proliferation in LFS-associated tumors.[13,19,20] Strong p53 positivity in this case therefore strongly suggests a missense *TP53* mutation, though p53 IHC cannot distinguish germline from somatic variants; germline sequencing remains the diagnostic gold standard.[16]

Genetic Counseling Considerations

Genetic counselling became the primary tool for risk stratification. Counseling in hereditary cancer differs fundamentally from counselling in sporadic cancers, as highlighted by Stembalska et al., it must address multigenerational implications, lifelong surveillance, and psychological burdens.[8] The counselor therefore discussed the implication of potential *TP53* test outcomes, a positive result would require intensive surveillance (e.g., whole-body MRI, brain MRI, targeted organ imaging, biochemical screening).[16] A negative result does not eliminate hereditary cancer risk because of possible undetected variants, mosaicism, or alternative predisposition genes.[8] The possibility of identifying a variant of uncertain significance (VUS) was also explained, emphasizing the need for periodic reinterpretation and management based on clinical and family history rather than the VUS itself as it cannot be interpreted as pathogenic or benign.[20] According to Miranda Alcalde et al., genetic testing is central to LFS management because it refines cancer-risk assessment, guides individualized surveillance, and improves diagnostic accuracy when clinical features overlap with other syndromes. However, in many resource-limited settings, access to testing and multidisciplinary services ideally involving oncologists, genetic counsellors, pathologists, and surgeons remains constrained by financial and infrastructural barriers.[23] This case demonstrates the crucial role of genetic counselling when molecular testing is inaccessible. Despite the absence of germline confirmation, counselling enabled structured risk communication, informed decision-

making, and tailored surveillance recommendations for at-risk relatives, underscoring its indispensable function in hereditary cancer care.[11,21]

Therapeutic Challenges in LFS

Management of MO and GBM in LFS is difficult because standard cancer therapies rely heavily on genotoxic agents, to which *TP53* mutation carriers are more vulnerable.[16] Mandibular osteosarcoma typically requires wide surgical resection plus MAP regimen (Methotrexate, Doxorubicin, and Cisplatin) chemotherapy. However, this tumor was unresectable, eliminating the strongest predictor of survival. Radiotherapy is avoided in LFS due to elevated risk of radiation-induced secondary cancers.[14,22] Glioblastoma necessitates temozolomide-based chemoradiation as per the Stupp protocol; despite increased radiosensitivity in LFS, the disease's aggressiveness leaves few alternatives.[4,5,21] Thus, treatment must balance immediate oncologic need and long-term risk, requiring multidisciplinary coordination among oncologists, surgeons, neurosurgeons, radiologists, pathologists, and genetics professionals.[16,23]

Outcome Interpretation

The poor prognosis in this case reflects both the biological aggressiveness of *TP53*-driven tumors and the clinical limitations encountered; unresectable MO (no chance of curative margins), intrinsically poor prognosis of GM, potential chemoresistance associated with mutant p53, limited access to genetic testing and comprehensive surveillance.[5,23] These factors collectively contributed to the patient's rapid decline and death six months after MO diagnosis.

CONCLUSION

This case illustrates an exceptionally rare presentation of Li-Fraumeni syndrome, marked by two distinct primary malignancies glioblastoma multiforme and unresectable mandibular osteosarcoma. The clinical, histopathological, and p53 IHC findings strongly suggest underlying *TP53* dysfunction, emphasizing the importance of recognizing LFS even when genetic testing is unavailable. The case further highlights the indispensable role of multidisciplinary management and specialized genetic counselling in guiding surveillance, family risk assessment, and therapeutic decision-making. In resource-limited settings where molecular testing is not accessible, structured genetic counselling and risk-adapted surveillance remain essential for optimizing care in hereditary cancer syndromes.

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