



# Recurrence of mucosal melanoma in Li-Fraumeni syndrome: A follow-up of an index case

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## INTRODUCTION

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant disorder caused by germline mutations in the TP53 gene, which greatly increase the risk for malignancy. The most common cancers associated with LFS include brain cancer, breast cancer, and soft tissue sarcoma.<sup>1</sup> Melanoma is rarely associated, with mucosal melanoma being particularly rare. Only 1 case of LFS presenting as mucosal melanoma has previously been reported. At the time of that publication, the patient was treated and had no evidence of local, regional, or distant disease, nor did she develop a second primary tumor. We provide an update of this index case of LFS-mucosal melanoma originally treated with surgical resection and adjuvant radiotherapy, but has now developed recurrent disease. In addition to re-highlighting a unique clinical scenario, this case description may help characterize the potential long-term efficacy of the treatment approach utilized and provide direction for future surveillance considerations of this rare disease.

## CASE REPORT

A 21-year-old Hispanic woman originally presented with left cervical lymphadenopathy and a concerning pigmented oral lesion (Fig 1). Biopsy of the oral lesion revealed malignant melanoma, and fine-needle aspiration of the lymph node confirmed regional metastases. Subsequent genetic analysis revealed LFS in the setting of a family history of leukemia in her father, uncle, and 3 of her cousins; all of these family members had the germline TP53

### Abbreviations used:

LFS: Li-Fraumeni syndrome  
MRI: magnetic resonance imaging

mutation and were deceased.<sup>1</sup> The patient's paternal grandfather died of an unknown cancer and it is unknown whether he had the TP53 mutation. One of the patient's 2 sisters, including that sister's 2 sons, also had the germline TP53 mutation, with one of these nephews developing leukemia. The patient is the only member of the family known to have developed mucosal melanoma. Her TP53 mutation was captured with PCR-based sequencing using a next-generation sequencing platform and was confirmed by Sanger sequencing. The mutation analysis revealed a nonsense mutation detected in codon 306, exon 8 (CGA to TGA) of the TP53 gene, which would change the encoded amino acid from Arginine to Stop. Gene mutations in TP53 can be observed in sporadic melanomas,<sup>2,3</sup> but to our knowledge, this specific mutation has not been previously described for a sporadic melanoma.

At that presentation, the patient displayed no evidence of local, regional, or distant disease, nor had she developed a second primary tumor.<sup>1</sup> She was treated with surgical resection and adjuvant radiotherapy, after which she underwent 4 cycles of adjuvant biochemotherapy with decarbazine, cisplatin, vinblastine, interferon alpha, and interleukin 2. The patient subsequently underwent 3 years of surveillance before being lost to follow up.

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**Fig 1.** The oral mucosal melanoma identified at the patient's initial presentation.

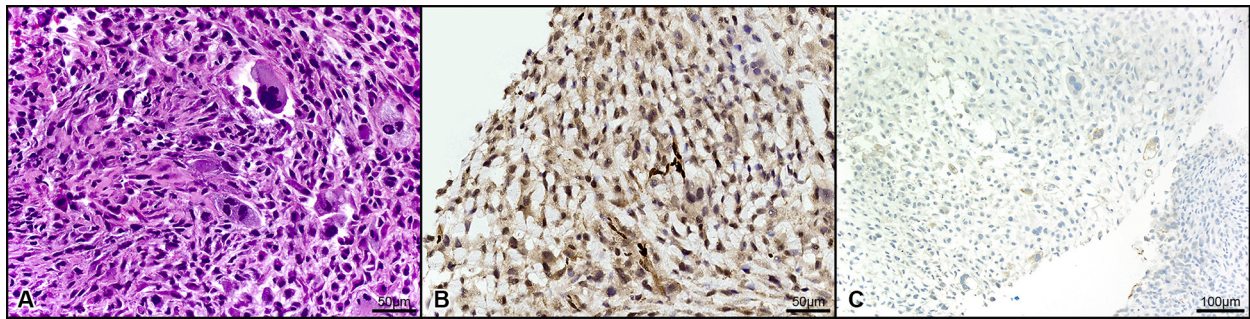
A total of 8 years after her initial diagnosis and treatment, she presented again with left cervical lymphadenopathy, with ultrasound-guided needle biopsy of the level IIB lymph node (a previously dissected lymph node) confirming presence of malignant melanoma. Specifically, histopathologic examination of the core biopsies revealed sheets of markedly atypical cells demonstrating wide pleomorphism with round, spindled, plasmacytoid, and rhabdoid morphology; occasional multinucleation, abundant eosinophilic cytoplasm, hyperchromatic nuclei, intranuclear inclusions, and scattered mitotic figures (Fig 2, A). Immunohistochemical studies showed that lesional cells were patchily positive for SOX10 (Fig 2, B) and ERG, weakly and patchily positive for HMB45 (Fig 2, C), diffusely positive for vimentin, and negative for myogenin, desmin, smooth muscle actin, MiTF, MART1, S100, pan-keratin, CAM5.2, CD30, and CD45. INI1 expression was retained. Lesional cells were compared to those seen in the patient's previous mucosal melanoma biopsy specimen, which expressed S100, HMB45, and MART1, and although the current specimen demonstrated a larger extent of pleomorphism, some similar-appearing lesional cells were present within both specimens. While the histopathologic differential diagnosis for the current specimen included melanoma, sarcoma, and sarcomatoid carcinoma, metastatic melanoma was favored based upon the cellular morphology and focal SOX10 and HMB45 expression.

PCR-based sequencing of this biopsy using a next-generation sequencing platform revealed ATRX and NF1 mutations, but not TP53 (a single-nucleotide variant missense mutation in exon 9 for ATRX and a frameshift deletion in exon 56 for NF1). Full skin examination and oral examination (Fig 3) revealed no concerning lesions. Brain magnetic resonance imaging (MRI) and computed tomography scanning of the body revealed no other evidence of metastatic disease.

## DISCUSSION

This case demonstrates recurrence of the original primary mucosal melanoma in this index patient, 8 years after therapy. Although PCR-based sequencing of the relapse biopsy revealed mutations separate from the TP53 mutation of the initial biopsy, a metastatic process was still favored, given the fact that discordances between primary and metastatic melanomas can be observed.<sup>4</sup> Original melanoma cells escaping the initial lymph node dissection, surviving aggressive radiation treatment, and then clinically re-emerging 8 years later represents the most likely explanation for this patient's recurrence. An additional possible explanation includes a Spitz nevus, which underwent benign metastasis and then transformed into melanoma after radiation therapy.<sup>5</sup> Another possible explanation would be nevi present in the patient's lymph nodes that transformed into melanoma under the influence of radiation.

Selecting the most appropriate therapy for these undescribed cases poses a significant challenge, as it is important to consider the benefits and risks of adjuvant therapy in LFS, along with the need for long-term follow-up to monitor for formation of second primary malignancies. Although radiation-induced tumors are rare and typically expected to occur more than 10 years after the radiation exposure, cases have been described in which this phenomenon occurs more frequently and much sooner for patients with LFS after undergoing radiotherapy. These findings suggest that employing a more conservative approach that avoids radiotherapy may represent the best treatment route.<sup>6,7</sup> Despite the increased theoretical risk of developing a second primary malignancy in patients with LFS after receiving radiotherapy,<sup>1,6-9</sup> this patient displayed no major evidence of a second primary malignancy. She instead developed recurrence of the initial aggressive malignancy targeted by the radiotherapeutic attempt for locoregional control. This case may provide support for using this same treatment strategy when confronted with similar scenarios in the future. Ongoing surveillance of this index patient remains crucial for further characterization of treatment roles in this rare disease. Recently proposed surveillance guidelines for LFS include annual clinical examination, with special attention to prior sites of radiotherapy, in addition to annual whole-body MRI, breast MRI for women between the age of 20 and 65, and annual brain MRI until the age of 50.<sup>10</sup> At the time of writing, the patient is undergoing another 4 cycles of immunotherapy with nivolumab and ipilimumab, with plans for repeat surgery.



**Fig 2.** **A**, High-power examination (magnification,  $\times 400$ ) of the Hematoxylin-eosin–stained sections revealed cells that appeared widely pleomorphic with round, spindled, plasmacytoid, and rhabdoid shapes and occasional multinucleated forms. **B**, Immunohistochemical testing with SOX10 showed patchy positivity within lesional cells (magnification,  $\times 200$ ). **C**, Immunohistochemical staining with HMB45 showed weak and patchy positivity within lesional cells (magnification,  $\times 200$ ).



**Fig 3.** The patient's well-healed surgical graft at the time of mucosal melanoma recurrence. No suspicious melanocytic lesions were identified.

LFS is a rare, malignancy-promoting disease with few reported treatment options. It is important to consider the increased risk of second primary malignancy formation after patients with LFS have undergone radiotherapy, and an approach that avoids radiation is supported. However, the risk of initial primary malignancy recurrence must also be considered, especially in cases where the primary malignancy is aggressive, such as mucosal melanoma. Regardless of the treatment approach that is chosen, long-term surveillance remains critical.

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**Conflicts of interest**

None declared.

**REFERENCES**

1. Klein JD, Kupferman ME. Li-Fraumeni syndrome presenting as mucosal melanoma: case report and treatment considerations. *Head Neck*. 2017;39(2):E20-E22.
2. Ragnarsson-Olding BK, Karsberg S, Platz A, Ringborg UK. Mutations in the TP53 gene in human malignant melanomas derived from sun-exposed skin and unexposed mucosal membranes. *Melanoma Res*. 2002;12(5):453-463.
3. Kong Y, Kumar SM, Xu X. Molecular pathogenesis of sporadic melanoma and melanoma-initiating cells. *Arch Pathol Lab Med*. 2010;134(12):1740-1749.
4. Bradish JR, Richey JD, Post KM, et al. Discordancy in BRAF mutations among primary and metastatic melanoma lesions: clinical implications for targeted therapy. *Mod Pathol*. 2015;28(4):480-486.
5. Raghavan SS, Kapler ES, Dinges MM, Bastian BC, Yeh I. Eruptive Spitz nevus, a striking example of benign metastasis. *Sci Rep*. 2020;10(1):16216.
6. Limacher JM, Frebourg T, Natarajan-Ame S, Bergerat JP. Two metachronous tumors in the radiotherapy fields of a patient with Li-Fraumeni syndrome. *Int J Cancer*. 2001;96(4):238-242.
7. Heymann S, Delaloge S, Rahal A, et al. Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. *Radiat Oncol*. 2010;5:104.
8. Kony SJ, de Vathaire F, Chompret A, et al. Radiation and genetic factors in the risk of second malignant neoplasms after a first cancer in childhood. *Lancet*. 1997;350(9071):91-95.
9. Newhauser WD, Durante M. Assessing the risk of second malignancies after modern radiotherapy. *Nat Rev Cancer*. 2011;11(6):438-448.
10. Frebourg T, Bajalica Lagercrantz S, Oliveira C, Magenheimer R, Evans DG, European Reference Network GENTURIS. Guidelines for the Li-Fraumeni and heritable TP53-related cancer syndromes. *Eur J Hum Genet*. 2020;28(10):1379-1386.