

## CLINICAL VIGNETTE

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# A Patient with Stage 3 Melanoma and Serendipitously Discovered Li Fraumeni Syndrome

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A 50-year-old woman ex-smoker with essential hypertension and hypothyroidism noticed a change in a pigmented area that had been present for years near her left knee. She underwent punch biopsy that revealed a 2.2 mm invasive melanoma without ulceration. She underwent a subsequent wider excision and sentinel lymph node mapping which revealed no additional melanoma in the wider excision specimen but one sentinel lymph node was positive for a micro-metastasis visible on hematoxylin and eosin (H & E) stain. Hence she had Stage 3A T3a (2-4 mm invasion without ulceration) and N1a (one clinically occult involved lymph node) which has a 5 year survival of 67%. She was started on adjuvant PD-L1 inhibitor immunotherapy with nivolumab. PD-L1 inhibitors represent the most effective class of adjuvant therapy, clearly better than both alpha interferon (α-IFN), the first therapy shown to improve survival after surgery in Stage 3 melanoma, and ipilimumab, the anti-CTLA 4 immunotherapy previously shown to be better than α-IFN.<sup>1</sup>

As part of her oncological assessment and given a possible familial predisposition to melanoma, her family malignancy history was obtained and was notable for testicular cancer in her father at age 60 and in her brother at age 25 and breast cancer in her mother at age 36. She had 4 sisters and 2 daughters without cancer. Based primarily on her mother with early onset, particularly under age 40, breast cancer, the patient underwent inherited cancer risk genetic testing. She was found to have a deleterious mutation (c.320\_327 del) p53 mutation, revealing Li Fraumeni syndrome. In addition to her planned full year of adjuvant nivolumab therapy and at least twice yearly total body dermatologist melanoma skin exams, she was told to have annual total body magnetic resonance imaging (MRI) cancer screening and every 1-2 year colonoscopy exams for malignancy surveillance.<sup>2</sup>

### Discussion

Melanoma risk is clearly increased by environmental factors, primarily unprotected exposure to ultraviolet (uv) radiation, but also by a family history of melanoma, suggesting an inherited component. Based on the current understanding of genetic risk factors for melanoma, genetic counseling and testing is recommended for patients with 3 or more relatives with melanoma, 3 or more separate personal melanoma diagnoses and earlier age of onset of melanoma.<sup>3</sup> While a number of genes have been

implicated in inherited melanoma risk, the most likely to be identified are CDKN2A or CDK4 mutations, which cause cell cycle arrest, but not p53.<sup>3</sup> This patient did not fit those screening criteria but rather the early onset breast cancer in a 1<sup>st</sup> degree relative suggested possible BRCA 1 or 2 mutations or other genes involved in repair of double stranded DNA breaks so her p53 mutation was discovered serendipitously.

Li Fraumeni syndrome is due to inherited mutations in p53. P53 is a critical tumor suppressor gene which induces cell cycle arrest in response to DNA damage and is mutated frequently in malignancy, conferring a worse prognosis. Criteria for genetic testing include a patient with sarcoma under age 45 or any first degree relative with cancer under age 45 or a first or second degree relative with sarcoma at any age,<sup>4</sup> which was true in the family of KB. In a multicenter cohort study of 1730 patients referred for genetic cancer risk testing, among 415 of whom had a p53 mutation, there was a 78% incidence of cancer and 43% incidence of multiple primary cancers.<sup>4</sup> In 132 Li Fraumeni children with malignancy, the distribution was 30% osteosarcoma, 27% adrenocortical carcinoma, 26 % primary brain tumors, including glial and medulloblastomas, and 23% soft tissue sarcomas. In 219 Li Fraumeni adults with malignancy, 73% were female breast cancer and 27% were soft tissue sarcomas in both sexes.<sup>4</sup> While there appears to be an increased risk of melanoma in Li Fraumeni syndrome, melanoma is not one of the characteristic malignancies. The lifetime risk of malignancy in Li Fraumeni syndrome is extremely high. In a cohort of patients followed by the National Cancer Institute (NCI), the risk of cancer by age 60 was 90% and by age 70 of nearly 100 %.<sup>5</sup> The distribution of cancers by age 70 included 54% breast cancer, 15 % soft tissue sarcoma, 6 % brain tumors and 5% osteosarcoma.<sup>5</sup>

Since p53 is critical for cell cycle arrest after DNA damage to allow for either DNA repair or cell apoptosis, there has been concern about radiation exposure in Li Fraumeni patients. Preclinical models predicted for an increased risk of malignancy from radiation exposure. In a French Li Fraumeni 47 family cohort study, 8 patients developed breast cancer. Six of the breast cancer patients underwent a lumpectomy and radiation and subsequently 3 developed an ipsilateral recurrence and 2 developed new primary breast cancers in the same breast.<sup>6</sup> This suggested a substantially higher risk of subsequent malignancy with therapeutic radiation. Based on concern about

increased sensitivity to radiation induced malignancies and the high risk of breast and brain cancers and soft tissue sarcomas in Li Fraumeni patients, total body MRI rather than CT has been recommended for annual imaging screening for occult malignancy.<sup>2</sup> Hence this patient will need annual screening total body MRIs and every 2 year colonoscopies and, based on her melanoma diagnosis, every 6 month total body skin exams with her dermatologist.

Fraumeni syndrome. *Radiat Oncol.* 2010 Nov 8;5:104. doi: 10.1186/1748-717X-5-104. PubMed PMID: 21059199; PubMed Central PMCID: PMC2988810.

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