CLINICAL VIGNETTE

Li-Fraumeni Syndrome and Multiple Primary Malignancies, including Systemic Mastocytosis

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Case Report

A 44-year-old woman was referred to Hematology/Oncology by rheumatology for possible systemic mastocytosis. She had history of Li-Fraumeni syndrome, osteosarcoma, breast cancer, and rectal cancer. Her oncologic history began at age 19 when she was diagnosed with osteosarcoma of her right tibia. She was treated with neoadjuvant methotrexate, doxorubicin, and cisplatin (MAP) chemotherapy followed by limb-sparing resection and cadaveric bone reconstruction, which were complicated by non-union and infection. She eventually required limb amputation. At age 37, she was diagnosed with clinical stage II invasive high grade breast ductal carcinoma, estrogen receptor negative, progesterone receptor negative, and HER2 negative (triple negative). She was referred for genetic counseling and germline genetic testing revealed she had a heterozygous pathogenic variant in TP53 (c.509_512delCGGA), consistent with Li-Fraumeni syndrome. She was given neoadjuvant chemotherapy with doxetaxel and carboplatin and underwent bilateral mastectomies. Surgical pathology showed a complete pathologic response to chemotherapy. At age 43, she underwent a surveillance colonoscopy for a history of multiple colonic polyps and was diagnosed with intramucosal rectal adenocarcinoma arising from a tubular adenoma. She underwent robotic transanal minimally invasive surgery. Surgical pathology revealed negative margins and mismatch-repair proficient status.

The patient was in her usual state of health until she developed extensive itching and flushing. Symptoms did not improve on antihistamines, aspirin, or prednisone. She had a consultation by rheumatology who initiated testing which included a tryptase level that was elevated to 69 mcg/L (reference range 2.2-23.2). CBC was unremarkable. Peripheral blood testing showed presence of KIT D816V mutation. Bone marrow aspiration and biopsy recommended by Hematology/Oncology, confirmed a diagnosis of systemic mastocytosis involving 20% of the marrow cells. Abnormal mast cells showed aberrant expression of CD2, CD25, CD117, and mast cell tryptase. There was increase in reticulin fibrosis within mast cell infiltrates. There were no excess blasts or dysplasia. Next generation sequencing of her marrow specimen confirmed her TP53 pathogenic variant with an allele frequency of 40% and the KIT D816V variant.

She was given symptom-directed treatment with antihistamines, cromolyn, and montelukast but continued to have severe itching and flushing. She was then started on midostaurin, a tyrosine kinase inhibitor with multiple receptor targets including KIT. Despite 3 months of therapy on midostaurin, she developed biopsy-proven involvement of her large intestine. Therapy was switched to avapritinib, a highly selective, potent inhibitor of mutated KIT and PDGFR. Shortly after, she transferred her medical care and was lost to follow up.

Discussion

Li-Fraumeni syndrome (LFS) is an autosomal dominant, cancer predisposition disorder characterized by an increased risk of various susceptible malignancies caused by a germline mutation in the TP53 tumor suppressor gene. LFS was first described by Frederick Li and Joseph Fraumeni in 1969 as a potential familial susceptibility to cancers based on four families manifesting an unusual frequency of cancers at a young age, including soft tissue sarcoma, breast cancer, and multiple primary cancers.[1] The genetic basis for LFS was eventually discovered in 1990 with the link to heterozygous mutations in TP53. TP53 is considered the “guardian of the genome” and its gene product, p53 protein, plays a crucial role in regulating cell cycle and apoptosis in response to DNA damage, maintaining genomic stability. p53 also regulates metabolic homeostasis and the tumor microenvironment, among other cellular processes. TP53 mutations are the most common genetic alteration in human cancers and lead to both impairment of tumor suppressor function and promotion of oncogenesis.[2]

One of the largest studies analyzing the clinical presentation of LFS was reported by Bougeard et al in 2015.[3] In this study, 1,730 patients with a history suggestive of LFS were tested for germline TP53 mutations and 415 patients were found to be carriers of 133 distinct TP53 mutations. Seventy eight percent of these carriers developed at least one malignancy with a mean age of onset of 25 years. There was significant incidence of malignancies in pediatric patients with 22% and 41% of affected carriers having developed malignancies by age 5 and 18 years. Forty three percent of affected carriers developed multiple malignancies. The most common malignancies in children were osteosarcoma (30%), adrenocortical carcinoma (27%), CNS tumors (26%), soft tissue sarcoma (23%), and leukemia (9%). Among adults, the most common malignancy by far was breast cancer (79% of women), followed by soft

tissue sarcoma (27%). Of women with breast cancer who were treated with radiation, 30% developed secondary tumors within the radiation field with a mean time interval of 11 years. Other than these "core" cancers in LFS, there are reports of an increased incidence of other cancers, including lymphoma, melanoma, lung cancer, pancreatic cancer, and prostate cancer. Colorectal and gastric cancers have also been known to occur early in LFS patients, but a true incidence increase is yet to be determined.[4] With regards to hematologic malignancies in LFS, hypodiploid acute lymphoblastic leukemia is the most common. Acute myeloid leukemia and myelodysplastic syndrome are also frequently reported, often preceded by prior DNA damaging chemotherapy, such as alkylators and topoisomerase inhibitors, or radiation.[5] This phenomenon is to be expected in the setting of impaired response to DNA damage seen in LFS.

To date, no case reports of LFS and systemic mastocytosis were found on PubMed literature search. Systemic mastocytosis (SM) is a rare malignancy with neoplastic mast cell infiltration of various organs, as compared to cutaneous mastocytosis (CM) which only involves the skin. CM typically presents in children and SM in adults. SM is most commonly driven by a somatic mutation in the KIT gene (KIT D816V found in >90% of SM), which leads to constitutive growth and activation of mast cells.[6] Other mutations in genes such as TET2, SRSF2, ASXL1, CBL, RUNX1, and RAS are associated with advanced SM (encompassing aggressive SM, SM with associated hematologic neoplasm, and mast cell leukemia), which have poor prognoses compared to non-advanced SM (indolent SM and smoldering SM). Manifestations of SM are varied, depending on the organs and mast cell mediators involved (e.g. histamine and tryptase), and include rash, flushing, pruritus, unexplained anaphylaxis, blood cytopenias, and diarrhea, among others. In addition to atypical mast cell infiltration in the bone marrow or other extracutaneous organs and discovery of a KIT mutation, tryptase level of >20 ng/mL can aid in the diagnosis as a minor criterion. Treatment of SM is aimed at symptom control using drugs such as antihistamines as well as cytoreductive therapy using chemotherapy or KIT targeting, including midostaurin and avapritinib. Our patient had advanced SM that progressed to involve of her GI tract despite treatment with midostaurin. Whether or not her LFS had a direct relationship to the development of SM is unknown but is consistent with the multiple malignancy phenotype.

Criteria for genetic testing for TP53 pathogenic variants, named "Chompret criteria," was proposed by the French LFS working group. The updated criteria includes: 1) Patients with LFS core malignancy (breast cancer, soft tissue sarcoma, osteosarcoma, CNS tumor, or adrenocortical carcinoma) before age 46 years and at least one first- or second-degree relative with a core malignancy before age 56 years. 2) Patients with multiple primary malignancies, including 2 LFS core malignancies, with first onset before age 46 years, regardless of family history. 3) Patients with breast cancer before age 31 years, regardless of family history. 4) Patients with rare malignancies, including adrenocortical carcinoma, choroid plexus carcinoma (a type of CNS tumor), or embryonal anaplastic rhabdomyosarcoma. Expert guidelines also recommend genetic testing for pediatric patients with hypodiploid acute lymphoblastic leukemia or patients who develop a second primary malignancy within the radiation field of a LFS core malignancy which developed before age 46 years.[7] First-degree relatives of patients with TP53 pathogenic variants should be offered testing for the same variant, including pediatric age patients if the variant or family history is high enough risk. Patients who qualify for genetic testing should have it done before treatment with chemotherapy or radiation therapy to potentially adjust management due to the risk of secondary malignancies.

Once a TP53 pathogenic variant is discovered in a carrier, intense surveillance for malignancy is indicated in hopes of early detection and curative management. In pediatric carriers, abdominal ultrasound to detect adrenocortical carcinoma should be performed every 6 months.[7] In adult carriers or pediatric carriers with higher risk (high risk variant or prior chemotherapy or radiation), whole-body MRI without gadolinium contrast should be performed annually. Whole-body MRIs have been shown in multiple studies to be effective cancer surveillance for carriers. One study of whole-body MRI reported an estimated 7% detection rate of localized malignancy on first imaging.[8] In female carriers, annual breast MRI is recommended starting at age 20. Risk-reducing mastectomy is an option that should be discussed with female carriers on an individual basis. Annual brain MRI is recommended for adult carriers or pediatric carriers with higher risk. Lastly, colonoscopy should be performed starting at age 18 years, every 5 years, for carriers with a history of prior abdominal radiation or a significant family history of colorectal cancer. Treatment of malignancies diagnosed in carriers typically follow the same protocols as those without TP53 mutations, except the avoidance of radiation and DNA damaging chemotherapy if possible, for the reason discussed above. Surgery or ablation is preferred over radiation for local therapy. In the management of breast cancer, mastectomy is preferred over lumpectomy and radiation. Prior to her LFS diagnosis, our patient was given genotoxic chemotherapy at age 19 for her osteosarcoma, which may have contributed to the development of her multiple other malignancies later on in her life. Thus, knowledge of LFS presentation, criteria for genetic testing, and optimal management could lead to better outcomes for these unfortunate patients.

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