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613.ACUTE MYELOID LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

Li-Fraumeni Syndrome: The Two Faces of a Coin in Myeloid Malignancies

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Background

Li-Fraumeni Syndrome (LFS) is a rare, autosomal dominant genetic disorder caused by germline mutations in the TP53 tumor suppressor gene. It is characterized by a predisposition to a wide range of cancers, including hematological malignancies. Hematological malignancies account for approximately 3-4% of all LFS-related cancers of which are acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Myelodysplastic syndromes (MDS) and lymphomas.

Method and Results

We retrospectively analyzed our clinical data for patients with hematological malignances from the period of Jan 2016-Jan 2022 at the national center for cancer care and research (NCCCR), the only tertiary hematology center in the country. We report on two cases with Li Fraumeni syndrome with acute leukemia and their variable spectrum of the disease manifestations and prognosis.

Case 1: 16 years old male known case of rheumatic heart disease presented with double malignancy; left mandible osteosarcoma and lymphoblastic leukemia/ lymphoma concurrently in 2020. For his Leukemia he received BFM*2009 protocol and after remission he underwent surgical resection and received radiotherapy for the osteosarcoma. Patient has family history of breast cancer in his maternal aunt and his paternal great aunt. Germline Genetic testing from buccal swab revealed a pathogenic variant in TP53 gene confirming Li Fraumeni syndrome which is most likely De novo as it was not detected in both parents and his 3 siblings.

In 2022 patient presented with pancytopenia and therapy related AML/MDS with complex Karyotype. He was started on salvage therapy and was planned for allogenic stem cell transplant (SCT) from his HLA matched brother, however, unfortunately, patient didn't achieve complete remission thus could not receive the SCT and he passed away one year later in 2023.

Case 2: 60-year-old female known case of hypertension who was diagnosed with right breast cancer in 2011 for which she underwent surgery, chemotherapy, and radiotherapy. A year later, patient was diagnosed with left upper lobe squamous cell lung carcinoma, and underwent left upper lobectomy, chemotherapy and radiotherapy. Patient was in remission for 6 years, until 2018 when she presented with pancytopenia and therapy related AML with complex monosomic Karyotype. Due to patient's age and comorbidities, she was unfit for intensive therapy, thus she received hypomethylation agent (Azacitidine) till disease progression and was referred to genetic counseling.

Patient has a family history of unknown cancer in her paternal half-sister at the age of 77 and an unknown cancer in her paternal cousin. Genetic testing reveled a mosaic pathogenic variant in TP53 gene present in 17% of the 1137 next generation sequencing reads. Shortly later, patient passed away without confirmatory fibroblast testing.

Conclusion:

Genetic testing indications for Li-Fraumeni syndrome present challenges as patients with full mutationin TP53 often but not always present with the full spectrum of the disease, whereas patients with mosaic profilepresent with a later onset of the disease and might not be identified early. In both scenarios, patients can be miss-identified and exposed to radiotherapy thus testing criteria warrants further evaluation. Acute Leukemia in Li-Fraumeni syndrome is associated with poor prognosis and usually presents in the context of therapy related myeloid malignancies . Identification of patients with Li-Fraumeni syndrome early on is crucial to avoid exposures to radiotherapy whenever possible thus reducing the risk of subsequent malignancies and the tragic outcomes of the disease. There are unmet clinical needs in Li-Fraumeni syndrome diagnostic and therapeutic approaches which needs further attention.

Disclosures No relevant conflicts of interest to declare.

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