Li-Fraumeni Syndrome

Li-Fraumeni Syndrome (LFS) is an autosomal dominant condition that predisposes children and young adults to a wide range of cancers. This is due to a mutation in the TP53 tumor suppressor gene. Individuals with this disease are susceptible to developing multiple cancers, most notably soft-tissue and bone sarcomas like osteosarcoma, breast cancer, brain tumors, leukemias, lymphomas, and adrenocortical carcinomas. Management is primarily supportive care.

PLAY PICMONIC

Pathophysiology

Autosomal Dominant

Domino

Li-Fraumeni syndrome is inherited in an autosomal dominant manner. This means that a single copy of the disease-associated gene is enough to cause the disease, and that the disease-associated gene is on an autosome. The abnormal gene can be inherited from either parent, and the risk of passing the altered gene from an affected parent to an offspring is 50% for each pregnancy. The risk is the same for males and females.

TP53 Mutation

Toilet-Paper (50)-cent (3)-tree Mutant

In Li-Fraumeni Syndrome, there is a failure to modulate the progression from G1 to S phase. Normally, p53, which is encoded by the TP53 gene, inhibits this progression of the cell cycle. In patients with LFS, one abnormal copy of the TP53 gene is inherited. As a result, modulation of the G1 checkpoint is diminished, and unrestrained progression of G1 to S phase occurs. The degree to which a TP53 variant causes cancer in a family or individual is called “penetrance.”

Loss of Heterozygosity

Lost Hat-arrow-Z-Goat

In Li-Fraumeni Syndrome, individuals inherit one abnormal copy of the TP53 gene. This individual is said to be "heterozygous", which means cells have one abnormal copy of TP53 gene and one normal copy. The normal allele produces a normal tumor suppressor protein. If the second allele is somatically mutated or deleted, the cell is said to have lost heterozygosity. This is also known as the two-hit hypothesis; if a heterozygous cell receives a second hit in its remaining functional copy of TP53 gene, it becomes homozygous for the mutated gene. These individuals then have two non-functional copies of TP53 and are unable to produce tumor suppressor protein. These cells experience unregulated proliferation and patients are at higher risk for developing cancer.

Clinical Features

Osteosarcoma

Ostrich-shark-comb

Clinical features of Li-Fraumeni Syndrome include multiple malignancies at an early age. One of the common manifestations is sarcoma, particularly osteosarcoma. Sarcomas arise from mesenchymal tissue, and osteosarcoma is a malignant tumor of the bone. It classically presents in the knee and in the metaphysis of long bones.

Breast Cancer

Breast Tumor-guy

Breast cancer can be subdivided into noninvasive and invasive carcinoma. Noninvasive carcinomas are considered "carcinoma in situ", and are characterized by absence of stromal invasion. Invasive breast carcinomas may further classified as ductal or lobular. Less common subtypes of invasive breast carcinoma include mucinous carcinoma, mixed carcinoma, tubular carcinoma, and papillary carcinoma.

Brain Tumors

Brain and Tumor-guy

Brain tumors are abnormal masses of cells within the brain. They can be primary (arising from the brain) or metastatic (arising elsewhere in the body), malignant or benign. Common tumors of childhood include medulloblastomas, ependymomas, pinealomas, craniopharyngiomas, and pilocytic astrocytomas. Common tumors of adulthood include glioblastoma multiforme, meningiomas, schwannomas, hemangioblastoma, prolactinomas, and oligodendrogliomas.

Leukemia/Lymphoma

Leukemia-Luke and Lime-Foam

Leukemia is characterized by an increase in premature leukocytes, which are released into the bloodstream. Leukemias include acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), and chronic lymphocytic leukemia (CLL). Lymphomas are related, but distinct. They are characterized by a discrete tumor mass in the lymph nodes, and are further categorized into Hodgkin and non-Hodgkin lymphomas.

Adrenocortical Carcinoma

Adrenal Cortez and Car-gnome

Adrenocortical carcinoma (ACC) is a rare, aggressive neoplasm of the adrenal cortex that is very locally invasive. They often invade the renal veins or inferior vena cava. Adrenocortical carcinomas also metastasize via the lymphatic system to the lung, liver, and bone. Most adrenocortical carcinomas are functional (hormone secreting), and may secrete any of the adrenal cortex hormones, such as glucocorticoids (most common), mineralocorticoids, or androgens.

Management

Supportive Care

Supportive IV bags

Currently, there is no standard treatment or cure for LFS. Generally, cancers in people with LFS are treated the same as for cancers in other patients, but research continues on how to best manage this disease. Individuals with LFS may have an elevated risk for radiation-induced cancers, so the use of radiotherapy or ionizing radiation (such as CT scans) in these patients should be limited. Individuals with LFS should ensure that they live a healthy lifestyle, such as using sun protection and the avoiding tobacco products. Additionally, because early detection of cancer can increase overall survival, and those diagnosed with LFS should seek to adhere to preventive screening.