Childhood Malignancy

Amar Taksande*, Aishwarya Jadhav**

*Professor, **Resident, Department of Pediatrics, Jawaharlal Nehru Medical College, Sawangi Meghe, Wardha, Maharashtra -442102.

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Childhood malignancies are relative rare and prognosis has been improving in the last three decades as a result of more accurate diagnosis and improved treatment strategies. Childhood cancers usually originate from the deeper, visceral structures and from the parenchyma of organs rather than from the epithelial layers that line the ducts and glands of organs and compose the skin. The most common pediatric cancers may be classified into 5 categories on the basis of the involved tissue or organ system: a) Lymphohematopoietic system, b) Nervous system c) Embryonal group d) Connective tissue and e) Gonadal system. The most common childhood malignancies are leukemia (30%), brain tumor (20%), lymphomas (12%), and followed by neuroblastoma, retinoblastoma and tumors affecting soft tissues, kidneys, bones and gonads. The causes of childhood malignancies are largely unknown. Specific chromosomal (eg. Down syndrome) and genetic abnormalities have been associated with increased risk of malignancies. Exposure to ionizing radiation, early-life exposures to infectious agents, exposures to environmental toxins such as pesticides, solvents, or other household chemicals, and parental occupational exposures to radiation or chemicals are associated with higher incidences of childhood malignancies. The age related manifestations of childhood malignancy are as follow First 2 yr. of life: Embryonal and intra abdominal tumors (e.g., Wilms tumor, Retinoblastoma, Teratoma and Neuroblastoma); From 2–5 yr.: Acute lymphoblastic leukemias, Non-Hodgkin lymphoma, and gliomas; Preschool aged & early school aged children: Leukemias, Lymphoma, and brain tumor; Adolescents: Bone tumors, Hodgkin disease, Sarcomas and genital or gonadal malignancies.

The symptoms and signs of cancer are more variable and nonspecific in pediatric than adult patients. In children, metastases are present at diagnosis in approximately 80% of cases. The most common signs and symptoms are abdominal mass, persistent lymphadenopathy, >1 abnormal hematopoietic lineage, specific neurologic deficit, increased intracranial pressure, diffuse enlargement of pons, proptosis, white pupillary reflex, unilateral knee or shoulder pain/swelling and vaginal bleeding or mass. The most common presentation of the childhood cancers in children is shown in table1. Because most childhood cancers are curable, early detection is crucial. In fact, early detection often minimizes the amount and duration of treatment required for cures and, therefore, may not only lead to a higher potential for cure but also spare the patient intensive or prolonged therapy. The minimum investigation required for common pediatric malignancies to assess primary tumor is shown in table 2. Diagnosis can be confirmed by bone marrow examination; the morphologic, cytochemical, immunophenotypic and genetic characteristics of the blast cells should be determined (1-3).

Leukemia

Leukemia is a malignancy that arises from clonal proliferation of abnormal hematopoietic cells leading

Corresponding Author: Amar M. Taksande, Department Of Pediatrics, Jawaharlal Nehru Medical College, Sawangi Meghe, Wardha, Maharashtra -442102.

Email: amar.taksande@gmail.com

to disruption of normal marrow function and various manifestation of leukemia. There are two main subtype acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). The chronic forms of leukemia as chronic myeloid leukemia (CML) are uncommon in children. ALL is the most common type of leukemia in children. In ALL, the lymphocyte cell line is affected and the bone marrow makes too many of these lymphocytes and they do not mature correctly. The lymphocytes overproduce, thus, crowding out other blood cells. This leukemia is more common in boys than girls, especially in adolescents with T-cell ALL. There is increase incidence of childhood ALL, due to ALL associated with a pre-B lineage. AML can occur at any age but incidence is more during adolescence. AML in which too many granulocytes are produced in the marrow. With AML, the bone marrow makes too many of these cells and they do not mature correctly. The granulocytes overproduce, thus, crowding out other blood cells.

Most of the time, the diagnosis of leukemia is delayed because early symptoms are nonspecific and may mimic those of viral infections. Most children who have this cancer present with generalized malaise, loss of appetite and a low-grade fever. Additional symptoms that should prompt concern include pallor, petechiae or ecchymoses, bone pain and significant weight loss. Chloromas are localized collection of leukemic cell seen exclusively in patients with AML. They may occur at any site including CNS, bones, and skin. Gingival hypertrophy may be present The physical examination may reveal no abnormalities, but the presence of significant lymphadenopathy or any hepatosplenomegaly should raise suspicion for leukemia.

A prudent approach to the child with any suspicious findings is to obtain a complete blood count (CBC) with a white blood cell differential and a reticulocyte count. The presence of blast cells on the peripheral smear is indicative of leukemia. In addition to a complete medical history and physical examination, diagnostic procedures for leukemia may include: bone marrow aspiration, CBC, CT scan, MRI, chest x-ray, ultrasound, lymph node biopsy, lumbar puncture. The diagnosis of ALL is made by bone marrow examination, which shows a homogeneous infiltration of leukemic blasts replacing normal marrow elements. The morphology of blasts on bone marrow aspirate can usually distinguish ALL from AML. Treatment may include chemotherapy, intrathecal medications, radiation therapy, bone marrow transplantation or peripheral blood stem cell transplantation(2-4).

Central Nervous System (CNS) Tumors

CNS tumors are the second most common childhood malignancy. About 50% of the common pediatric brain tumors occur above the tentorium and 50% in the posterior fossa. In the very young child, posterior fossa tumors are more common. Most childhood brain tumors can be divided into two categories according to the cell of origin: (1) glial tumors, such as astrocytomas and ependymomas, or (2) nonglial tumors, such as medulloblastoma and other primitive neuroectodermal tumors. Some tumors contain both glial and neural elements (eg, ganglioglioma). Children, who have infratentorial lesions usually present with ataxia and other gait disturbances, frequently have hydrocephalus as a result of aqueduct compression and may also have cranial nerve abnormalities from brainstem compression. Supratentorial tumors occur at any age. These lesions can present with signs of elevated intracranial pressure (headache and vomiting, or an enlarging head in infants) and focal neurologic deficits. School failure and personality changes are common in older children. Irritability, failure to thrive, and delayed development are common in very young children with brain tumors. For primary brain tumors, MRI is the neuroimaging standard(5).

Lymphoma

The term lymphoma refers to a malignant proliferation of lymphoid cells, usually in association with and arising from lymphoid tissues (ie, lymph nodes, thymus, spleen). They may spread to bone marrow and other organs, which can cause different symptoms depending on where the cancer is growing. The most common form is Hodgkin disease, which represents nearly half of all cases. The remaining subtypes, referred to collectively as non-Hodgkin lymphoma, are divided into four main groups: lymphoblastic, small noncleaved cell, large B-cell, and anaplastic large cell lymphomas. The incidence of Hodgkin's lymphoma increases throughout childhood and peaks in the late teenage years. This form most often presents with a painless mass in the neck. Other presentations include a persistent cough secondary to a mediastinal mass or, less commonly, splenomegaly or enlarged axillary or inguinal lymph nodes. This investigation should

include a lymph node biopsy. Non-Hodgkin lymphoma (NHL) is characterized on basis of their T-cell or B-cell nature. Lymphoblastic lymphomas are T-cell derived, while undifferentiated lymphomas (Burkitt and Non-Burkitt) are B-cell derived. Children with NHL typical present with extranodal disease involving the mediastinum, abdomen or head and neck region. NHL is more likely to occur in younger children than Hodgkin lymphoma, but it is still rare in children younger than 3.

The most frequent sites of this malignancy are the abdomen, mediastinum and head and neck. When the abdomen is affected, the most common presenting features are abdominal pain with vomiting or diarrhea, a palpable mass, and intussusceptions. In the absence of a palpable mass, persistent abdominal pain with vomiting or diarrhea, especially when accompanied by significant weight loss, should prompt a thorough investigation, including diagnostic imaging. In the child with a persistent cough, a chest radiograph may reveal a mediastinal mass or mediastinal widening. Scanning performed with gallium/ PET scan can be helpful in evaluating a child with systemic symptoms of lymphoma but no signs of a mass (6-9).

Neuroblastoma

Neuroblastoma, a neuroendocrine tumor of the sympathetic nervous system, is the most common intraabdominal solid tumor of childhood. It accounts for 8.2 percent of all cancers diagnosed in children less than 15 years of age. The most common sites of primary tumors are the adrenal glands(30%), paravertebral retroperitonium(28%), posterior mediastinum, pelvis and neck. Symptoms include abdominal pain, emesis, weight loss, anorexia, fatigue, and bone pain. Hypertension is an uncommon sign of the disease and is generally caused by renal artery compression, not catecholamine excess. Chronic diarrhea is a rare presenting symptom secondary to tumor secretion of vasoactive intestinal peptide secretion. Bone and bone marrow metastases are common. These metastases cause bone pain and, possibly, signs of bone marrow failure (i.e., anemia and purpura). The skull is a frequent site of bone metastases, which commonly present as proptosis and periorbital ecchymoses. Rare but characteristic presentations include transverse myelopathy (tumor spinal cord compression), Horner's syndrome (cervical tumor), opsoclonus myoclonus syndrome and ataxia (suspected paraneoplastic cause). The gold standard for diagnosis of neuroblastoma is examination of tumor tissue by histopathology and immunochemistry. In about 90% of cases, elevated levels of catecholamine or their metabolites (Dopamine, homovanillic acid (HVA), and/or vanillylmandelic acid (VMA)) are found in the urine or blood. When the lesion is localized, it is generally curable. Despite aggressive multimodality therapy (Chemotherapy, Surgery, Radiation therapy, Stem cell transplant, 13-cis-retinoic acid, and Immunotherapy with anti-GD2 monoclonal antibody therapy), the outcome is poor for children with advanced-stage disease(10).

Wilms Tumor

Wilms tumor (Nephroblastoma) is the most common malignant tumor of the kidney. The peak age of diagnosis is 2-3 years, 6% patients have bilateral disease and 1% cases are familial. It can present as an abdominal mass, abdominal pain, gross hematuria and hypertension. When an abdominal mass is detected in a child, ultrasound examination of the abdomen should be performed within 24 hours. If the ultrasound examination does not clearly identify the origin of the mass, abdominal CT scanning should be performed. Abdominal magnetic resonance imaging (MRI) is reportedly the most sensitive imaging modality for determination of caval patency and may be important in determining whether the inferior vena cava is directly invaded by the tumor. Histopathologic confirmation of Wilms tumor is essential. If the tumor is only in the kidney, it can be removed along with the whole kidney (a nephrectomy). Usually all modality of treatment : surgery, chemotherapy and radiotherapy are required(11).

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) arises from primitive muscle cells, but tumors can occur anywhere in the body. The most common sites are the head and neck (28%), extremities (24%), and genitourinary (GU) tract (18%). Other notable sites include the trunk (11%), orbit (7%), and retroperitoneum (6%). This is the most common type of soft tissue sarcoma in children. It usually manifests as an expanding mass and symptoms depend on the location of the tumor. It is the most common non-ocular orbital tumor in young children usually presenting with proptosis or swelling of the eyelids. If metastatic disease is

present, symptoms of bone pain, respiratory difficulty, anemia, thrombocytopenia, and neutropenia may be present. Treatment consists of chemotherapy, radiation therapy and sometimes surgery. Surgery to remove the tumor may be difficult or impossible depending on the location of the tumor. If there is no evidence of metastasis, surgery combined with chemotherapy and radiation offers the best prognosis(11,12).

Bone Tumors

Primary bone cancers occur most often in older children and teens, but they can develop at any age. Primary bone cancer is different from metastatic bone cancer. Metastatic bone cancer is more common than primary bone cancer because many types of cancer can spread to the bone. Two main types of primary bone cancers occur in children:

Osteosarcoma is the most common bone tumor. It generally develops during puberty and occurs primarily in the distal femur and proximal tibia. It often causes no pain or symptoms until swelling starts, but sometimes there is bone pain that gets worse at night or with activity.

Ewing sarcoma is a less common primary bone cancer, which can also cause bone pain. It is most often found in young teens. The most common sites are the bones in the pelvis, the chest wall, or in the middle of the long leg bones. Ewing's sarcomas have been known to occur in children as young as three years of age and in adults well beyond 30 years of age. In addition to occurring in the extremities, these tumors often develop in the bone and soft tissue of the central axis, including the skull, vertebral bodies, rib cage, skull, abdomen and pelvis. Some patients may present with an isolated soft tissue mass without evidence of bone involvement(13).

Retinoblastoma

Retinoblastoma is the most common primary ocular tumor of childhood, a tumor of the embryonic neural retina. The hereditary form is associated with inactivation of the retinoblastoma gene (RB1), which is located on chromosome 13q14 and encodes the retinoblastoma protein (pRb), a tumor suppressor protein that controls cell-cycle phase transition and has roles in apoptosis and cell differentiation. It usually occurs in children around the age of 2 years. This tumor may involve one (75% of cases) or both (25% of cases) eyes in a child. Leukocoria (white

pupillary reflex or cat's eye reflex) is the most common presenting sign. Other signs and symptoms include deterioration of vision, strabismus, a red and irritated eye with glaucoma, and delayed development . Ultrasonography, CT scan, X-rays, MRI, spinal tap, bone marrow biopsy etc. may be done to establish the diagnosis and to find out the extent of the disease. The treatment modalities are: Enucleation, External beam radiation, Localized Plaque radiation therapy, Photocoagulation, Cryotherapy and chemotherapy(14).

Histiocytosis

Histiocytosis Syndromes of childhood is a diverse group of disorders in which there is a prominent proliferation or accumulation of cells of monocyte-macrophage system of bone marrow origin characterized by lytic bone lesion, seborrhic eczema like skin lesions, different endocrinopathy, soft tissue infiltration & hepatosplenomegaly.

Class I: *Langerhans cell histiocytosis (LCH)* can occur as an isolated lesion or as widespread systemic disease involving virtually any body site. Eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease are all syndromes encompassed by this disorder. LCH is not a true malignancy, but instead is a clonal, reactive proliferation of normal histiocytic cells, perhaps resulting from an immunoregulatory defect. Bone involvement is observed in 78% of patients with Langerhans cell histiocytosis and often includes the skull (49%), innominate bone (23%), femur (17%), orbit (11%), and/or ribs (8%). Lesions of other bones are less common. These lesions can be painful. Patients can also present with localized disease of the skin, often as a diaper rash that does not resolve. Bony lesions, fever, weight loss, otitis media, exophthalmos, and diabetes insipidus occur in a small number of children with the disease. Diagnosis is made with biopsy of the involved organ. The outcome in LCH is extremely variable, but the process usually resolves spontaneously. Isolated lesions may need no therapy at all. Intralesional corticosteroids, curettage, and low-dose radiation therapy are useful local treatment measures for symptomatic focal lesions.

Class II: Hemophagocytic lymphohistiocytosis (HLH) is caused by an immune deficiency of cytolytic T-lymphocyte or natural killer cell functions that regulate macrophage responses. HLH may be primary (inherited) or secondary (usually associated with infections or malignancy). Physical examination often reveals hepatosplenomegaly, lymphadenopathy,

respiratory distress, and symptoms of CNS involvement.The diagnosis rests on the pathologic findings in skin or bone marrow biopsy. Associated laboratory findings include hyperlipidemia, hypofibrinogenemia, elevated levels of hepatic enzymes, extremely elevated levels of circulating soluble interleukin-2 receptors released by the activated lymphocytes, very high levels of serum ferritin, and cytopenias. Prompt treatment with immunochemotherapeutic approaches is critical. The only known curative treatment for primary HLH is allogeneic bone marrow transplantation. Genetic counseling is critical for families with primary HLH.

Class III: Malignant Histiocytosis, Acute monocytic leukemia, true histiocytic lymphoma, are unequivocal malignancies of cells of monocyte-macrophage lineage (15-16).

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