Childhood Leukemias and Lymphomas

3.0 Contact Hours

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Childhood Leukemias and Lymphomas

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Abstract

About 1% of the new cases of cancer in the United States occur in children. Malignancy is the second leading cause of death in children in the United States. The leukemias are the most common malignant neoplasms in childhood, accounting for about 41% of all malignancies that occur in children younger than 15 years of age. Leukemia is a cancer of blood forming cells. Acute lymphoblastic leukemia (ALL) accounts for about 77% of cases of childhood leukemias.

Lymphoma is the third most common cancer in children in the United States, with an annual incidence of 13 to 14 per million children. There are two types of lymphomas – Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma. Hodgkin's disease arises in lymphoid tissue and spreads to adjacent lymph node areas. Hematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow, or brain, and is usually associated with systemic symptoms. Non-Hodgkin lymphoma (NHL) results from malignant clonal proliferation of lymphocytes of T-, B-, or indeterminate cell origin.

The distinction between lymphoma and leukemia is sometimes blurred. When bone marrow and peripheral blood involvement dominate the clinical picture, the disease is classified as a lymphoid leukemia. When lymph nodes and/or other extranodal sites of disease are the dominant sites of involvement, the tumor is called a lymphoma.

Objectives:

Upon completion of this course, the learner will be able to:

1. Define leukemia
2. Define lymphoma
3. Discuss the various types of leukemias
4. Discuss the management of leukemias
5. Discuss the various types of lymphomas
6. Discuss the management of lymphomas

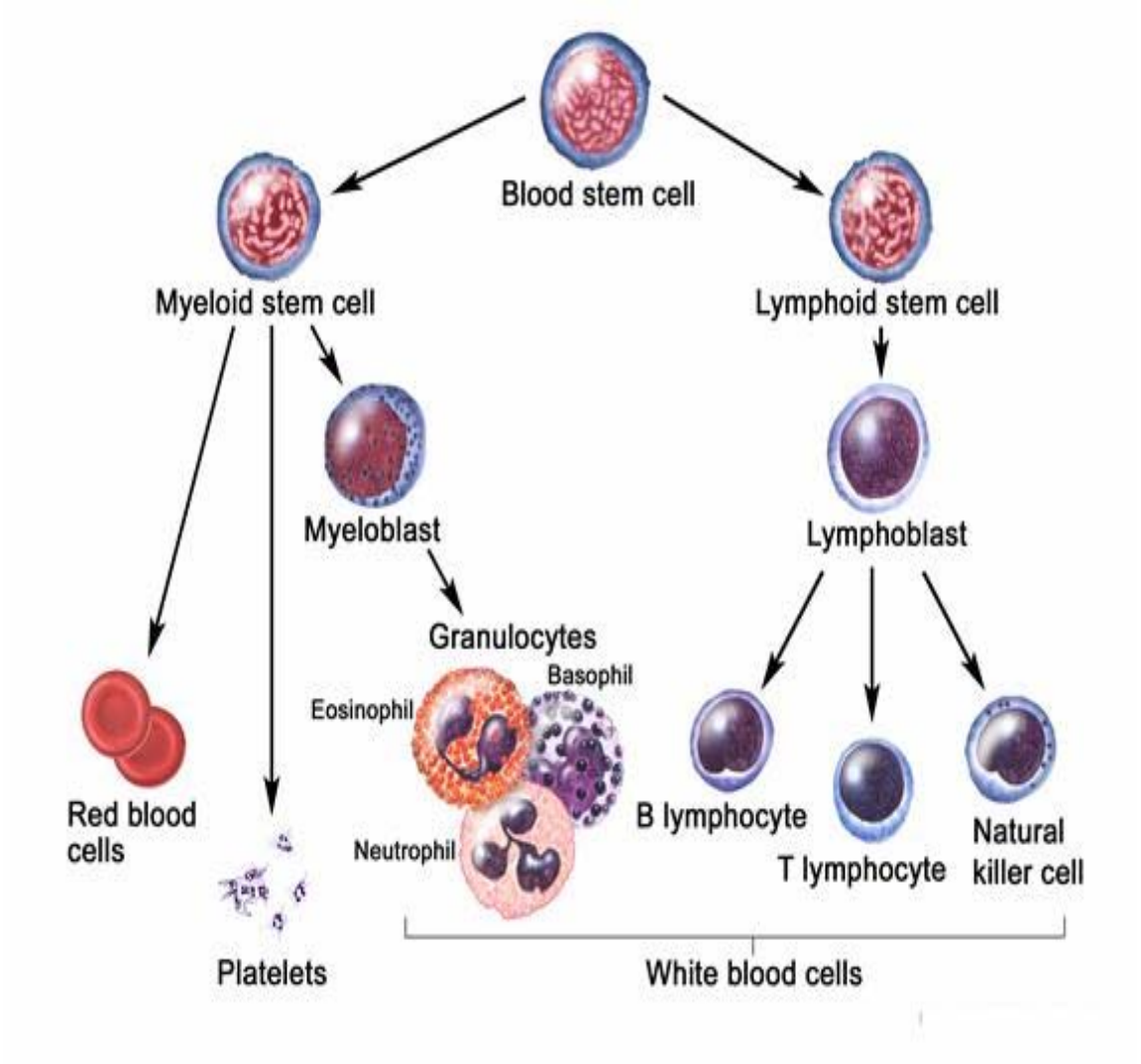

Figure 1: Hematopoiesis (Blood cells production)

A. Leukemia

About 1% of new cancer cases in the United States occur in children age 19 years or younger. The leukemias are the most common malignant neoplasms in childhood, accounting for about 41% of all malignancies that occur in children younger than 15 years of age. Pediatric cancers differ markedly from adult malignancies in their prognosis and their distribution by histology and tumor site. Acute lymphoblastic leukemia, brain cancers, lymphomas, and sarcomas of soft tissue and bone are predominate in children and adolescents. Malignant neoplasms remain the second leading cause of death (10.6% of all deaths) among 1 to 14 year olds in the United States.

Leukemia is the cancer of blood forming cells. It starts in blood-forming tissue such as the bone marrow and causes large numbers of blood cells to be produced and enter the bloodstream. The leukemias may be defined as a group of malignant diseases in which genetic abnormalities in a hematopoietic cell give rise to a clonal proliferation of cells. The cells formed from them have a growth advantage over normal cells due to an increased rate of proliferation, a decreased rate of spontaneous apoptosis, or both. The result is a disruption of normal bone marrow function and, ultimately, marrow failure.

Epidemiology

The leukemias are the most common malignant neoplasms in childhood, accounting for about 41% of all malignancies that occur in children younger than 15 years of age. The annual incidence is 4.1 new cases per 100,000 children younger than 15 years of age. The estimated new cases in the US in 2008 are 44,270 and the number of deaths is 21,710.

Types

Based on the cellular components, leukemia is divided into four types. They are:

- Acute
    - Acute lymphocytic leukemia (ALL)
    - Acute myeloid leukemia (AML)
- Chronic

- Chronic lymphocytic leukemia (CLL) – **This rarely affects children**
- Chronic myeloid leukemia (CML)

Acute lymphocytic leukemia (ALL)

Acute lymphocytic leukemia (ALL) is a malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow. Acute lymphocytic leukemia is the most common type of leukemia in children. It accounts for 77% of all cases of leukemia. It is the first form of disseminated cancer that was found to be curable with appropriate chemotherapy and irradiation.

Approximately 2,800 children are diagnosed with ALL in the United States annually. It is more common in boys than in girls. The peak incidence is between 2 to 6 years of age. Among identical twins, the risk to the second twin if one develops leukemia is greater than that in the general population. Though the cause is unknown, the disease is more common in children with certain chromosomal abnormalities such as Down syndrome, Bloom syndrome, ataxia-telangiectasia, and Fanconi syndrome. Exposure to medical diagnostic radiation both in utero and in childhood has been associated with an increased incidence of ALL. Epstein Barr virus is associated with the B cell variety of ALL.

The malignant cells of ALL are the lymphoblasts which are the lymphoid precursor cells. They are arrested in an early stage of development. This arrest is caused by an abnormal expression of genes, often as a result of chromosomal translocations. Phenotypically, surface markers show that about 85% of cases of ALL are derived from progenitors of B cells, about 15% are derived from T cells, and about 1% is derived from B cells. The French-American-British (FAB) system distinguishes three sub-types – L_1, L_2 and L_3.

Clinical features

The clinical features in acute lymphocytic leukemia are due to either the infiltration of the malignant cells in the bone marrow and other organs or due to bone marrow failure. The various signs and symptoms attributed to ALL are:

- Anemia

- Anorexia
- Fatigue
- Bone pain
- Splenomegaly
- Breathlessness
- Petechiae and purpura
- Increased intracranial tension and cranial nerve palsies

Diagnosis

There are a few conditions which may mimic acute lymphocytic leukemia which include aplastic anemia, myelofibrosis, infectious mononucleosis and malignant deposits of other tumors like neuroblastoma and rhabdomyosarcoma in the bone.

The following are the various investigations that need to be done in cases of acute lymphocytic leukemia and the findings:

- Peripheral blood smear – Anemia, thrombocytopenia. White blood cell count may be normal, low or high. Blast cells may be seen.
- Bone marrow aspiration/ biopsy – Marrow replaced by leukemic lymphoblasts
- Cerebrospinal fluid – Leukemic cells found if the central nervous system is involved
- Chest x-ray – May show mediastinal mass

Treatment

Uric acid level and renal function should be determined before the treatment is started. Without treatment, the disease is fatal. The choice of treatment of ALL is based on the estimated clinical risk of relapse in the patient, which varies widely among the subtypes of ALL. Three of the most important predictive factors are the age of the patient at the time of diagnosis, the initial leukocyte count, and the speed of response to treatment. The treatment includes both chemotherapy and radiotherapy. There are three stages of treatment: remission induction, consolidation or intensification, and maintenance therapy, with CNS sanctuary therapy generally provided in each stage. A

combination of prednisone, vincristine and asparginase produces remission in about 98% within 4 weeks.

Once remission has been achieved, systemic treatment in conjunction with central nervous system sanctuary therapy follows. The maintenance therapy in most protocols includes daily oral mercaptopurine and weekly oral methotrexate. If the patient has not had cranial radiation, intrathecal chemotherapy for CNS sanctuary therapy is continued during maintenance therapy.

Acute Myeloid leukemia

AML comprises 11% of the cases of leukemia in childhood in the United States, with approximately 380 children diagnosed with AML annually. Over 90% of myeloid leukemias are of acute variety. In AML, the myeloid stem cells usually develop into a type of immature white blood cell called myeloblasts. The myeloblasts in AML are abnormal and do not become healthy white blood cells. There are seven sub-types of AML according to the French-American-British (FAB). They are:

M1	Acute myeloblastic leukemia without maturation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyeloblastic leukemia
M4	Acute myelomonocytic leukemia
M5	Acute monocytic leukemia
M6	Erythroleukemia
M7	Acute megakaryocytic leukemia

Clinical features

Like ALL, the clinical features of AML are due to either the infiltration of the malignant cells in the bone marrow and other organs or due to bone marrow failure. In addition to the features described under ALL, a few other features are also seen in AML. They are:

- Subcutaneous nodules or “blueberry muffin” lesions
- Infiltration of the gingiva

- Disseminated intravascular coagulation
- Chloromas or granulocytic sarcomas – These are localized masses of leukemic cells which herald the onset of AML and these are usually in orbital or subdural locations.

Diagnosis

Bone marrow aspiration or biopsy is the most important investigation performed for diagnosing acute myeloid leukemia. The specimen will show the following findings:

- Hyper cellular bone marrow
- At least 25% of the cells should be myeloblasts in the bone marrow for diagnosing AML
- The myelogenous origin of the cells is confirmed with special stains which stain only the myeloperioxidase containing myelogenous cells.

Treatment

Aggressive multiagent chemotherapy is successful in inducing remission in about 80% of patients. Up to 6 weeks or longer may be required to induce remission and for the marrow to recover from the effects of chemotherapy. The commonly used agents are cytosine arabinoside and anthracycline with or without other agents. About 10% of the patients die before induction of remission due to induction failure, infection or hemorrhage. Supportive care with broad spectrum antibiotics, antifungals, blood products and nutritional products should be provided. CNS prophylaxis with intrathecal chemotherapy is also essential to prevent CNS relapse.

Once induction of remission is achieved either bone marrow transplantation or peripheral blood stem cells from a HLA matched sibling should be given for long term disease-free survival. Continued chemotherapy for patients who do not have a matched donor is less effective than marrow transplantation, but nevertheless is curative in some patients.

Chronic myelogenous leukemia (CML)

Chronic myelogenous leukemia (CML) is a clonal disorder of the blood forming cells. Less than 10% of the myeloid leukemia belongs to the chronic variety. Although CML has been diagnosed in very young children, most patients are 6 years or older. The most specific feature of CML is its association with the Philadelphia chromosome. This is characterized by the translocation between chromosomes 9 and 22, i.e., t (9; 22). The disease has been associated with exposure to ionizing radiation but very few children with CML have a history of such exposure.

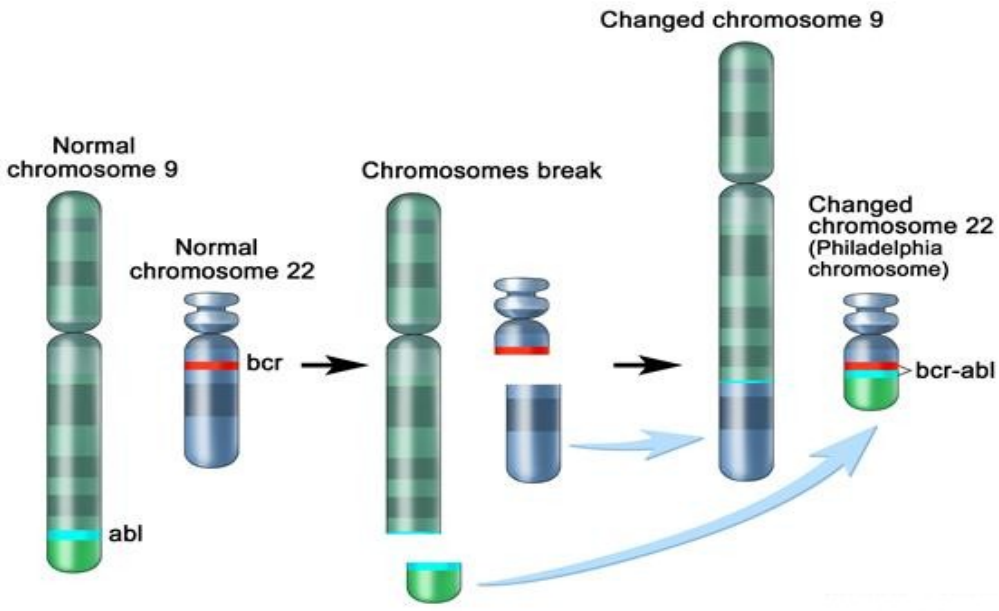

Figure 2 - Philadelphia chromosome. A piece of chromosome 9 and a piece of chromosome 22 break off and trade places. The bcr-abl gene is formed on chromosome 22 where the piece of chromosome 9 attaches. The changed chromosome 22 is called the Philadelphia chromosome.

Clinical features

Chronic myeloid leukemia has three phases: an initial chronic phase to be followed by the accelerated and blast crisis phase.

Chronic phase – This lasts for 3 to 4 years. During this phase the malignant clone produces an elevated leukocyte count with predominance of mature forms but with increased numbers of immature granulocytes. The white blood cell count can be easily controlled with low dose chemotherapy. During this phase the spleen is often greatly enlarged, resulting in pain in the left upper quadrant of the abdomen. There may be mild anemia and thrombocytosis. The increased white cell count produces symptoms like weakness, fever, night sweats, bone pain, respiratory distress, priapism, and, rarely, hearing loss and visual disturbances.

Accelerated phase - During this phase the white blood cell count rises dramatically. It cannot be controlled with chemotherapeutic drugs. It is characterized by progressive splenomegaly, thrombocytopenia, and increased percentage of peripheral and bone marrow blasts, along with accumulation of karyotypic abnormalities in addition to the Philadelphia chromosome.

Blast crisis – This crisis is mainly noticed in the bone marrow. The bone marrow shows greater than 30% blasts. Approximately two thirds of blast crisis is myeloid and the remainder lymphoid, usually of B lineage. The clinical picture is indistinguishable from acute leukemia. Patients in blast crisis will die within a few months.

Diagnosis

The various features of chronic myeloid leukemia are:

- Elevated white blood cell count – May exceed 100000/ cubic millimeter
- All forms of myeloid cells are seen in the blood smear
- Platelet counts may be high
- Serum vitamin B_{12} and uric acid levels are increased
- Reduced or absent white blood cell alkaline phosphatase activity
- Bone marrow hyper cellular with normal myeloid cells in all stages of development with more than 30% blast cells.
- Molecular study shows Philadelphia chromosome

Treatment

The signs and symptoms of CML in the chronic phase can be controlled with hydroxyurea, which will gradually return the leukocyte count to normal. However, this treatment is not definitive and does not eliminate the abnormal clone or prevent progression of the disease. Therapy with interferon-α produces hematologic remission in up to 70% of patients and cytogenetic remission in about 20% of patients.

The best treatment for children with chronic myeloid leukemia is allogenic bone marrow transplant. When an HLA-matched family donor is used in the treatment of patients in early chronic phase, survival of up to 85% can be expected. Transplantation in accelerated or blast crisis as well as a second chronic phase significantly reduces survival to fewer than 50%.

Imatinib mesylate is the new drug introduced in the treatment of CML. It targets the BCR-ABL tyrosine kinase of the Philadelphia chromosome. Although this drug is very effective in adult patients, trials in children are just in the initial stages.

Other Leukemias

Down syndrome and Acute Leukemia and Myeloproliferation

Acute leukemia occurs about 14 times more frequently in children with Down syndrome than in the general population. Patients with Down syndrome demonstrate a remarkable sensitivity to methotrexate and other antimetabolites, which can result in substantial toxicity if standard doses are administered. In AML, patients with Down syndrome have much better outcomes, with a greater than 80% long-term survival rate. Neonates with Down syndrome are prone to develop a transient leukemia or myeloproliferative syndrome characterized by high leukocyte counts, blast cells in the peripheral blood. This resolves within days to a few weeks after onset. But close follow-up is needed as 20–30% will develop typical leukemia within the first few years of life.

Juvenile Chronic Myelogenous Leukemia

Juvenile chronic myelogenous leukemia (JCML), also known as juvenile myelomonocytic leukemia, is a clonal proliferation of hematopoietic stem cells that typically affects children younger than 2 years of age. Patients with this disease do not have the Philadelphia chromosome that is characteristic of CML. They present with rashes, lymphadenopathy, and splenomegaly. The bone marrow shows less than 30% of blast cells. Patients with neurofibromatosis have a predilection for this type of leukemia. Stem cell transplantation is the treatment of choice.

B. Lymphomas

Lymphoma is the third most common cancer in children in the United States, with an annual incidence of 13 to 14 per million children. There are two types of lymphomas: Hodgkin's Lymphoma and Non-Hodgkin's Lymphoma. Hodgkin's disease arise in lymphoid tissue and spreads to adjacent lymph node areas. Hematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow, or brain, and is usually associated with systemic symptoms. Non-Hodgkin lymphoma (NHL) results from malignant clonal proliferation of lymphocytes of T-, B-, or indeterminate cell origin.

Hodgkin's Lymphoma

Hodgkin's lymphoma, also known as Hodgkin's disease, is a type of lymphoma first described by Thomas Hodgkin in 1832. It is the cancer of the immune system that is marked by the presence of a type of cell called the Reed-Sternberg cell. It is one of the most curable forms of cancers. For Hodgkin's disease arising in young adults, genetic susceptibility may be a factor for some cases. The role of Epstein-Barr virus (EBV) in the pathogenesis is supported by serologic studies and the frequent presence of EBV genome in biopsy material.

Hodgkin's disease appears to arise in lymphoid tissue and spreads to adjacent lymph node areas in a relatively orderly fashion. Hematogenous spread also occurs, leading to involvement of the liver, spleen, bone, bone marrow, or brain, and is usually

associated with systemic symptoms like fever and night sweats. Three forms of Hodgkin's disease have been identified in epidemiologic studies: a childhood form (≤ 14 years of age), a young adult form (15–34 years of age) and an older adult form (55–74 years of age). In the United States, it accounts for about 5% of cancers in persons younger than 15 years of age and for about 15% in persons 15–19 years of age. Males predominate in patients younger than 10 years of age at diagnosis, with roughly equal gender incidence in adolescence.

Reed-Sternberg cell

The Reed-Sternberg cell, a large cell (15–45 μm in diameter) with multiple or multilobulated nuclei, is considered the hallmark of Hodgkin's disease, although similar cells are seen in infectious mononucleosis, NHL, and other conditions.

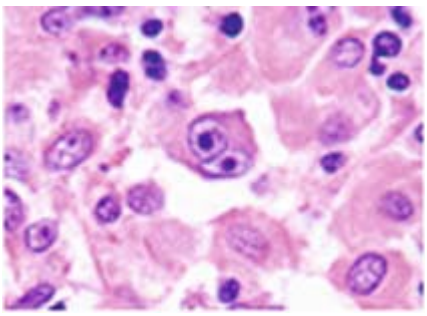

Figure 3 - A classic Reed-Sternberg

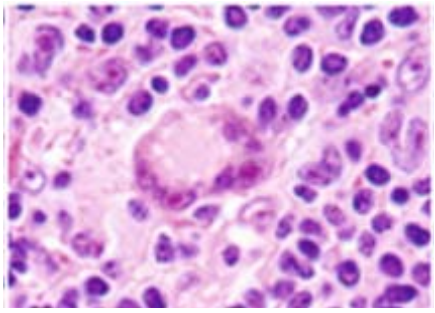

Figure 4 - A highly lobated Reed-Sternberg cell nucleus cell with bilobed nucleus

There are four major histological sub-types of Hodgkin's lymphoma which are of prognostic significance. They are:

- Lymphocyte predominant,
- Nodular sclerosing – Most common type
- Mixed cellularity
- Lymphocyte depleted

Clinical features

Painless, firm, cervical or supraclavicular lymphadenopathy is the most common presenting sign. Inguinal or axillary lymphadenopathy sites are uncommon areas of presentation. Depending on the extent and location of nodal and extranodal disease, patients might present with symptoms and signs of airway obstruction, pleural or pericardial effusion, hepatocellular dysfunction, or bone marrow infiltration (anemia, neutropenia, or thrombocytopenia). Nephrotic syndrome is a rare but recognized presenting manifestation of Hodgkin's disease. Systemic symptoms include unexplained fever, weight loss, drenching night sweats, pruritus, lethargy, anorexia, or pain that worsens after ingestion of alcohol.

Diagnosis

Any patient with persistent, unexplained lymphadenopathy unassociated with an obvious underlying inflammatory or infectious process should have a chest radiograph to identify the presence of a mediastinal mass before undergoing node biopsy. Unless signs or symptoms dictate otherwise, additional laboratory studies can be delayed until the biopsy results are available. Excisional biopsy is preferred over needle biopsy. Other investigations to be performed are:

- Complete blood count – to know whether bone marrow is involved
- Erythrocyte sedimentation rate – For assessing the outcome
- Chest radiograph – To look for mediastinal mass
- Abdominal CT / MRI – To look for the involvement of abdominal viscera
- Bone marrow biopsy – For staging the disease
- Staging laparotomy – Rarely indicated these days

After the diagnosis is made, staging of the disease has to be done for further management. The Ann Arbor Staging system is commonly used:

- Stage I – Involvement of a single node region or of a single extra-lymphatic organ or site

- Stage II - Involvement of two or more lymphoid regions on the same side of the diaphragm or localized involvement of an extra-lymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm
- Stage III - Involvement of lymphoid regions on both sides of the diaphragm which may be accompanied by localized involvement of an extra-lymphatic organ or site or by splenic involvement
- Diffused or disseminated involvement of one or more extra-lymphatic organs or tissues with or without lymph node enlargement

Stages are further categorized as 'A' or 'B' based on the absence or presence respectively, of systemic symptoms of fever and weight loss.

Treatment

Hodgkin's lymphoma is one of the most curable forms of cancers. Hodgkin's lymphoma can be cured with radiation therapy alone, chemotherapy alone, or a combination of both. Treatment is largely determined by disease stage, patient's age at diagnosis, the presence or absence of "B" symptoms, and the presence of hilar lymphadenopathy and/or bulky nodal disease.

Because of the late effects of radiotherapy, the concept of treating Hodgkin's lymphoma has changed. Multiagent chemotherapy supplemented in selected cases by relatively low-dose involved-field irradiation (2,000–2,500 cGy) is the treatment of choice now. The chemotherapy regimens in current use are based on MOPP (Mustargen, Oncovin, procarbazine, and prednisone), or ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) or variations and combinations of the two together with additional active agents such as etoposide and methotrexate. Most treatment programs result in disease-free survival rates of more than 60%, with overall cure rates greater than 90% in those with early stage disease and more than 70% in more advanced cases.

Non-Hodgkin's lymphoma

Non-Hodgkin lymphoma (NHL) results from malignant clonal proliferation of lymphocytes of T-, B-, or indeterminate cell origin. Non-Hodgkin's lymphoma is the fifth most common cancer in the United States, accounting for about 4% of all

malignancies in both men and women. NHL accounts for approximately 50% of all lymphomas in children and adolescents. It represents 8 -10% of all malignancies in children between 5 -19 years of age with an annual incidence in the USA of 750-800 cases per year in children < 19 years of age. B-cell lymphomas represent most cases of non-Hodgkin's lymphoma, and T-cell lymphomas account for the rest.

Though in most of the patients the cause is unknown, in a small percentage of patients it develops secondary to inherited or acquired immune deficiencies (e.g., severe combined immunodeficiency syndrome, Wiskott-Aldrich syndrome), viral etiologies (e.g., HIV, EBV) or as part of genetic syndromes (e.g., ataxia- telangiectasia, Bloom syndrome).

The four major pathological subtypes of childhood and adolescent NHL are Burkitt lymphoma (BL) constituting 40% of NHL; lymphoblastic lymphoma (LL), accounting for 30%; diffuse large B-cell lymphoma (DLBCL), constituting 20% and anaplastic large cell lymphoma (ALCL), accounting for 10%. Most childhood and adolescent NHL are high-grade tumors with an aggressive clinical behavior compared to those of adult NHL, which usually are low- to intermediate grade indolent tumors.

Clinical features

The signs and symptoms depend on the sub-type of the disease and the site of involvement.

- Lymphoblastic NHL - mediastinal mass, dyspnea, chest pain, dysphagia, pleural effusion, superior vena cava syndrome, cervical or axillary lymphadenopathy. Central nervous system may be involved.
- Small non-cleaved cell lymphoma - abdominal tumor, jaw involvement, abdominal pain or distention, bowel obstruction, changes in bowel habits, intestinal bleeding, intestinal perforation. Central nervous system may be involved.
- Large cell lymphoma – It involves abdomen and mediastinum**.** Extramedullary sites include skin, bone, and soft tissues.

Diagnosis

Prompt tissue diagnosis and staging is important because of the rapid growth rate of lymphomas, especially small non-cleaved cell lymphoma. To ensure adequate tissue for accurate diagnosis and subtyping, multiple needle biopsy specimens or a large wedge of tumor should be obtained. The following investigations have to performed for staging the disease:

- Complete blood cell count
- Serum electrolytes, uric acid, lactate dehydrogenase, creatinine, calcium, phosphorus
- Liver function tests
- Chest radiograph and chest CT if abnormal
- Abdominal and pelvic ultrasonography and/or CT
- Gallium scan and/or bone scan
- Bilateral bone marrow aspirate and biopsy
- Cerebrospinal fluid cytology

St. Jude's staging system is used to stage the disease. There are four stages as per this classification which includes (simplified):

- Stage I - localized disease
- Stage II to regional disease (except for mediastinal tumors, which are designated stage III)
- Stage III to extensive disease
- Stage IV to disseminated (CNS and/or bone marrow) disease.

Treatment

Multiagent chemotherapy is the primary treatment. Surgical excision of localized intra-abdominal tumors often precedes the diagnosis of NHL and should always be attempted, if feasible. Unlike Hodgkin's lymphoma, NHL is considered a disseminated disease from the time of diagnosis.

Patients with stage I/II NHL, irrespective of histologic subgroup, are effectively treated with six cycles of COMP (cyclophosphamide, Oncovin, methotrexate, and prednisone) or three cycles of COPA (substituting doxorubicin for methotrexate) followed by 6 months of mercaptopurine and methotrexate. About 90% of cases are cured with these regimens.

Patients with stage III/IV NHL are best treated with therapy based on the histologic subtype.

- Lymphoblastic lymphoma - Intensive chemotherapy regimens are given for a 2 year duration. Cranial radiation, intrathecal chemotherapy, and/or high-dose methotrexate are important for prevention of CNS disease
- Small non-cleaved cell lymphoma - It is treated with relatively short-duration (3–6 months) intensive chemotherapy regimens and intrathecal therapy
- Large cell lymphoma - It is treated with intensive multiagent chemotherapy regimens

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