

Lymphoma Teaching Points

Lymphomas (~1700 cases/yr.) are the third most common subgroup of pediatric cancers in the U.S., comprising about 15% of cancer that occurs before age 20. The incidence of lymphomas increases significantly from 0-20, with lymphomas accounting for about 3% of tumors 0-5 years and 24% 15-19 years. The two major subcategories of lymphoma are Hodgkin's disease (HD; 850-900 cases/yr) and Non-Hodgkin's lymphoma (NHL; 750-800 cases/yr.). NHL is more common in younger children, and HD is more common in adolescents.

Hodgkin's Disease:

Reed Sternberg cells are the malignant cells in Hodgkin's disease (HD). These are atypical, multinucleated giant cells that are pathognomonic of HD. There is a background mixture of benign lymphocytes, inflammatory cells, and stromal cells that make up the rest of the tumor. HD is the only lymphoma where the malignant cells are vastly outnumbered by benign cells in a given tumor.

HD is highly associated with prior Epstein-Barr virus infection.

There are four subtypes of HD:

Lymphocyte Predominant. (10-15% of cases). Fibrosis not generally seen, mainly lymphocytes. Can be mistaken for reactive hyperplasia, and often many cuts from tumor necessary to identify Reed Sternberg cells. Usually localized, seen more often in males and young patients.

Mixed Cellularity. (30% of cases, more common in children.) Numerous Reed- Sternberg cells present, small areas of fine fibrosis also present. Background of inflammatory cells. Usually presents with advanced disease with nodal involvement.

Lymphocyte Depleted. Common in HIV-infected patients and rare in children. Many Reed-Sternberg cells, and malignant reticular cells, and few lymphocytes. Can have diffuse fibrosis and necrosis. Often present with disseminated disease involving bone and bone marrow.

Nodular Sclerosing. (Represents 40% of younger patients, 70% of adolescents.) Orderly collagenous bands divide tumor into nodules. Usually involves nodes in the lower neck and mediastinum.

Systemic symptoms including fatigue, anorexia and slight weight loss are common in HD. Itching and pain upon alcohol consumption are also associated with HD. A minority of patients has more extensive weight loss, fatigue, and fever defined as "B" symptoms: (1) unexplained weight loss >10% within the prior 6 months; (2) unexplained fever >38C on a daily basis for 2 weeks; (3) "drenching" night sweats (like wetting the bed). The presence of any of these 3 qualifies as B symptoms, and are associated with a poor prognosis.

Patients present most commonly with painless supraclavicular or cervical lymphadenopathy. Supraclavicular adenopathy is always pathologic; however, it must be distinguished from low cervical adenopathy. Supraclavicular nodes grow up over the clavicle from below. Some children

have axillary or inguinal adenopathy. Subdiaphragmatic only diseases occurs in <5% of pediatric HD patients.

Affected lymph nodes are usually described as firm and rubbery. They may be tender, but do not usually have the classic signs of infection (heat, redness, pain). Nodes may grow very slowly and are often described as being present for months.

Two-thirds of patients have mediastinal involvement. This may be asymptomatic, or may cause non-productive cough, wheezing or symptoms of tracheal compression. A chest X-ray is key if one is concerned about the possibility of HD. Tracheal compression can lead to sudden death during anesthesia, and sedatives and heavy anesthesia should be avoided in patients with significant airway compression. Any patient with a mediastinal mass should be carefully evaluated by an experienced anesthesiologist prior to sedation.

Differential diagnosis includes lymphadenitis, mononucleosis, other inflammatory causes of lymphadenopathy, NHL (usually grows much faster than HD), other cancers such as nasopharyngeal carcinoma (nodes are rock hard and fixed). It can sometimes be difficult to distinguish a large thymus in a young child from a mediastinal mass.

Excisional biopsy is the method of diagnosis. Fine-needle aspirates lead to sampling error, and may falsely reassure the practitioner.

HD spreads along contiguous lymph node chains until late in the disease. Patients are staged I (single lymph node or region), II (two or more nodal regions on same side of diaphragm), III (disease above and below the diaphragm), IV (disseminated disease outside of lymph nodes).

Treatment of HD includes chemotherapy alone for localized disease, and chemotherapy plus involved field radiation for advanced stage disease. Optimal treatment depends on the stage of the disease, the size of the nodal aggregates, and whether or not patient has B symptoms. Patients with lymphocyte predominant disease are treated differently than those with other subtypes.

Nodal masses may not disappear completely, especially with NS HD. Because of this, patients often have residual masses of scar tissue. Nuclear medicine studies can be used to determine if a residual mass still has active disease. Until recently, Gallium scans were used. Positron emission tomography (PET) scans are now becoming the scan of choice for following HD.

Prognosis: HD carries an overall prognosis of 85-90% event free survival. High risk features include bulky mediastinal disease, extranodal extension of disease, B-symptoms, and advanced stage disease (stage III or IV).

Long-term side effects of treatment include risk of infertility, hypothyroidism, secondary breast cancer from radiation therapy, and pulmonary fibrosis from bleomycin.

Non-Hodgkin's Lymphoma (NHL):

Malignancy can arise in any subset of lymphoid cells, and lymphomas are treated based on their subtype and cell of origin.

B and T-cell lymphomas often arise from mutations that occur when T-cell receptor or immunoglobulin genes undergo rearrangement.

B-Cell lymphomas.

Burkitt's lymphoma, Burkitt's-like lymphoma, and large B-cell lymphoma can be considered together as they are closely related and respond similarly to treatment. They represent a continuum of tumors that arise from common mutations.

Burkitt's Lymphoma

Burkitt's lymphomas are mature B-cell lymphomas that express surface immunoglobulin. In equatorial African Burkitt's lymphoma, the tumor typically arises in the jaw in lymphatic tissue that is present in the area of erupting teeth. African BL is highly associated with EBV (95% of cases), whereas non-African Burkitt's generally is not.

In the US and Europe, BL is termed "sporadic". These lymphomas typically arise in the abdomen in mesenteric lymph nodes, though they can arise in any lymphatic tissue. 15% are associated with EBV infection. Intussusception due to a bowel wall primary tumor is not unusual. BL should be high in the differential diagnosis of any child older than 3-4 years of age with intussusception (a common Board question).

These differences may be related to the age at which patients are infected with EBV and other socioeconomic factors. The immunosuppressive effect of malaria may also play a role in the pathogenesis of BL in Africa.

BL is associated with HIV infection and immunosuppression in general, particularly T-cell immunosuppression.

BL is associated with nonrandom reciprocal translocations between chromosome 8 and 14. These juxtapose the c-myc gene to the region of the immunoglobulin heavy chain, which places c-myc (normally not very active) under the regulation of the immunoglobulin locus (very active in lymphocytes). c-myc is involved in cell proliferation, and translocation leads to a proliferative state.

Histologically, BL has a "starry sky" pattern due to light staining macrophages within the bulk of the darkly staining tumor cells.

BL is a very aggressive malignancy, with the shortest doubling time of all pediatric malignancy. As a result, tumors grow rapidly and patients often have evidence of tumor lysis from tumor turnover at the time of diagnosis. They can present with or rapidly develop renal failure following treatment. One must be very careful giving corticosteroids to a patient with active Burkitt's lymphoma.

Major advances have been made in the treatment of advanced stage BL. When these tumors were treated like other pediatric NHL, patients fared very poorly. Development of extremely aggressive and short multi-agent chemotherapy regimens dramatically improved outcome for patients with BL and event-free survival exceeds 90% for localized disease and between 70-90% for disseminated disease. Relapses typically occur within the first year of cessation of therapy, and patients are highly unlikely to recur after that time. Prevention and management of tumor lysis are critical at the

outset of treatment. Intrathecal therapy to prevent recurrence in the central nervous system is required. Unlike HD, radiation therapy is not part of up-front treatment of non-Hodgkins B-cell lymphomas. BL typically express CD20 on the surface and the anti-CD20 monoclonal antibody Rituximab is now being tested in these patients.

Large B-cell Lymphoma (LBLC)

More common in adults than in children.

A variety of mutations can lead to this morphologic subtype of B-cell lymphoma. 5-10% have t(8;14). Other translocations involved the bcl-6 gene due to a t(14;18), and these are more common in adults.

Mediastinal tumors can arise from the malignant counterpart of the B-cells normally present in the thymus.

Burkitt's-like Lymphoma (BLL).

Histologically, these tumors are similar to BL, but have more variability in size and shape of the cells. BL and BLL are not distinct entities, and many BLL contain the t(8;14) that is associated with BL. These tumors are treated identically to BL and have a similar prognosis.

T-cell Lymphomas:

Lymphoblastic lymphoma:

Patients typically present with a mediastinal mass, which often is more rapidly growing than Hodgkin's disease. Patients may present with pleural effusions, pericardial effusions, and superior vena-cava syndrome.

Tracheal compression can lead to sudden death during anesthesia, and sedatives and heavy anesthesia should be avoided in patients with significant airway compression.

Patients with mediastinal masses should undergo a bone marrow aspirate. Many patients with a rapidly growing mediastinal mass due to NHL will also have bone marrow involvement. If there is > 25% marrow involvement, it is considered to be T-cell ALL. The bone marrow aspirate/biopsy may prevent the need for an intrathoracic biopsy. Similarly, cervical or axillary nodes are preferentially biopsied, even if smaller than the intrathoracic nodes, often using light anesthesia with the patient sitting upright.

Lymphoblastic lymphomas are usually of the T-cell phenotype. However, a small percentage arise from B-cells. These tumors usually present with very limited disease, in contrast to T-cell lymphoblastic lymphoma, including tumors of the bone, skin, or isolated lymph nodes.

Treatment of T-cell lymphoblastic lymphoma is similar to treatment of T-cell acute lymphocytic leukemia, and begins with more intense treatment followed by approximately 2 years of maintenance therapy. Treatment includes intrathecal chemotherapy. Radiation therapy is not typically used in these patients unless they have CNS disease.

Prognosis: Lymphoblastic lymphomas have a long-term event free survival in the 80-90% range.

Anaplastic large cell lymphoma.

Anaplastic large cell lymphoma is unlike the other NHL's of childhood in that it can present with a more indolent course. Like patients with HD, these patients frequently have fever and weight loss.

Unlike other NHL's, these tumors most often arise in lymph nodes. They can also involve the skin and bone. A classic finding is lymph node involvement and skin, especially the skin of the lateral thorax. GI tract is rarely involved.

80% of children with ALCL have a 2;5 translocation. This juxtaposes the tyrosine kinase ALK with the nucleophosmin causing inappropriate expression of an activated ALK protein.

Histologically, tumors contain large cells of varying shapes, with horse-shoe nuclei. Some cells may resemble Reed-Sternberg cells. Tumors almost always express CD30 (Ki-1) and ALK.

In adults, ALCLs can transform from more indolent lymphomas such as Hodgkin's disease or cutaneous T-cell lymphomas.

Current treatment approaches combine initial high dose chemotherapy with a more prolonged maintenance phase, similar to but shorter than therapy for acute lymphocytic leukemia.

Post-Transplant Lymphoproliferative Disease (PTLD):

NHL can occur in patients who are immunosuppressed following solid organ transplant. These lymphomas are usually of B-cell origin and frequently are activated by EBV. PTLD is a spectrum of disease that ranges from polyclonal to monoclonal tumors indistinguishable from Burkitt's lymphoma. Treatment of PTLD includes decreasing or discontinuing immunosuppression (if feasible), and chemotherapy. Most PTLD are CD20 positive and Rituximab is often included in therapy. PTLD can often be cured by less intensive chemotherapy than typically used for other NHL.[1-5]

Questions:

1. A patient presents with a history of “constipation” and is anuric. Patient’s abdomen is very distended and hard. CT shows an enormous mass that appears to be arising from the bowel. What is the likely diagnosis?

Answer: This patient most likely has “sporadic” Burkitt’s lymphoma. This is the way most patients with BL present in the US. The anuria is due to tumor lysis, which frequently complicates BL at diagnosis. Successful treatment depends on successfully managing tumor lysis syndrome, particularly the hyperkalemia that is associated with renal failure.

2. A patient presents with a history of chronic cough that has been present for 5 months. Over this time frame the patient has had persistent low-grade fevers and a 12% weight loss. The patient has had drenching night sweats. The patient has firm lymphadenopathy at the base of the neck, and CXR shows a mediastinal mass. What does this patient most-likely have?

Answer. This patient most likely has Hodgkin’s disease, although could also have lymphoblastic lymphoma. The B-symptoms include drenching night sweats, >10% weight loss, and fever are associated with a more aggressive course,

3. A patient presents with a history of facial swelling and shortness of breath. CXR performed in outlying ER shows a massive mediastinal mass. What does this patient most-likely have?

Answer. This patient most likely has lymphoblastic lymphoma, although they could also have T-cell leukemia or less likely, Hodgkin’s disease. This case illustrates the more rapid onset of lymphoblastic lymphoma, although these tumors can be indolent. A critical piece to initial management is the anesthesia, which can be difficult to impossible in a patient with tracheal compression.

4. A patient presents with axillary lymphadenopathy and papular skin lesions that appear and disappear. The patient has had low grade fevers. The lymphoma that this patient most-likely has is:

Answer. Anaplastic large cell lymphoma. One way that these patients will present is with lymphadenopathy associated with papular skin rash that can be indolent and can wax and wain.

Bibliography:

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