Leukemia and Lymphoma

Acute Leukemias

- Acute leukemia is a hematologic malignancy characterized by infiltration of the bone marrow, blood, and other tissues by uncontrolled proliferation and abnormal delayed differentiation of clonal myeloid or lymphoid precursor cells, exceeding 20% of the bone marrow or blood.

- In adults, acute myeloid leukemia (AML) is more common than acute lymphoblastic leukemia (ALL)

Acute Myeloid Leukemia

- AML typically manifests with anemia, thrombocytopenia, or functional neutropenia secondary to bone marrow replacement with abnormal myeloblasts.

- Petechiae, epistaxis, and other mucosal hemorrhages occur when the platelet count dips below 20,000/RL (20 x 109/L).

- Symptoms of anemia vary more with patient's age and comorbidities.

- Although the leukocyte count is typically elevated, the absolute neutrophil count tends to be low, which confers an increased risk of infection

- Cytogenetic and molecular classification of AML has gained increasing importance in recent years.

- In the 1970s, a group of French, American, and British leukemia experts divided AML into subtypes, M0 through M7, based on the type of cell the leukemia develops from and how mature the cells are. This was based largely on how the leukemia cells looked under the microscope after routine staining.

- Subtypes M0 through M5 all start in immature forms of white blood cells. M6 AML starts in very immature forms of red blood cells, while M7 AML starts in immature forms of cells that make platelets.

Poor prognostic features
> 60 years
> 20% blasts after first course of chemo
cytogenetics: deletions of chromosome 5 or 7

FAB subtype	Name
M0	Undifferentiated acute myeloblastic leukemia
M1	Acute myeloblastic leukemia with minimal maturation
M2	Acute myeloblastic leukemia with maturation
M3	Acute promyelocytic leukemia (APL)
M4	Acute myelomonocytic leukemia
M4 eos	Acute myelomonocytic leukemia with eosinophilia
M5	Acute monocytic leukemia
M6	Acute erythroid leukemia
M7	Acute megakaryoblastic leukemia

Acute promyelocytic leukemia (M3)

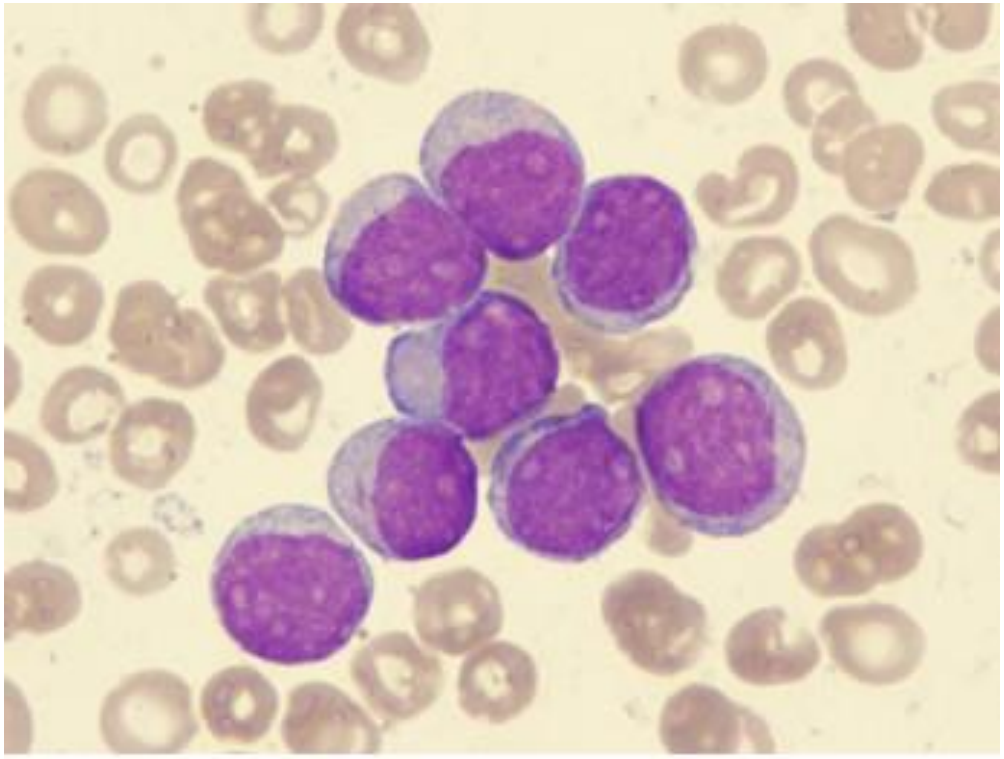
- Acute promyelocytic leukemia, characterized by poorly differentiated leukocytes with distinctive primary granules that contribute to coagulopathy.

- Chromosomal translocation t (15;17).
- **It presented in younger ages and has good prognosis.**

- Many patients achieve cure with all-trans retinoic acid, which targets the underlying defect in cell differentiation.

Diagnosis

Myeloblasts are usually seen in the peripheral blood smear but may be absent despite unequivocal bone marrow infiltration.



This peripheral blood smear shows an immature granulocyte with a rod-shaped inclusion body (Auer rod) characteristic of acute myeloid leukemia.

- The treatment of AML consists of induction therapy with an anthracycline (such as daunorubicin) and infusional cytarabine.

- The goal is to ablate the bone marrow, eliminating the blasts, although this transiently destroys the normal hematopoietic cells as well. Cells are expected to recover after a period of aplasia, which extends for 3 to 4 weeks, during which time the patient is supported by transfusions (erythrocytes and platelets) and prompt antibiotic treatment of neutropenic fever.

- Complete response is achieved in 60% to 85% of patients younger than 60 years.

Acute Lymphoblastic Leukemia

- ALL is more common in children and adolescents than in adults.

- Although ALL in children is often curable, survival in adult patients (older than 19 years) remains inferior despite the adoption of pediatric ALL regimens.

- ALL presents with malaise, bleeding, infections, bone pain, or a combination of these symptoms, with a small subset (<10%) having symptomatic central nervous system involvement at diagnosis.

- In adults, 75% of ALL is of B-cell lineage

- mature B-cell ALL can present as extramedullary disease, including gastrointestinal or testicular involvement.

- A mediastinal mass with wheezing and stridor or skin involvement can be the presenting features of T-cell ALL.

- ALL is classified by immunophenotype, cytogenetics, and molecular abnormalities.

- The most important cytogenetic abnormality in adult ALL is the Philadelphia chromosome, found in 20% to 30% of patients.

- Philadelphia chromosome-positive ALL had a poor prognosis.

- Treatment regimens are complex. Regimen backbones include vincristine, anthracycline, corticosteroids, and L-asparaginase.

- Unlike in AML, central nervous system prophylaxis is essential during ALL therapy.

Good prognostic factors: French-American-British (FAB) L1 type, common ALL pre-B phenotype, low initial WBC, del(9p)

Poor prognostic factors: FAB L3 type, T or B cell surface markers, Philadelphia translocation, t(9;22), age < 2 years or > 10 years, male sex, CNS involvement high initial WBC (e.g. > 100 * 10^9/l), non-Caucasian

- Adult survivors of childhood leukemia face higher risks of secondary cancer, cardiovascular disease, and the metabolic syndrome (high BMI, truncal obesity, dyslipidemia, insulin resistance, and hypertension) compared with age-matched controls.

- Screening for lipid profile, diabetes, and hypertension is recommended.

- Echocardiography to screen for left ventricular dysfunction should be performed at intervals of 3 to 5 years, particularly if anthracycline exposure was high or if chest radiation was used.

- Female survivors have a higher risk of myocardial dysfunction during pregnancy.

- High-dose glucocorticoids, typical of ALL regimens, pose a risk for osteopenia.

- The cumulative incidence of secondary cancer after radiation therapy for childhood ALL reaches 11% at 30 years; tumors include skin cancer, thyroid and parotid tumors, sarcomas, and brain tumors.

- Cranial radiation also increases the risk for stroke and neurocognitive defects.

Lymphoid Malignancies

- Lymphoma classified into Hodgkin and non-Hodgkin lymphoma.
- The incidence of non-Hodgkin lymphoma rises with increased age
- The incidence of Hodgkin lymphoma shows a bimodal age distribution, with an early peak in the second and third decades of life, then a decline, followed by a sustained increase with older age.

Risk factors

- Most cases seem sporadic.
- familial clustering can be seen, with an increased relative risk in first degree relatives.
- Patients with both congenital and acquired immunosuppression (such as HIV infection, organ transplantation, or an inherited immunodeficiency) are at greater risk.
- Various viral infections are also associated with increased risk. Epstein-Barr virus is associated with Burkitt lymphoma, seen in African pediatric patients, as well as some cases of Hodgkin lymphoma.
- Human T-cell lymphotropic virus type 1 (HTLV-1) is associated with T-cell leukemias and lymphomas.
- Hepatitis C virus is associated with an increased risk of lymphoma, particularly splenic marginal zone lymphoma.

- HIV infection is associated with an increased risk of principally B-cell lymphomas, typically with aggressive histology, more advanced stage, more B symptoms, and a higher risk of extranodal and central nervous system involvement.

- Kaposi sarcoma herpesvirus (human herpesvirus 8) is associated not only with Kaposi sarcoma but also with primary effusion lymphoma.

- Patients with autoimmune rheumatic disorders, such as Sjogren syndrome, systemic lupus erythematosus, and rheumatoid arthritis, have an increased risk of non-Hodgkin lymphoma. The strongest association is with Sjogren syndrome and extranodal marginal zone lymphomas.

Evaluation and Diagnosis

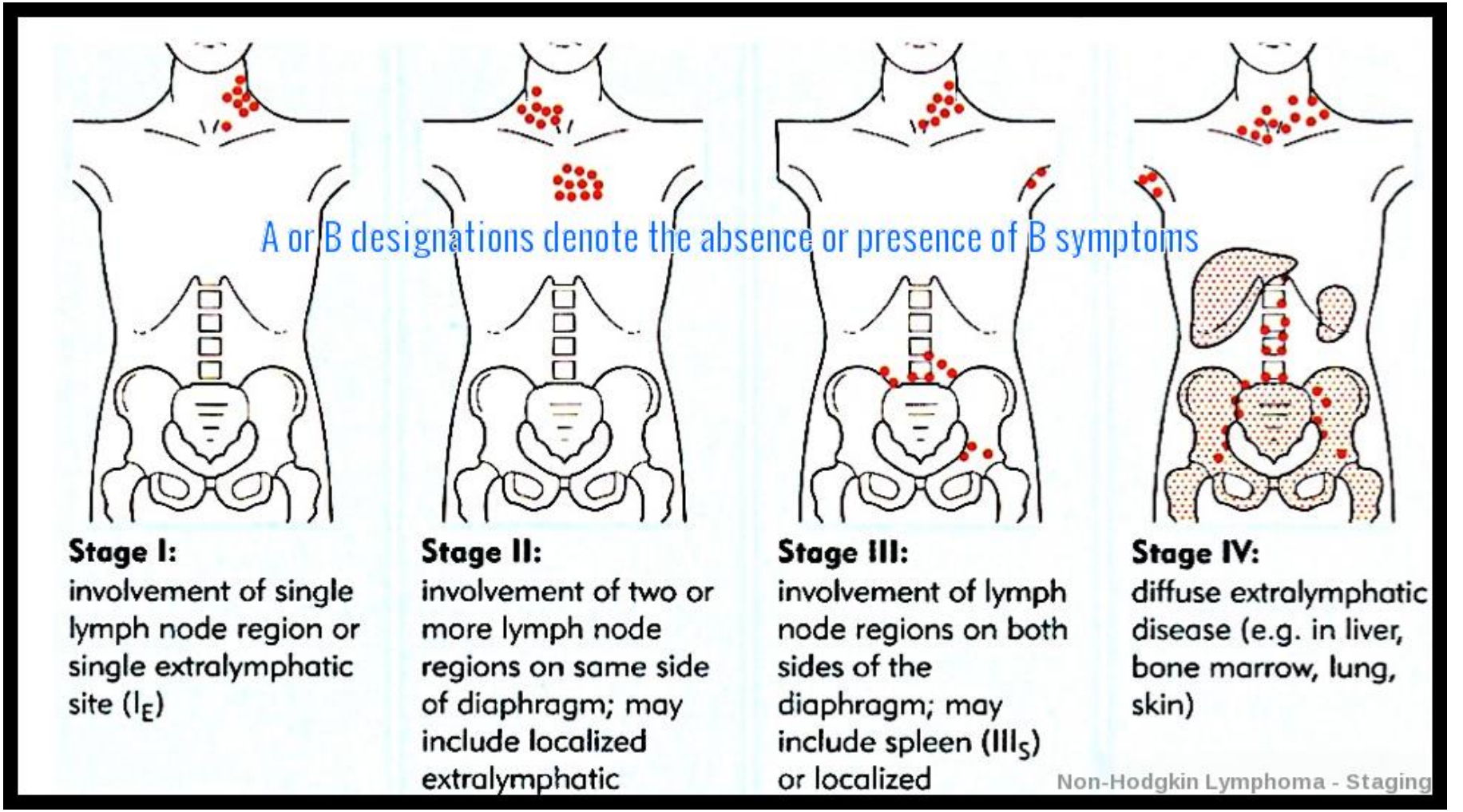
- Enlarged lymph nodes are the most common sign of lymphoma
- The size, distribution, or persistence of enlarged lymph nodes or systemic symptoms raises concern for lymphoma.
- Systemic symptoms (B symptoms) indicates the presence of one or more of the following: fever, drenching night sweats, or unexplained weight loss.
- CT scan of the chest, abdomen, and pelvis can assess palpable lymph nodes not amenable to physical examination .
- Diagnosis is generally established based on lymph node biopsy. An excisional biopsy is often preferable to a core needle biopsy as it may better determine nodal architecture.
- Flow cytometry on cytology can demonstrate B-cell or T-cell markers, as well as features consistent with monoclonality.

Staging

- Lymphomas are staged I to IV based on the number of sites of disease and the presence of extranodal involvement.

- Staging involves physical examination, CT scans, and PET scans in most patients.

- Lymphoma stages are also designated A or B; A indicates no systemic symptoms are present, and B indicates the presence of one or more of the B symptoms.


A or B designations denote the absence or presence of B symptoms
Stage I:
involvement of single lymph node region or single extralymphatic site (I_E)
Stage II:
involvement of two or more lymph node regions on same side of diaphragm; may include localized extralymphatic
Stage III:
involvement of lymph node regions on both sides of the diaphragm; may include spleen (III_S) or localized
Stage IV:
diffuse extralymphatic disease (e.g. in liver, bone marrow, lung, skin)
Non-Hodgkin Lymphoma - Staging

While differentiating Hodgkin's lymphoma from non-Hodgkin's lymphoma is done by biopsy certain elements of the clinical presentation can help point towards one rather than the other:

Lymphadenopathy in Hodgkin's lymphoma can experience alcohol-induced pain in the node.
'B' symptoms typically occur earlier in Hodgkin's lymphoma and later in non-Hodgkin's lymphoma
Extra-nodal disease is much more common in non-Hodgkin's lymphoma than in Hodgkin's lymphoma

Non-Hodgkin Lymphomas

B-Cell lymphomas

Indolent B-Cell Lymphomas

Follicular Lymphoma
Mucosa-associated Lymphoid Tissue Lymphoma
Chronic Lymphocytic Leukemia
Hairy Cell Leukemia

Aggressive B-Cell Lymphomas

Diffuse large B-cell lymphoma
Burkitt lymphoma
Mantle Cell Lymphoma

T-cell lymphomas

Cutaneous T-Cell Lymphoma
Peripheral T-Cell Lymphoma, Not Otherwise Specified
Anaplastic Large Cell Lymphoma
Angioimmunoblastic T-Cell Lymphoma

Follicular Lymphoma

- Follicular lymphoma is the most common indolent B-cell lymphoma.
- They demonstrate lymph node architecture with a follicular morphology.
- They arise from the germinal center B cells of the lymph node.
- They characterized by the presence of a 1(14:18) translocation that causes an overexpression of the BCL2 oncogene.
- Many patients are not symptomatic at diagnosis and in some cases do not require therapy for many years.

- Histologic transformation, most typically to a diffuse large B-cell lymphoma, occurs in approximately 30% of patients with follicular lymphomas and is associated with an aggressive course and poor prognosis.

- Transformation may be suggested by a change in the clinical pattern of disease with new systemic symptoms or rapid progression of a localized area of disease, a rise in serum lactate dehydrogenase, or markedly higher areas of standardized uptake values on PET scans.

- New biopsy is required to establish that transformation has occurred.

Mucosa-associated Lymphoid Tissue Lymphoma

- Mucosa-associated lymphoid tissue (MALT) lymphoma is an extranodal marginal zone lymphoma.

- Gastric MALT lymphoma may be the best known, particularly given its common association with Helicobacter pylori infection.

- H. pylori-associated gastric MALT lymphoma should be treated with antibiotics and proton pump inhibitors initially.

Chronic Lymphocytic Leukemia

- Chronic lymphocytic leukemia (CLL) is generally easy to diagnose because it manifests as an increase in absolute lymphocytes on complete blood count.

- The lymphocytes are predominantly small and mature appearing, although they may be fragile and form "smudge cells" on the peripheral smear.

- Flow cytometry using peripheral blood is essential in establishing the diagnosis and will reveal B-cell antigens (CDI9, 20, and 23), coexpression of CD5 (normally a T-cell marker), and low levels of a monoclonal surface immunoglobulin.

- CLL and small lymphocytic lymphoma represent the same disease, with the designation as leukemia or lymphoma based on the dominant clinical manifestation in either peripheral blood and marrow or nodal involvement, respectively.

- Both CLL and small lymphocytic lymphoma are treated the same.

- CLL is now grouped more with the lymphomas than with the leukemias in treatment centers.

- CLL is typically an indolent disease, patients with low-stage, asymptomatic chronic lymphocytic leukemia can be observed without therapy for decades.

- Patients with CLL are prone to infection, in part related to commonly associated hypogammaglobulinemia.

- Patients with CLL and small lymphocytic lymphoma may also develop autoimmune cytopenias such as immune thrombocytopenic purpura and autoimmune hemolytic anemias.

- Transformation to a large cell lymphoma (known as Richter transformation) occurs in about 5% of patients with CLL and small lymphocytic lymphoma and is generally associated with a poor prognosis and refractory disease.

Diffuse Large B-Cell Lymphoma

- Diffuse large B-cell lymphoma represents approximately 30% of non-Hodgkin lymphomas.
- Patients often present with symptomatic enlarging lymphadenopathy in the neck or abdomen.
- Approximately 40% may have symptoms or signs of extranodal disease, and one third have systemic symptoms.
- Biopsy specimens show diffuse effacement of normal nodal architecture by large, atypical lymphoid cells with prominent nucleoli and basophilic cytoplasm.
- Flow cytometry reveals B-cell antigens, and most patients have monoclonal surface immunoglobulin.

- Sixty percent of patients have advanced (stage III or IV) disease at diagnosis, and standard therapy is R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone).

- Patients with poor prognostic features, such as elevated serum lactate dehydrogenase level, extensive tumor burden, and poor performance status, may receive more aggressive initial therapy.

Burkitt Lymphoma

- Burkitt lymphoma is remarkable for its extremely rapid growth.
- The endemic form occurs primarily in Africa, is a common cause of childhood cancer, and is associated with Epstein-Barr virus infection. Patients may present with a large jaw mass .
- The sporadic form is more typically seen in the United States, occurs at a somewhat later age, and is more likely to present with abdominal or pelvic involvement.
- A third variety of Burkitt lymphoma is the immunodeficiency-associated form and occurs in HIVinfected patients.
- MYC gene activation is characteristic of this lymphoma.

- Early signs of the tumor lysis syndrome are often present in patients with Burkitt lymphoma even before treatment is initiated and should be anticipated because the tumor is quite chemosensitive.

- Various aggressive multi-agent chemotherapy regimens with rituximab have been associated with high cure rates.

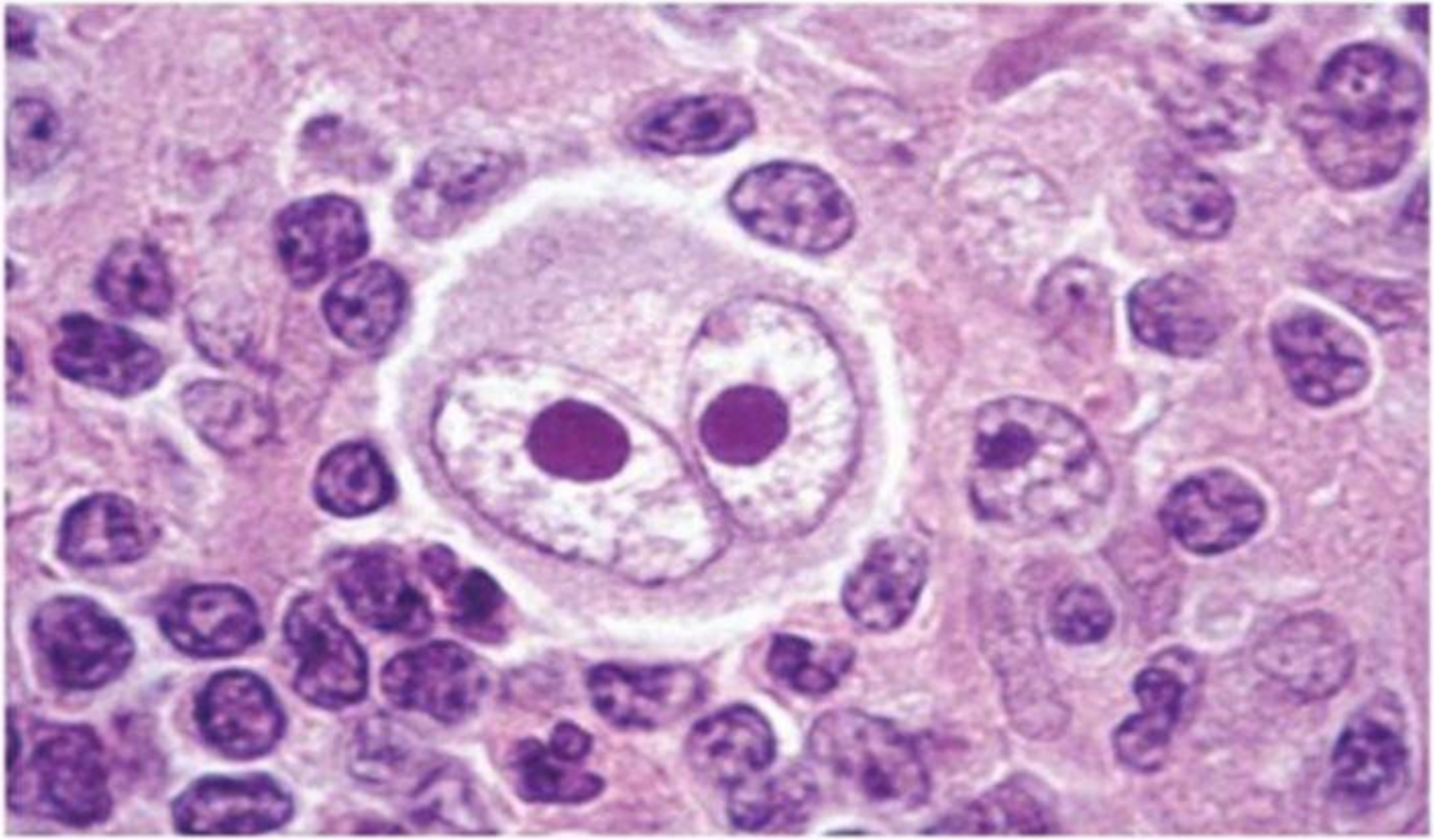
Hodgkin Lymphoma

- Hodgkin lymphoma represents approximately 10% of lymphomas and is curable in most, but not all, patients.
- It has a bimodal incidence, although it most commonly presents in young adults.
- Presentation with mediastinal, cervical, and supraclavicular involvement is particularly common for the nodular sclerosing subtype .
- Patients may also present with B symptoms, although that is more commonly seen in elderly patients with more advanced disease.
- Pruritus may also be a presenting symptom.

- The diagnosis is established with a lymph node biopsy specimen showing Reed-Sternberg cells.

- Reed-Sternberg cells are large and either are multinucleated or have a bilobed nucleus ("owls eye" appearance) with prominent eosinophilic inclusion-like nucleoli. They can be seen with light microscopy in biopsies from individuals with Hodgkin lymphoma. They are usually derived from B lymphocytes. When seen against a sea of B cells, they give the tissue a "starry sky" or "motheaten" appearance. The absence of Reed-Sternberg cells has very high negative predictive value for Hodgkin disease.

- The number of Reed-Sternberg cells and variability in the composition of the infiltrate lead to pathologic subtypes, including nodular sclerosis, mixed cellularity, lymphocyte predominant, and lymphocyte depleted.



Histological classification

Type	Frequency	Prognosis	Notes
Nodular sclerosing	Most common (around 70%)	Good prognosis	More common in women. Associated with lacunar cells
Mixed cellularity	Around 20%	Good prognosis	Associated with a large number of Reed-Sternberg cells
Lymphocyte predominant	Around 5%	Best prognosis	
Lymphocyte depleted	Rare	Worst prognosis	

- 'B' symptoms imply a poor prognosis

weight loss > 10% in last 6 months

- fever > 38ºC
- night sweats

Other factors associated with a poor prognosis identified in a 1998 NEJM paper included:

age > 45 years

- stage IV disease
- haemoglobin < 10.5 g/dl
- lymphocyte count < 600/µl or < 8%
- male
- albumin < 40 g/l
- white blood count > 15,000/µl

- More than 90% of patients present with "classic" Hodgkin lymphoma pathology and, even with early-stage disease, receive chemotherapy because this has been shown to result in higher cure rates.

- The doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) regimen is most commonly used.

Thank you.