Lymphoma and Plasma Cell Neoplasms

SESSION OBJECTIVES:

Use these session objectives to test your knowledge of the important concepts presented in this chapter and as study topics to return to prior to your exams.

1. Describe available tools applied in the diagnosis and classification of hematopoietic neoplasms (please review: Diagnosing Hematolymphoid Neoplasms)
2. Identify the major categories of lymphomas.
3. Identify the chromosomal translocations in follicular, Burkitt, and mantle cell lymphoma and how these genetic changes contribute to cancer.
4. Recognize the clinical presentation and diagnostic findings in follicular lymphoma, Hodgkin lymphoma, chronic lymphocytic leukemia, and multiple myeloma.
5. Recognize the morphology of a Reed-Sternberg cell in classical Hodgkin lymphoma.

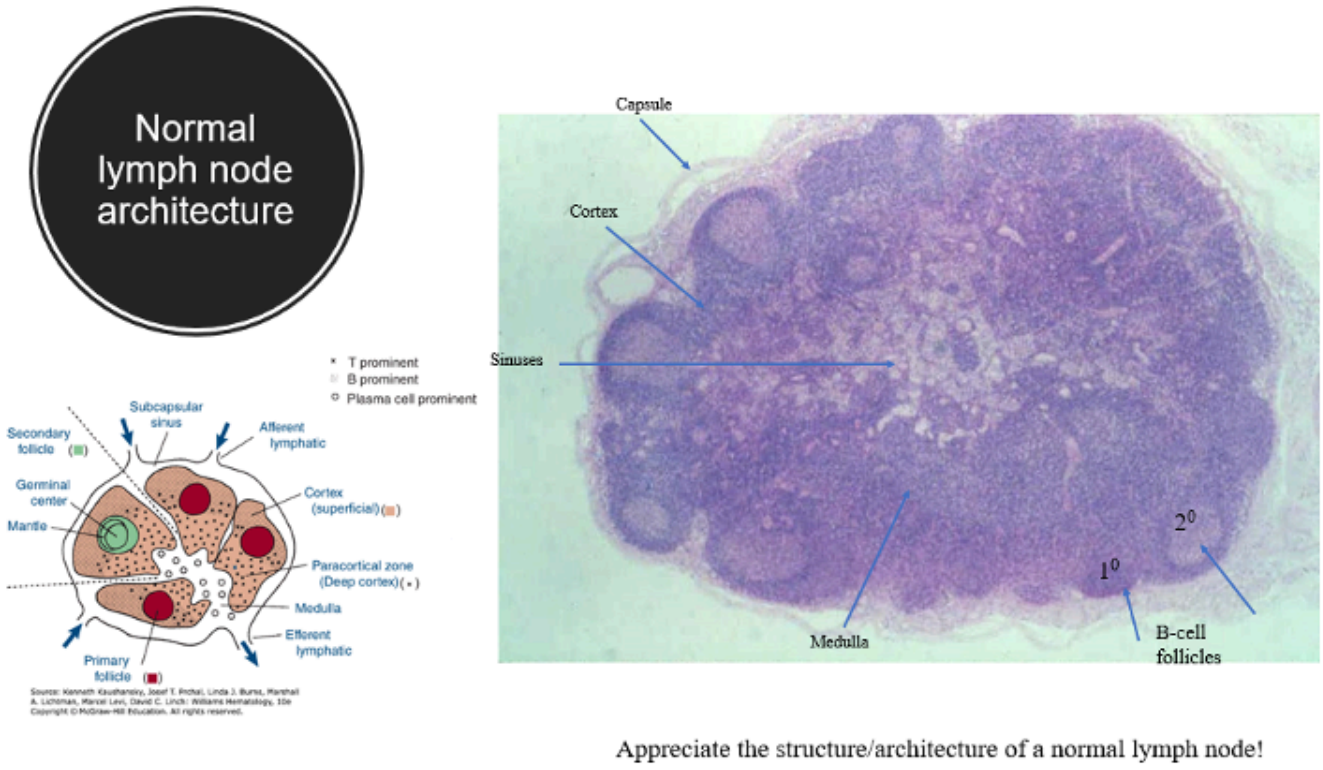
OPTIONAL PRE-CLASS MATERIALS FOR THIS SESSION:

- Textbook Reading: Part IV White Blood Cell Disorders
  - Chapter 22: Non-Hodgkin Lymphomas and Chronic Lymphocytic Leukemias
  - Chapter 23: Hodgkin Lymphoma
  - Chapter 24: Multiple Myeloma and Related Disorders

A brief forward: Many thanks to Dr. Corliss Newman, MD for contributing this material.

OVERVIEW

Lymphoid neoplasms represent a diverse group of cancers originating from B-cells, T-cells, and plasma cells at different stages of development. These malignancies exhibit a wide range of clinical behaviors, from slow-growing (indolent) forms to highly aggressive diseases, necessitating tailored treatment approaches based on the specific hematopoietic malignancy as determined by a thorough diagnostic workup (review: Diagnosing Hematolymphoid Neoplasms)



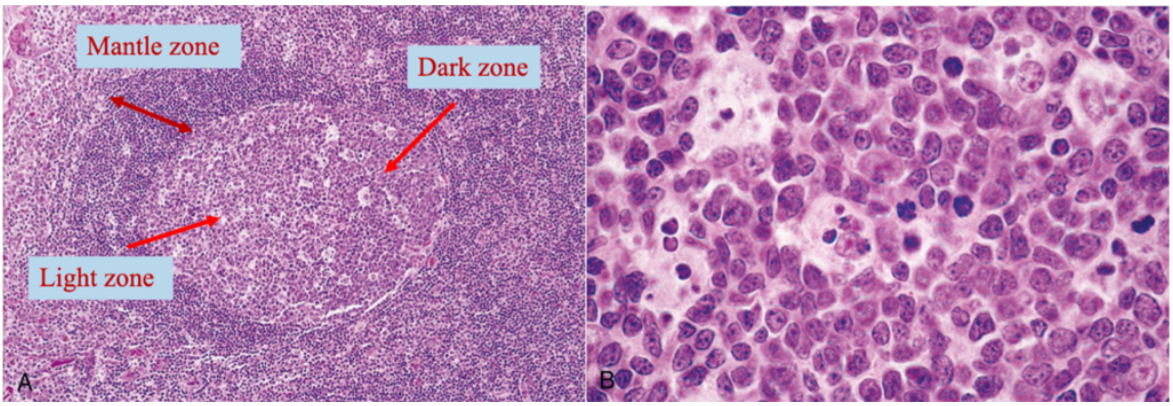
Appreciate the structure/architecture of a normal lymph node!

REACTIVE LYMPHADENOPATHY:

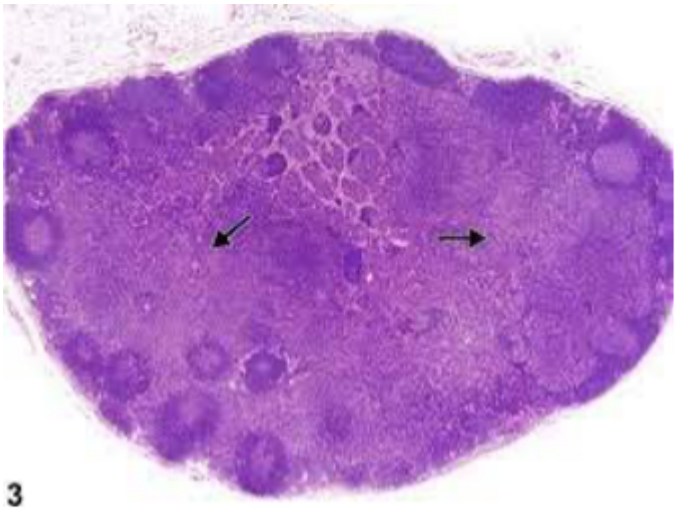
It is essential to distinguish malignant lymphomas (which will be discussed in detail below) from **reactive lymphadenopathy**, which refers to the benign enlargement of lymph nodes in response to infection, inflammation, or immune activity. Lymphadenopathy, a general term for lymph node enlargement, is typically considered significant when the node exceeds 1 cm in size (although this threshold may vary by lymphatic region). In contrast to lymphoma, where the lymph node architecture is disrupted by clonal malignant cells, reactive lymphadenopathy retains normal lymph node structure with a polyclonal population of cells. Reactive lymphadenopathy usually resolves once the underlying cause is treated, whereas lymphomas are persistent, progressive, and worsen without appropriate intervention.

- **Clinical Features**: Adenopathy in younger patients is often reactive, with cervical nodes commonly enlarging due to oral infections or viruses. Other features that favor a reactive process include localized adenopathy, rapid growth, pain, and the absence of **B-symptoms** (fever, night sweats, weight loss). See Table 1 below for a comparison of reactive lymphadenopathy vs lymphoma.
- **Etiologies**:
  - Follicular or interfollicular hyperplasia of a lymph node
  - Viral (EBV, HSV) or bacterial infections
  - Granulomatous disease (sarcoid, tuberculosis, fungal infection)
  - Autoimmune diseases (lupus, others)
  - Castleman Disease (a rare, nonclonal lymphoproliferative disorder)
  - Exogenous material (tattoos, silicone)
- **Histology**: Preserved lymph node architecture with hyperplastic follicles or paracortex.
  - **Follicular Hyperplasia**: Seen in infections or autoimmune diseases.
    - Variably sized, polarized germinal centers surrounded by small naïve B cells in mantle zone
      - Dark zone: proliferation of blast-like B cells (centroblasts)
      - Light zone: B cells with irregular or cleaved nuclear contours (centrocytes)

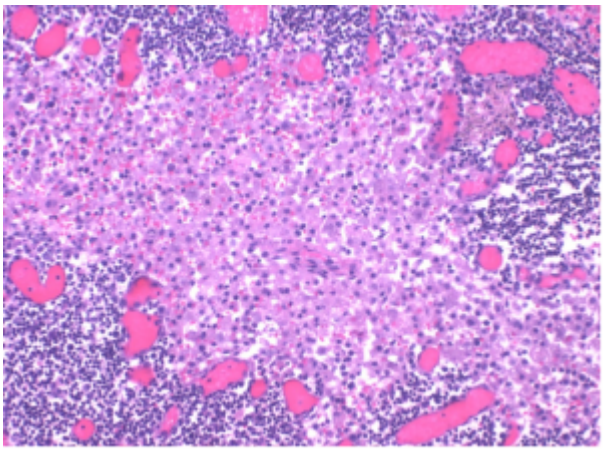
- Presence of tingible body macrophages



- **Paracortical Hyperplasia**: Typically associated with viral infections.
  - Histology: T-cell region is expanded with occasional enlarged immunoblasts.



- **Sinus Histiocytosis**: Common in lymph nodes draining foreign material, pigment, infections, or malignancies.
  - Histology: Expanded lymphatic sinusoids filled with intra-sinusoidal macrophages.



Feature	Reactive Lymphadenopathy	Lymphoma
Age	Younger patients	Older patients
Location	Cervical	Supraclavicular nodes are uncommonly enlarged
Extent	Localized	Generalized*
Node Consistency	Soft, mobile	Firm, rubbery, fixed
Architecture	Preserved	Disrupted
Painful	Often painful	Typically painless
B-symptoms	Rare	Common**
Etiology	Infection, autoimmunity	Neoplastic B-cell/T-cell origin
Time course	Rapid	Persistence. >3-4 months
Resolution	Resolves with treatment	Progressive without treatment

* NOTE: Generalized adenopathy is more commonly associated with serious infections, autoimmune disease, and disseminated malignancy—particularly in patients with leukemias and lymphomas. Hodgkin Lymphoma, however, typically starts in local lymph nodes and progresses through nodes in anatomic sequence.

** NOTE: also seen with TB

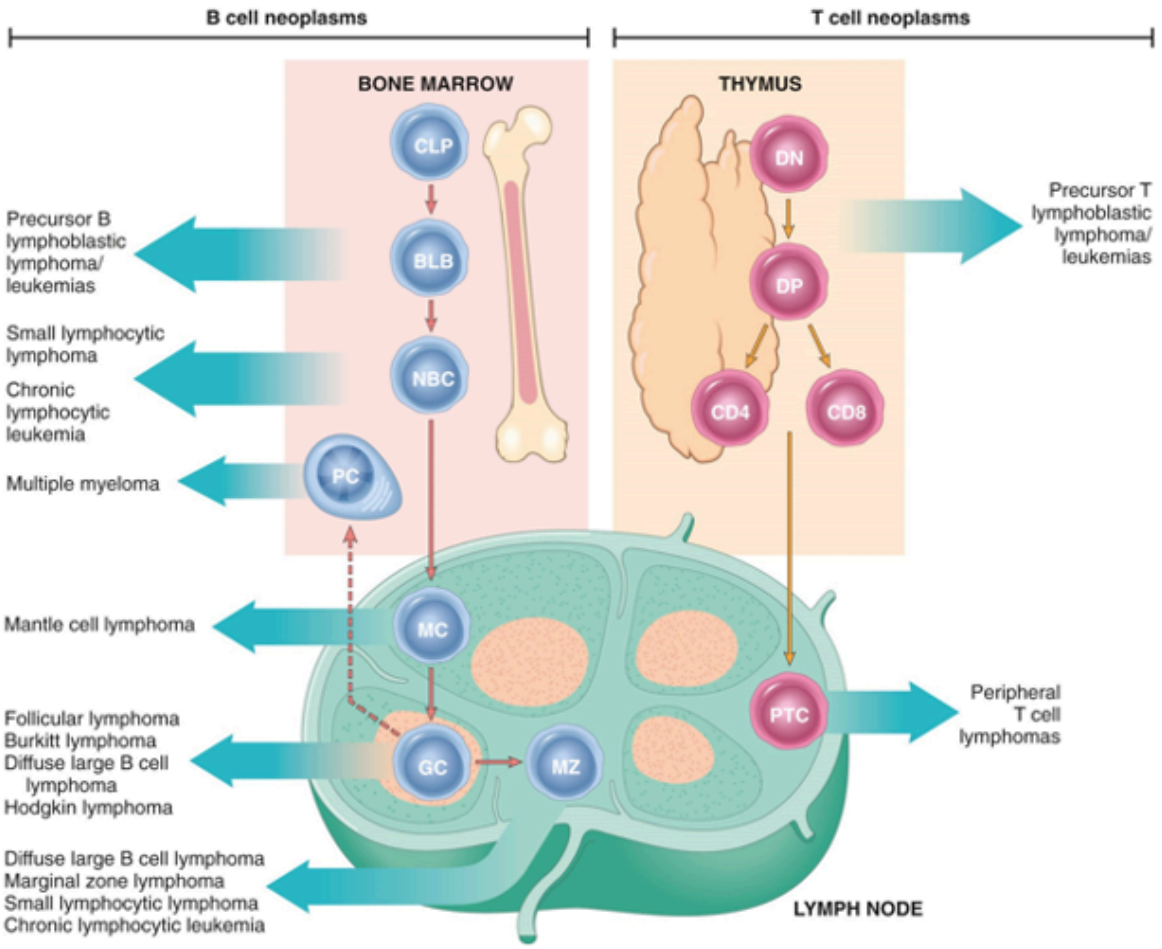
LYMPHOMAS

Lymphomas are characterized by the neoplastic transformation of B-cells, T-cells, or plasma cells, resulting in abnormal cell growth within the lymphatic system. They histologically demonstrate disrupted lymph node architecture, often with clonal populations of malignant cells replacing the normal polyclonal cellular composition.

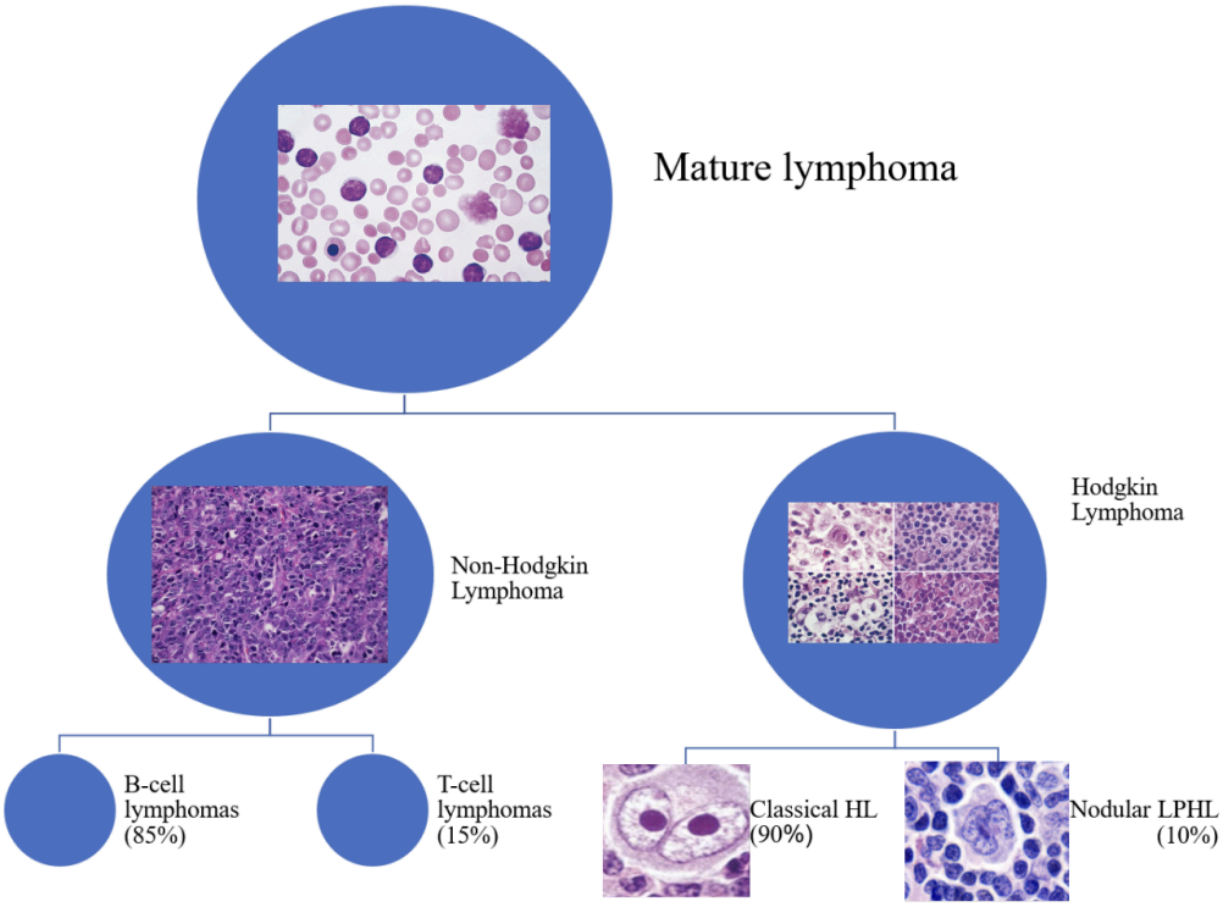
How we classify Lymphoid and Plasma Cell Neoplasms:

To better understand and manage these neoplasms, we can classify them in several ways: based on the cell lineage, by traditional categories, or according to their clinical behavior. This multi-dimensional classification helps guide both diagnosis and treatment strategies.

- ***Cell-lineage***: A very general break down of lymphoid malignancies can be based upon whether the cells have T or B cell markers. Lymphoid malignancies can present in the form of leukemias or predominantly involve lymph nodes (lymphomas). A general schematic is shown below:



- ***Traditional classification***: Lymphomas can also be categorized as being either Hodgkin Lymphoma (a special type of lymphoma that is defined by the presence of giant **Reed-Sternberg cells**, which are of B-cell lineage) vs Non-Hodgkin Lymphoma (all other lymphomas, the majority of which are also of B-cell lineage).



- ***Clinical presentation and behavior***:
  - **Aggressive NHL** typically grow rapidly and are associated with constitutional symptoms (fever, weight loss) and an elevated risk for tumor lysis syndrome.
    - Examples: Diffuse large B cell lymphoma, Burkitt lymphoma, Precursor B cell lymphoblastic leukemia/lymphoma, Precursor T cell lymphoblastic leukemia/lymphoma, Adult T cell leukemia-lymphoma, some peripheral T cell lymphomas
  - **Indolent NHL** wax and wane, with slow growth over months to years. Often unaccompanied by symptoms, they may be associated with hepatomegaly/splenomegaly. Indolent NHL is treated only when symptoms indicate the need for intervention.
    - Examples: Follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, marginal zone lymphoma

Etiology of lymphoma:

Causes of lymphomas are multifactorial and can include the following:

- **Genetic mutations/translocations**: Mutations can occur in oncogenes (such as tyrosine kinase mutations and MYC translocations), pro-survival genes (*BCL2* translocation, which is anti-apoptotic), and transcription factors (like *KMT2A* translocation and *PML*::*RARA* fusion).
  - Inherited genetic risks: Fanconi anemia and Ataxia Telangiectasia are both associated with increased risks of lymphoma/leukemia.
- **Chronic Inflammation & Infection**: which can include infections

- Viruses: EBV (Epstein-Barr Virus), HHV-8 (Human Herpesvirus, also called Kaposi sarcoma Herpesvirus), and HTLV-1 (Human T-lymphotropic Virus type 1) are associated with risk of lymphoid malignancy.
- H. pylori is associated with gastric adenocarcinoma and MALT (Mucosa-associated lymphoid tissue) lymphoma, the latter of which can go into remission following treatment of the infection.

- **Iatrogenic Factors**: Radiation

Workup of Lymphomas:

The detailed workup of hematologic malignancies, including diagnostic tools and testing strategies, has been thoroughly covered in the detail in Diagnosing Hematolymphoid Neoplasms. In brief:

1. **Clinical Evaluation:**

   - **History and symptoms**: Persistent lymphadenopathy (>3-4 months is a significant indicator of potential malignancy), B-symptoms (fever, night sweats, weight loss), and extra-nodal involvement. Notably, monoclonal antibodies or antibody fragments can cause organ damage (particularly kidney damage) or autoimmune phenomena (e.g. hemolytic anemia in CLL).
   - **Physical Examination**: Check for palpable lymph nodes and splenomegaly.

2. **Laboratory Studies:**

   - **Complete blood count (CBC)**: To evaluate cytopenia (low WBC, RBC, and/or platelets- which may present with infection, fatigue, or bleeding) or elevated lymphocytes. Sometimes a healthy patient has elevated lymphocytes found on a CBC during a routine health care check-up (this is the most common way that chronic lymphocytic leukemia/CLL is diagnosed) without any associated symptoms.
   - **Lactate dehydrogenase (LDH)**: May be elevated in aggressive lymphomas, indicating higher cell turnover.
   - **Serum protein electrophoresis**: To assess for monoclonal protein spikes, especially in **plasma cell neoplasms**.

3. **Imaging: CT or PET scans**: Essential for staging, determining the extent of lymphadenopathy, and detecting extra-nodal involvement.

4. **Tissue Biopsy:**

   - **Excisional biopsy** (gold standard): Preserving lymph node architecture helps distinguish between reactive and neoplastic processes, as lymphomas are characterized morphologically by cell size (small or large cell) and how cells disrupt the lymph node architecture (nodular vs diffuse infiltration of the lymph node)
   - **Core needle biopsy**: Acceptable if excisional biopsy is not feasible but less informative.
   - **Fine needle aspiration (FNA)**: Often inadequate for lymphoma diagnosis.

5. **Flow Cytometry and Immunophenotyping:** Flow cytometry is used to assess clonality (normal cells are polyclonal, neoplasia is not) and cell lineage.

   - **B-cell markers**: **CD19**, **CD20**, **CD5**, **CD10**, **BCL2**, **BCL6**, **Pax5.** If the B-cell population is clonal, then all the cells will express either **Kappa** or **Lambda** light chains
   - **T-cell markers**: **CD2**, **CD3**, **CD4**, **CD7**, and **CD8**

NOTE: The immunophenotype (cell surface markers) present on the malignant monoclonal lymphocytes can be used to help diagnose the type of lymphoma/leukemia.

- **CD5** is a T cell marker abnormally expressed in certain B-cell lymphoid malignancies, including Chronic Lymphocytic Leukemia (CLL), Mantle Cell Lymphoma, and Diffuse Large B-cell Lymphoma.
- **CD10** is an abnormally expressed in Follicular Lymphomas, Burkitt's Lymphoma, and Diffuse Large B-cell Lymphoma.
- **CD5** and **CD10** negative abnormal B-cells are seen in Marginal Zone Lymphomas, Hairy Cell Leukemia, and Diffuse Large B-cell lymphoma.
- **CD23** is a membrane glycoprotein that is expressed by activated B-cells, monocytes, follicular dendritic cells, subsets of eosinophils, and a subset of platelets- is also expressed on CLL cells and follicular lymphoma cells.

6. **Cytogenetic and Molecular Studies:**

- **Cytogenetics**: Translocations between the IgH (heavy chain) enhancer/promoter on chromosome 14 and either an oncogene or anti-apoptosis gene on another chromosome resulting in over-expression of that gene are associated with certain types of lymphomas.
- **FISH (Fluorescence In Situ Hybridization)**: Used to detect chromosomal translocations.
- **PCR (Polymerase Chain Reaction)**: Helps identify specific gene rearrangements.

The following table is a summary of several more common lymphoid malignancies, their cell types/cell of origin, gene mutations, and clinical features. We'll go over some of these in more detail below.

B-cell Non-Hodgkin lymphoma

Neoplasms of Mature B Cells.	Cell of Origin	Genotype	Clinical features
Burkitt lymphoma	Germinal center B cell	Translocations involving *MYC* and Ig loci, usually t(8;14); subset EBV-associated	Adolescents or young adults with extranodal masses; uncommonly presents as "leukemia"; aggressive
Diffuse large B-cell lymphoma	Germinal center or post–germinal center B cell	Diverse chromosomal rearrangements, most often of *BCL6* (30%), *BCL2* (10%), or *MYC* (5%)	All ages, but most common in older adults; often appears as a rapidly growing mass; 30% extranodal; aggressive
Extranodal marginal zone lymphoma	Memory B cell	t(11;18), t(1;14), and t(14;18) creating *MALT1-IAP2*, *BCL10-IGH*, and *MALT1-IGH* fusion genes, respectively	Arises at extranodal sites in adults with chronic inflammatory diseases; may remain localized; indolent
Follicular lymphoma	Germinal center B cell	t(14;18) creating *BCL2-IGH* fusion gene	Older adults with generalized lymphadenopathy and marrow involvement; indolent
Hairy cell leukemia	Memory B cell	Activating *BRAF* mutations	Older men with pancytopenia and splenomegaly; indolent
Mantle cell lymphoma	Naive B cell	t(11;14) creating cyclin D1– *IGH* fusion gene	Older men with disseminated disease; moderately aggressive
Multiple myeloma/solitary plasmacytoma	Post–germinal center bone marrow homing plasma cell	Diverse rearrangements involving *IGH* ; 13q deletions	Myeloma: older adults with lytic bone lesions, pathologic fractures, hypercalcemia, and renal failure; moderately aggressive Plasmacytoma: isolated plasma cell masses in bone or soft tissue; indolent
Small lymphocytic lymphoma/chronic lymphocytic leukemia	Naive B cell or memory B cell	Trisomy 12, deletions of 11q, 13q, and 17p; *NOTCH1* mutations; splicing factor mutations	Older adults with bone marrow, lymph node, spleen, and liver disease; autoimmune hemolysis and thrombocytopenia in a minority; indolent

Robbins & Cotran Pathology

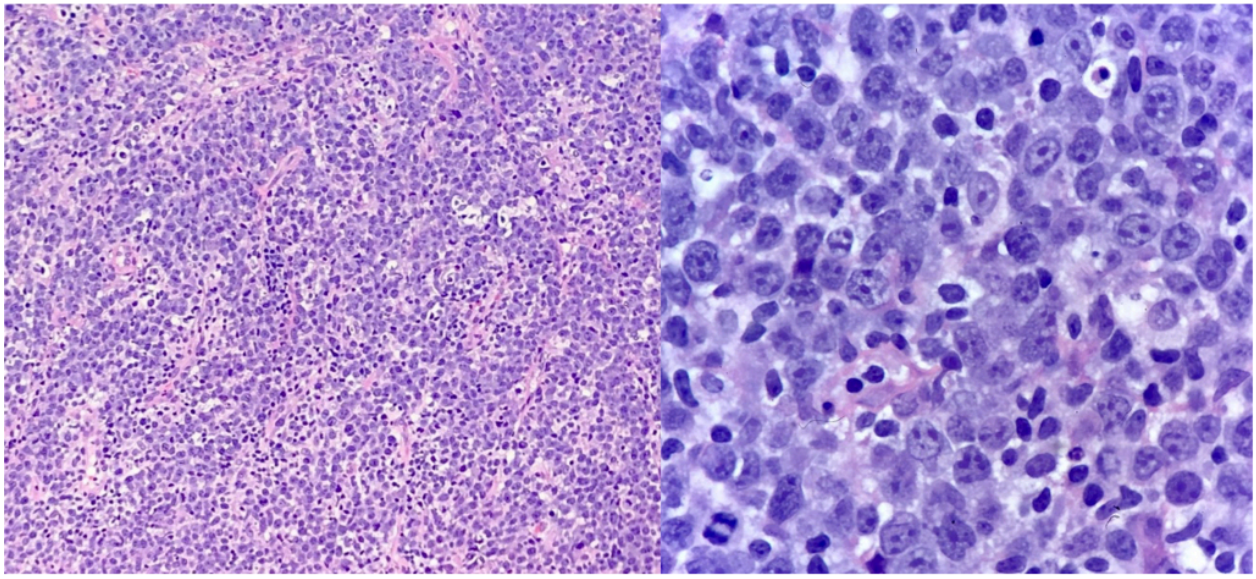
There are more than 60 specific NHL subtypes. These are some of the most common and their associated features.

LYMPHOMAS TO KNOW:

Diffuse Large B-Cell Lymphoma (DLBCL): Most common form of aggressive non-hodgkin lymphoma, there are a number of subtypes.

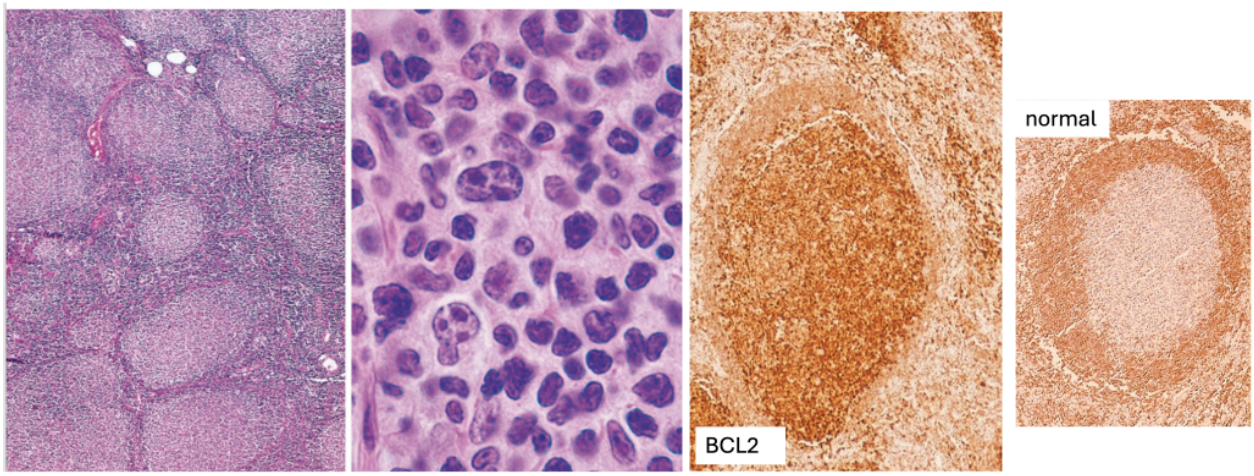
- **Presentation**: Rapidly enlarging mass (nodal or extranodal) +/- B-symptoms; can occur at any age (median: 60)
- **Etiology**: Sometimes more indolent lymphomas such as follicular lymphoma and small lymphocytic lymphoma/CLL can transform to DLBCL
- **Histology**: Large, atypical B-cells infiltrating lymph nodes or extra-nodal tissues.
- **Immunophenotyping**: **CD19+**, **CD20+**, **BCL6+**
- **Genetics**: **BCL6**, **MYC**, and **BCL2** rearrangements;
- **Treatment**: **R-CHOP** chemotherapy is the standard regimen (and can be curative).
- **Prognosis**: Generally rapidly progressive and fatal without treatment; "double-hit" lymphomas have a particularly poor prognosis

Classic pathology in Diffuse Large B-cell lymphoma. Note loss of follicles/typical lymph node architecture on lower power view (left) and higher power (right).



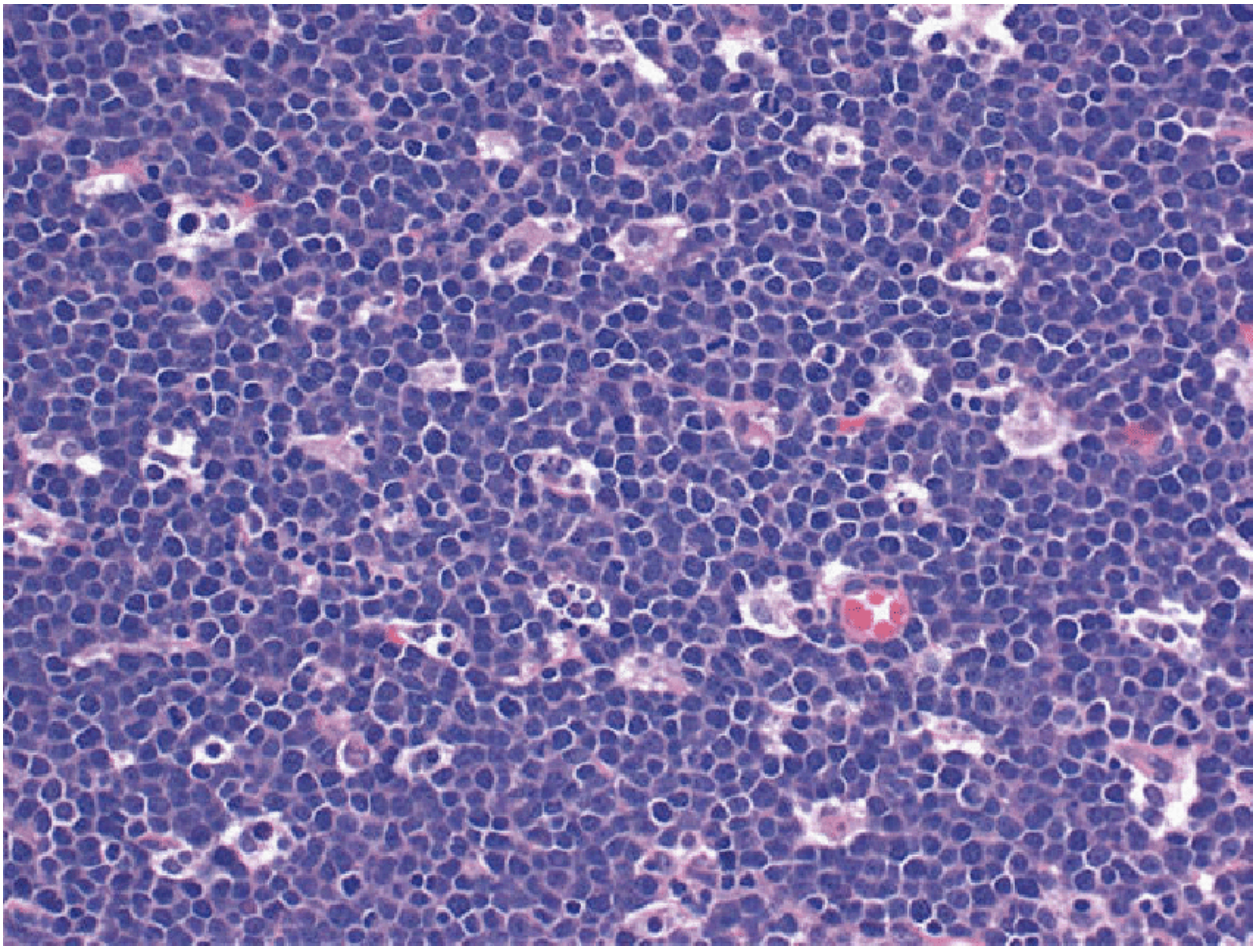
Follicular Lymphoma: second most common Non-hodgkin lymphoma (NHL) and most common indolent NHL diagnosed in the USA.

- **Clinical presentation**: Most patients diagnosed at middle age
- **Histology**: Back-to-back follicles composed of centrocytes (small cells with cleaved/irregular nuclear contour) and centroblasts (large cells with several membranous-bound nucleoli), see image below.
- **Immunophenotyping**: **CD10+**, **BCL2+**, **BCL6+**
- **Genetics**: **t(14;18)** results in IgH::BCL2; this translocation inhibits apoptosis due to over-expression of **BCL2**
- **Treatment**: Observation for asymptomatic cases; rituximab and chemotherapy for symptomatic patients
- **Prognosis**: Indolent course; 30-50% change of transformation (most commonly to DLBCL)



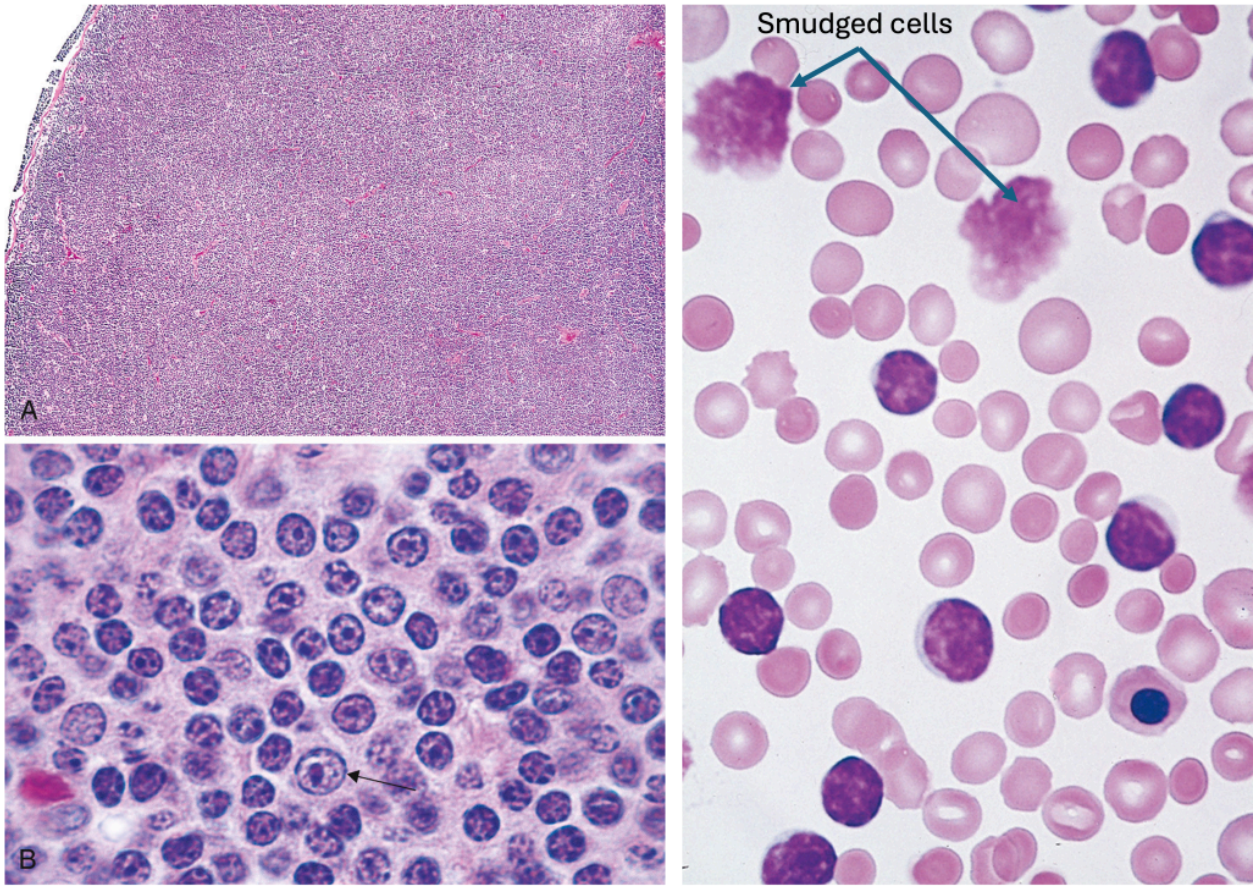
Burkitt Lymphoma:

- **Presentation**: Rapidly enlarging nodal masses or extranodal masses, may be endemic, sporadic, or HIV-associated:
  - ***Endemic***: Seen mainly in children in Africa, it is associated with EBV and has a predilection for the jaw
  - ***Sporadic/non-endemic***: More common in children and young adults, it is less commonly associated with EBV (~15-20%)
    - While it can be identified anywhere, it has been associated with lymphomas of the ileocecum and peritoneum, resulting in bowel obstruction with a mass and adenopathy subsequently found
  - ***HIV-associated***: ~25% of Burkitt Lymphomas in HIV positive patients are associated with EBV
- **Histology**: Diffuse lymphoid infiltrate with a very high rate of proliferation and apoptosis resulting in "Starry sky" pattern due to macrophages clearing apoptotic cells
- **Immunophenotyping**: Markers are those of B-cells of germinal center origin (**CD10+**, **BCL6+**, and **Ki-67** near 100%)
- **Genetics**: most commonly **t(8;14)** which results in IgH::MYC fusion, but MYC can also fuse with kappa light chain promoter on chromosome 2 **t(2;8)** or a lambda light chain promotor on chromosome 22 **t(8;22)**
- **Treatment**: High-dose chemotherapy with intensive supportive care
- **Prognosis**: Very aggressive



Small Lymphocytic Lymphoma (SLL)/Chronic Lymphocytic Leukemia (CLL): CLL and SLL are actually the same disorder.

- **Presentation**: Most patients are symptomatic, incidentally found to have a high WBC with elevated lymphocytes. Others present with adenopathy, fatigue, weight loss, lack of appetite, or infection (secondary to hypogammaglobulinemia/ low antibody levels). Occasionally associated with production of abnormal antibodies that cause hemolytic anemia and/or thrombocytopenia.
  - **CLL**: >5 X 109/L monoclonal B cells are found in the peripheral blood.
  - **SLL**: <5 X 109 cells/L monoclonal B cells (that mark as CLL) but with nodal, splenic, or extramedullary involvement.
  - ***NOTE:*** It is not uncommon to detect a small population of monoclonal cancerous lymphocytes in the blood of patients with a diagnosis of SLL. Likewise, adenopathy in patients with CLL (due to the cancerous lymphocytes tracking to lymph nodes as well as blood) is common.
- **Histology**: Diffuse infiltration of small, mature lymphocytes with occasional smudge cells on peripheral blood smear (an artifact due to CLL cells rupturing during smear preparation).



- **Immunophenotyping**: **CD5+**, **CD19+**, **CD20+**, **CD23+**.
- **Prognosis**: CLL prognosis varies based on genetic mutations and clinical staging. Deletion of 13q (includes miR-15a/16-1 microRNA) is associated with a favorable outcome, while 11q deletion (includes *ATM* and *BIRC3*), 17p deletion (includes *TP53*), *NOTCH1* mutations, and *TP53* mutations indicate a poor prognosis (as does ZAP70 and CD49d expression). Trisomy 12 and 6q deletion carry intermediate risk.
    - USA uses Rai Staging while the Binet staging system is used more commonly in Europe.

Modified Rai clinical staging system for chronic lymphocytic leukemia

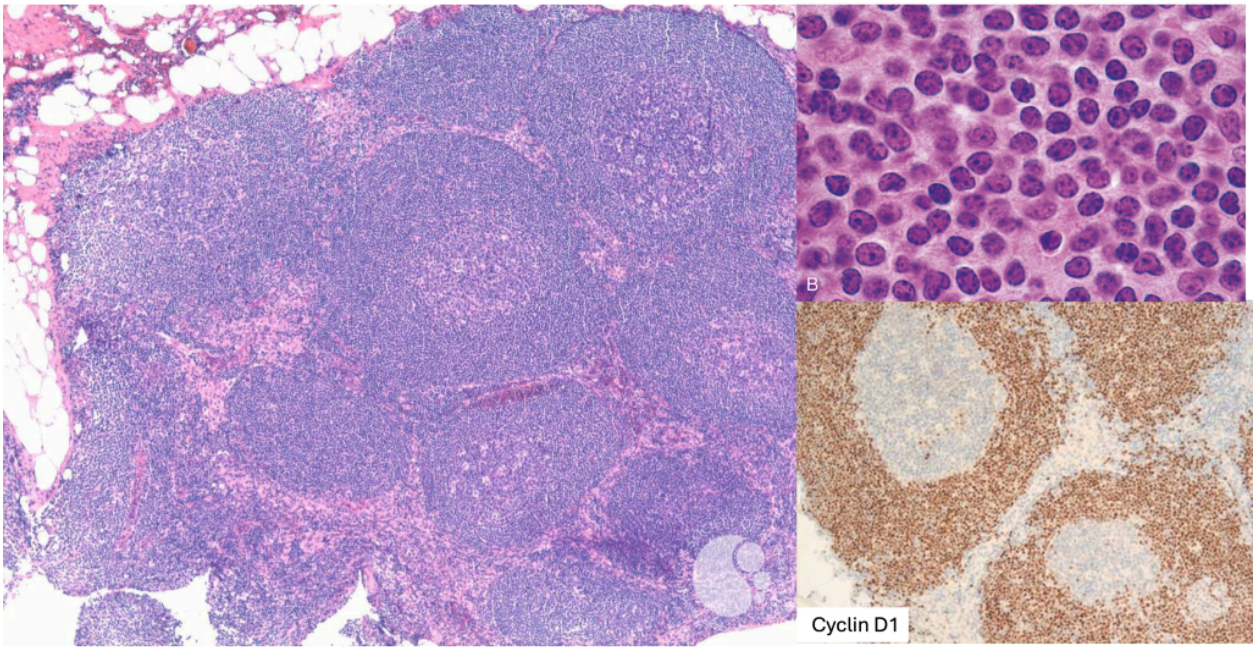
Risk	Stage	Description
Low	0	Lymphocytosis in blood or bone marrow
Intermediate	I	Lymphocytosis + enlarged lymph nodes
	II	Lymphocytosis + enlarged liver or spleen with or without lymphadenopathy
High	III	Lymphocytosis + anemia (Hgb <11 g/dL) with or without enlarged liver, spleen, or lymph nodes
	IV	Lymphocytosis + thrombocytopenia (platelet count <100,000/microL) with or without anemia or enlarged liver, spleen, or lymph nodes

- **Treatment**: Observation for indolent cases, targeted therapies like **ibrutinib** for more advanced disease.

NOTE: Approximately 5% of patients with CLL/SLL will have their disease transform to a more aggressive type of lymphoma, i.e. **Richter's Transformation**). Diffuse large B-cell lymphoma due to Richter's transformation, which is often associated with acquisition of a *TP53* or MYC mutation), has a poor prognosis. Less commonly, CLL/SLL can transform to Hodgkin's Lymphoma.

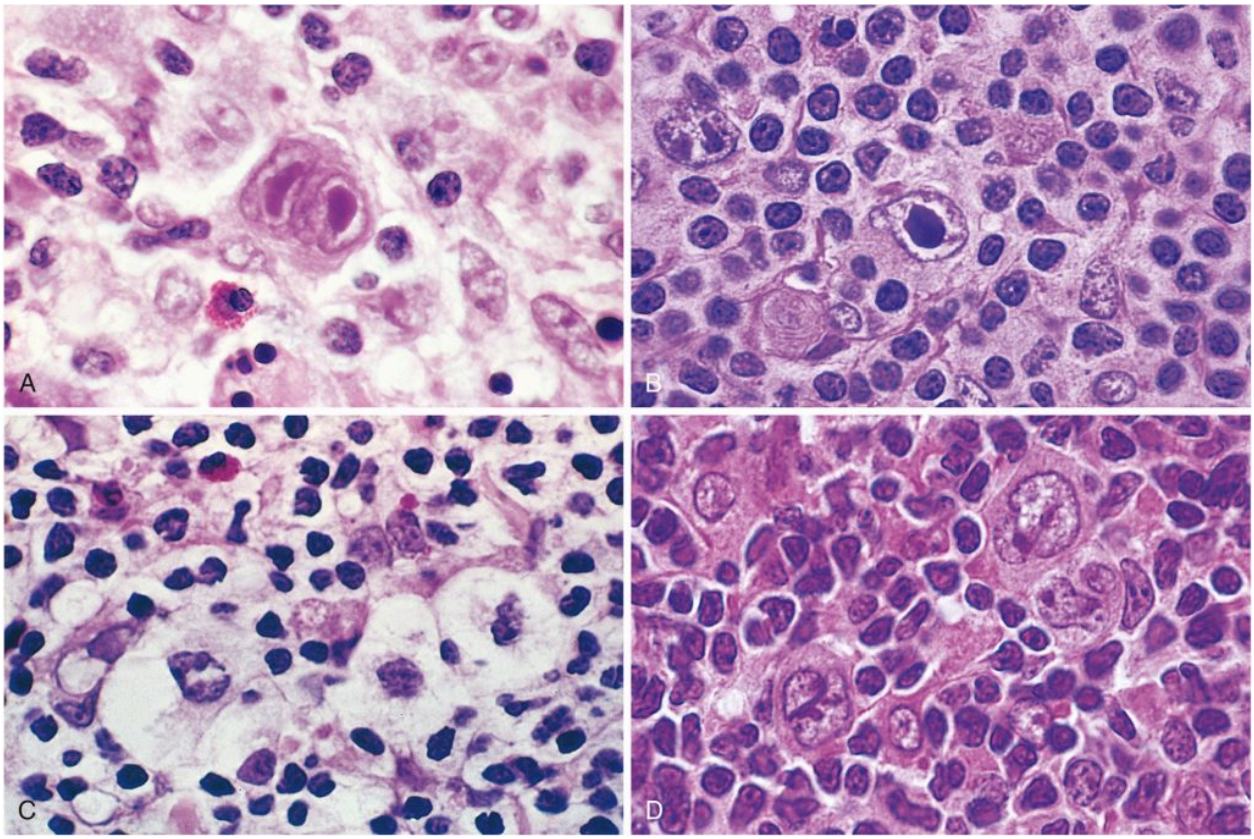
Mantle Cell Lymphoma (MCL): much less common form of lymphoma, and comprises 2.5 % of the NHL diagnoses in the USA

- **Presentation**: Most patients present with generalized adenopathy and less commonly (20-40%) with leukemic involvement; mucosal involvement of small bowel or colon cancer can also be seen.
- **Histology**: Infiltration of the mantle zone around lymphoid follicles by small to medium-sized lymphocytes with nuclear indentations, resulting in nodular LN architecture.
- **Immunophenotyping**: Resemble normal mantle zone B-cells surrounding the germinal center; **CD5+**, **CD19+**, **Cyclin D1+**, **CD23-**
- **Genetics**: **t(11;14)** translocation between IgH and **CCND1** (aka BCL1). Cyclin D1 stimulates cell growth by promoting the progression of cells from G1 phase to S phase of the cell cycle by stimulating hyperphosphorylation of RB.
- **Treatment**: Intensive chemotherapy, with autologous stem cell transplant for eligible patients.
- **Prognosis**: Variation in their clinical behavior, but overall tend to be moderately aggressive and difficult to cure (particularly those with *TP53* mutations, which behave more aggressively).



Hodgkin Lymphoma (HL) is divided into **Classical HL (90%)** and **Nodular Lymphocyte Predominant HL (10%)**, which differ in clinical behavior, histology, and treatment. Classical HL includes **Nodular sclerosis (65-70%)**, **Mixed cellularity (20-25%, linked to HIV/EBV)**, **Lymphocyte-rich**, and **Lymphocyte-depleted** subtypes.

- **Clinical Presentation**: Painless lymphadenopathy, often localized to the neck/mediastinum, with contiguous spread to adjacent lymph nodes.
- **Histology**: Characterized by the presence of **Reed-Sternberg (RS) cells**, which have large inclusion-like nucleoli about the size of small lymphocytes (see image below). RS cells release cytokines that attract and accumulate non-neoplastic lymphocytes, macrophages, neutrophils, and eosinophils, creating a reactive cellular background.
- **Immunophenotyping**: **CD15+**, **CD30+**, **PAX5+, CD20-**.
- **Genetic Findings**: RS cells show IgH gene rearrangements and NF-kB activation.
- **Treatment**: Chemotherapy (e.g., ABVD regimen) and radiation for localized disease.



PLASMA CELL NEOPLASMS

While plasma cells normally produce various antibodies, leading to a polyclonal distribution on serum protein electrophoresis (SPEP), plasma cell neoplasms demonstrate a monoclonal overgrowth, meaning all cells produce the same type of antibody (that appears as an **M-Spike** on SPEP, as below). Occasionally only light chain is produced, which due to its small size is excreted in urine (Bence Jones proteins).

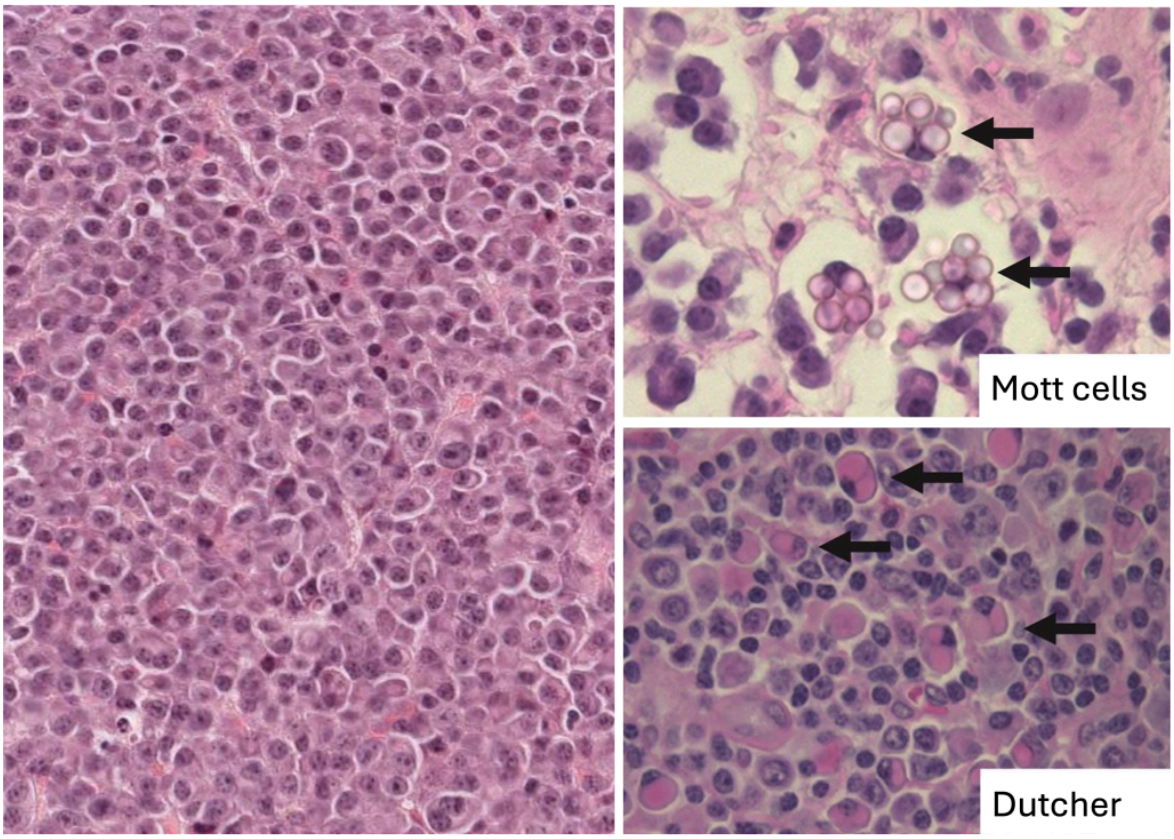
Monoclonal gammopathy of undetermined significance (MGUS): Characterized by an M-spike (<30 g/L) on serum protein electrophoresis, <10% clonal plasma cells in bone marrow, and no end-organ damage. There's a 1% annual risk of progression to multiple myeloma.

Smoldering (asymptomatic) Plasma cell neoplasm (Smoldering Myeloma): Defined by >10% clonal plasma cells or >30 g/L M-spike without organ damage. These patients are generally observed without treatment. The risk of progression to Multiple Myeloma is about 10% per year for the first 5 years after diagnosis, 3% per year for the next 5 years, then 1 to 2% for the following 10 years. Hence, these patients are follows more closely than MGUS patients for the first 10 years of diagnosis.

Multiple Myeloma (MM) is the most common plasma cell neoplasm. It is characterized by >10% clonal plasma cells in the bone marrow and presence of organ damage.

- **Clinical Presentation**: Patients with multiple myeloma can present in various ways, including new-onset renal insufficiency, bone fractures from lytic lesions, or confusion due to hypercalcemia. They may also experience recurrent infections because their monoclonal antibodies are dysfunctional or they have low levels of normal antibodies. Fatigue and anemia may prompt further workup leading to diagnosis. Additionally, some patients present with amyloidosis, with **AL-type** amyloid identified in affected organs through biopsy.

- **Histology**: characterized by sheets or clusters of **plasma cells,** that display an eccentric nucleus with a clock-face chromatin pattern and abundant basophilic cytoplasm. There may be **Russell bodies** (intra-cytoplasmic inclusions) or **Dutcher bodies** (intra-nuclear inclusions).



- **Immunophenotyping**: Monoclonal (express either **kappa** or **lambda**), **CD38+** & **CD138+** (usually), **CD19-**; they also often aberrantly express **CD56** and sometimes **CD117**.
- **Genetics**: High-risk patients may have **17p deletions** or **t(4;14)** translocations.
- **Treatment**: Although risk stratification influences treatment considerations like stem cell transplantation, most eligible patients receive aggressive therapies regardless of their risk category in order to prevent further end organ damage and/or to potentially reverse some of the end organ damage. Treatment includes immunomodulatory drugs (e.g., lenalidomide), proteasome inhibitors (e.g., bortezomib), and autologous stem cell transplantation.
- **Prognosis**: Genetics and staging based on serum albumin and **Beta-2 microglobulin** levels help predict prognosis.

Prognostic Factor		Criteria	Median survival (months)
ISS Stage	I	Serum beta2 microglobulin <3.5 g/dL Serum Albumin > 3.5 g/dL	62
	II	Serum beta2 microglobulin <3.5 g/dL and Albumin < 3.5 g/dL OR Serum beta2 microglobulin 3.5-5.5 g/dL (albumin has no effect)	44
	III	Serum beta2 microglobulin >5.5 g/dL	29
Cytogenetic Risk	Standard (60%)	t(11;14) t(6;14) (*Cyclin D3* gene) Hyperdiploid	
	Intermediate (20%)	t(4;14) (*FGFR3* gene) Del 13 Hypodiploid	
	High	Del 17p t(14;16) (*MAF* gene) t(14;20) (*MAFB* gene)	

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