Board Review- Part 2B: Malignant HemePath

4/25/2018

Small Lymphocytic Lymphoma

SLL: epidemiology

- SLL: 6.7% of non-Hodgkin lymphoma.
- Majority of patients >50 y/o (median 65).
- M:F ratio 2:1.

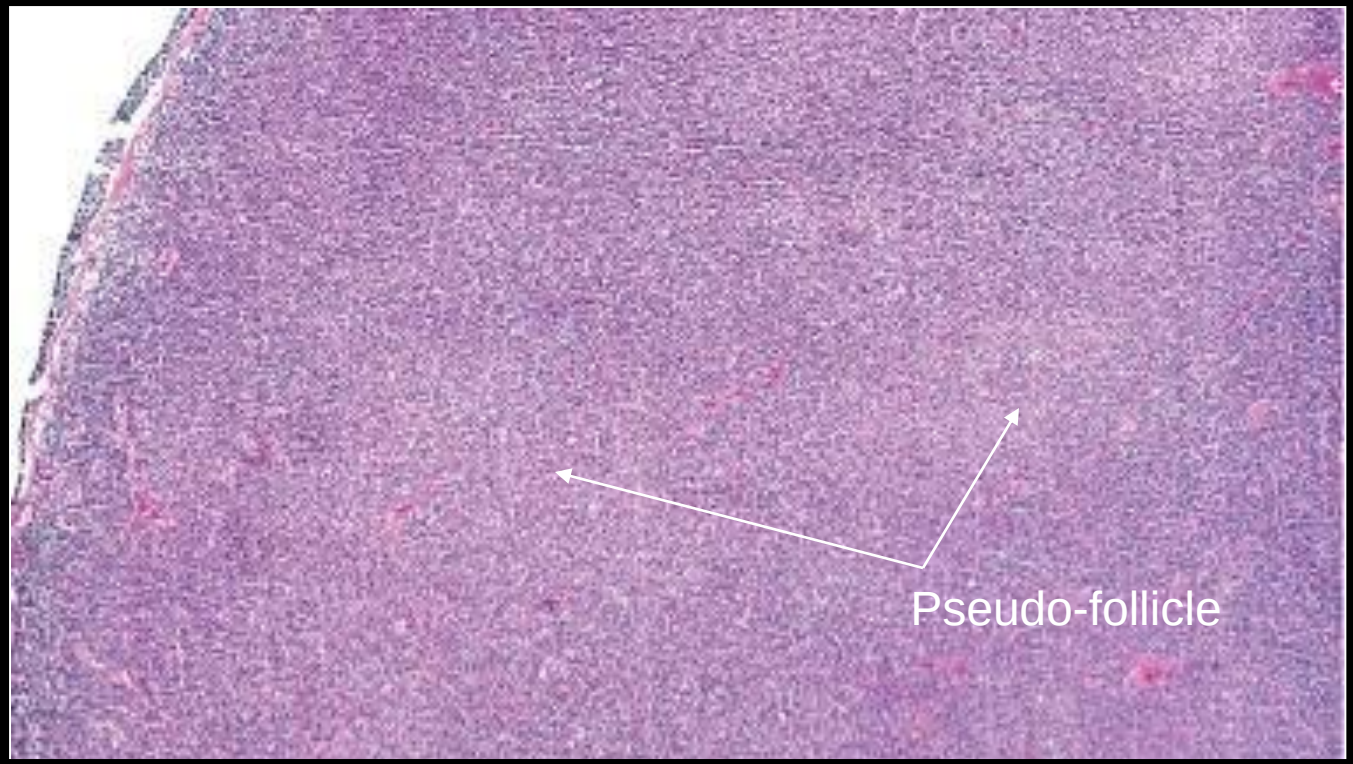
Morphology

- Lymph nodes
  - Effacement of architecture, pseudofollicular pattern of pale areas of large cells in a dark background of small cells. Occasionally is interfollicular.
  - The predominant cell is a small lymphocyte with clumped chromatin, round nucleus, ocassionally a nucleolus.
  - Mitotic activity usually very low.

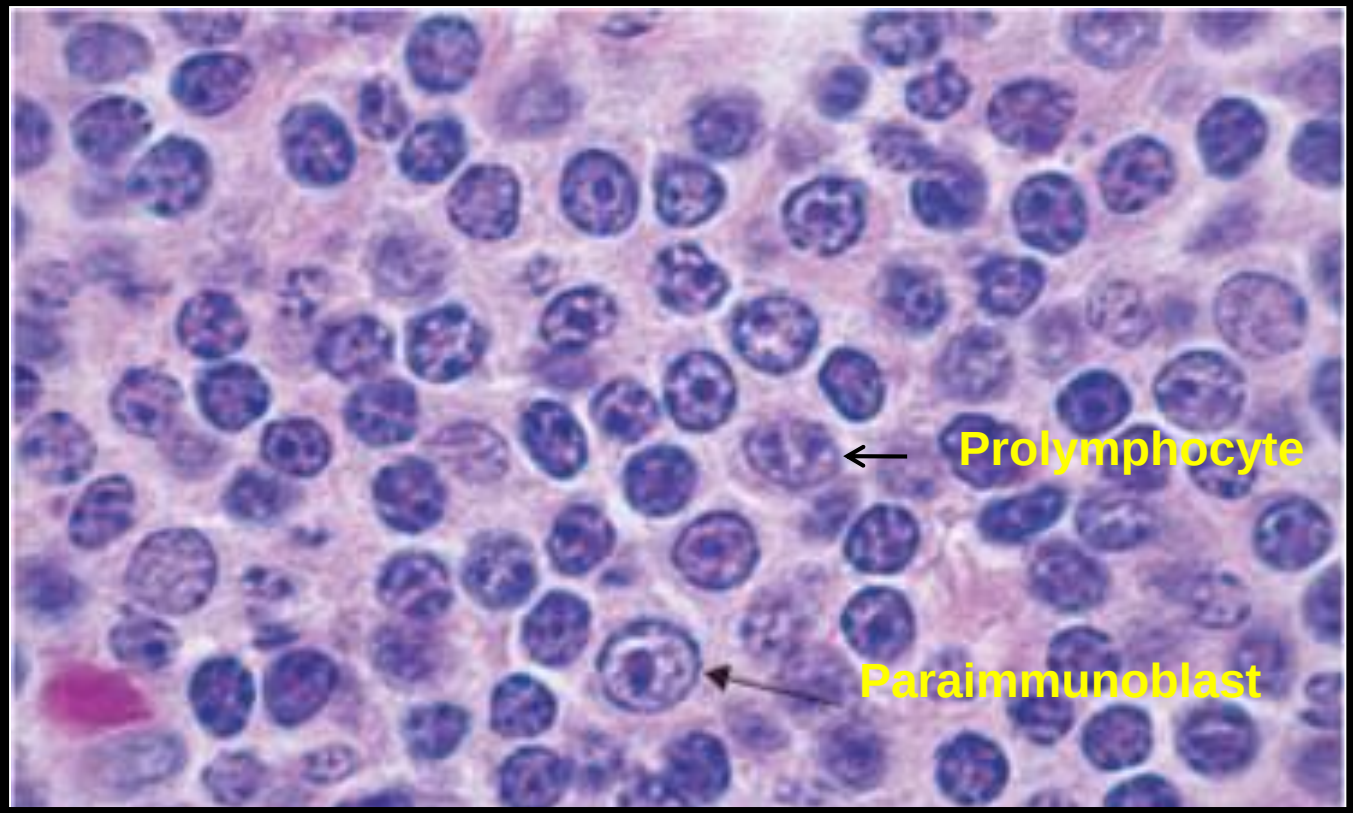
Morphology

- Pseudofollicles or proliferation centers contain small, medium and large cells.
- Prolymphocytes are medium-sized with dispersed chromatin and small nucleoli.
- Paraimmunoblasts are medium to large cells with round to oval nuclei, dispersed chromatin, central eosinophilic nucleoli and slightly basophilic cytoplasm.

Small Lymphocytic Lymphoma



Small Lymphocytic Lymphoma



Immunophenotype

- Express weak or dim surface IgM or IgM and IgD, CD5, CD19, CD20 (weak), CD22 (weak), CD79a, CD23, CD43, CD11c (weak).
- CD10-, cyclin D1-.
- FMC7 and CD79b negative or weak.

Immunophenotype

- Cases with unmutated Ig variable region genes are reported to be CD38+ and ZAP70+.

Immunophenotype

- Cytoplasmic Ig is detectable in about 5% of the cases.
- CD5 and CD23 are useful in distinguishing from MCL. Rarely CLL is CD23-. Rarely MCL is CD23+. Perform Cyclin D1 in CD5+/CD23- cases.
- Some cases with typical CLL morphology may have a different profile (CD5- or CD23-, FMC7+ or CD11c+, or strong sIg, or CD79b+).

Genetics

- Antigen receptor genes:
  - Ig heavy and light chain genes are rearranged. Suggestion of 2 distinct types of SLL defined by the mutational status of the IgVH genes: 40-50% show no somatic mutations of their variable region genes (naïve cells, unmutated). 50-60% have somatic mutations consistent with derivation from post-germinal center B-cells.
  - DNA sequencing shows no hypermutation if there is >98% homology with germline
  - Unmutated: poor prognosis; hypermutated: better prognosis

Genetics

- Cytogenetic abnormalities and oncogenes:
  - About 80% of the cases have abnormal karyotypes by FISH.
  - Trisomy 12 reported in 20% of cases. Have predominantly unmutated Ig variable region genes.
  - Deletions at 13q14.3 in up to 50%. Have mutations more often (Ig variable region genes).

Genetics

- Cytogenetic abnormalities and oncogenes:
  - Deletions at 11q22-23 are found in 20% of cases. Most often unmutated.
  - Deletions at 17p13 (p53 locus) are seen in 10% of cases, respectively. Most often unmutated.
  - t(11;14) and bcl-1 gene rearrangement have been reported. These cases may have been leukemic MCL and misdiagnosed as CLL.

Prognosis and predictive factors

- Clinical course is indolent, not considered to be curable with available therapy.
- Purine nucleoside analogues, such as fludarabine, may result in sustained remissions.
- 5 year OS of SLL was 51% . Overall median survival is 7 yrs.

Prognosis and predictive factors

- Transformation to high grade lymphoma (Richter syndrome) occurs in aprox. 3.5% of cases. Usually DLBCL (3%), HL (0.5%), particularly in patients treated with purine nucleotide analogues.

WHO 2016: SLL/CLL

- Cytopenias or disease-related symptoms are now insufficient to make a diagnosis of CLL with <5 x 10^9/L PB CLL cells.
- Large/confluent and/or highly proliferative proliferation centers are adverse prognostic indicators.
- Proliferation centers (PC) can have cyclin D1 expression
- In up to about 30% of CLL/SLL, PC express MYC protein, and, PCs which are large/confluent and/or have a high proliferative fraction are a significant and independent adverse prognostic indicator.

WHO 2016: Monoclonal B-cell lymphocytosis (MBL)

- MBL precedes virtually all cases of (CLL/SLL).
- Must distinguish “low-count” from “high-count” MBL.
- “low-count” MBL, defined as a PB CLL count of <0.5 x 10^9/L, must be distinguished from because low count MBL has significant differences from CLL, an extremely limited chance of progression, and does not require routine follow-up outside of standard medical care.
- In contrast, “high-count” MBL [0.5-5 x 10^9/L] requires routine/yearly follow-up, and has very similar phenotypic and genetic/molecular features as Rai stage 0 of CLL.
- The best candidates for tissue-based MBL: lymph nodes with CLL/SLL in which proliferation centers were not observed and patients in whom adenopathy was <1.5 cm based on CT scans

Hairy Cell Leukemia

Hairy Cell Leukemia

Clinical features:

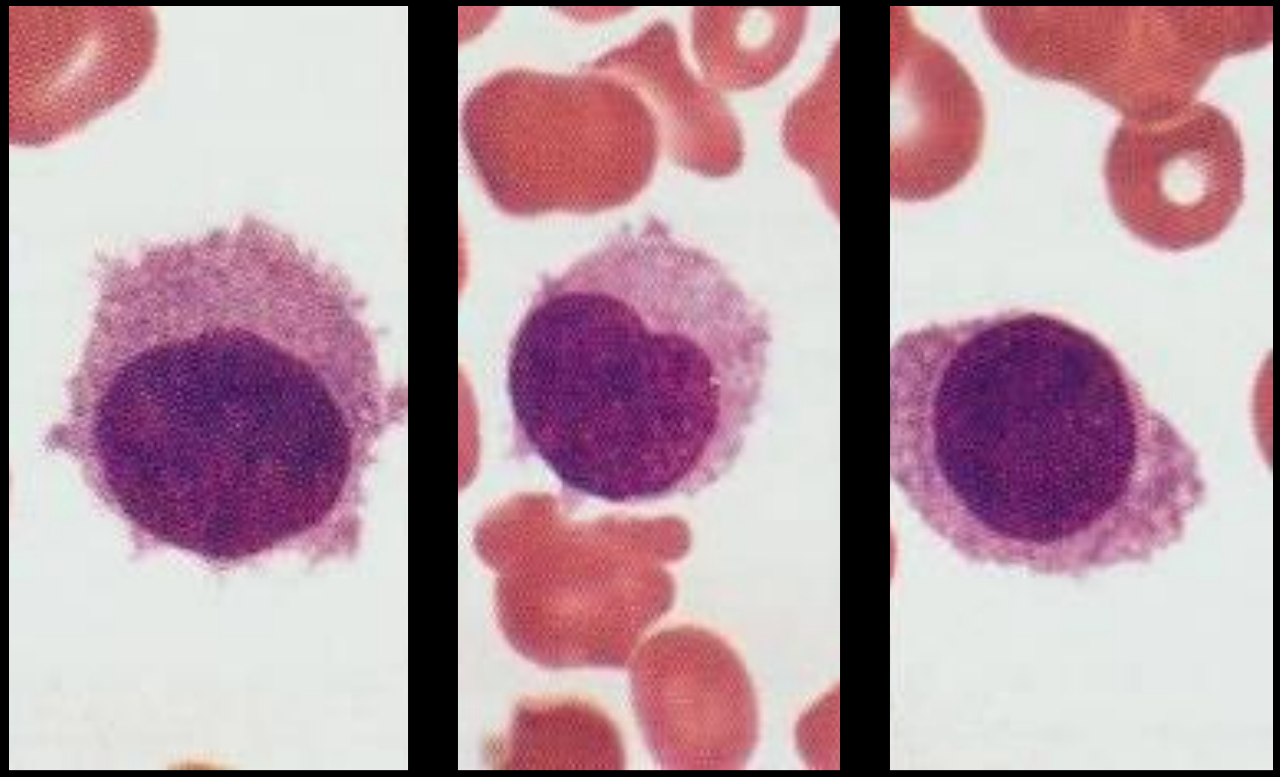
-Splenomegaly
-Pancytopenia
-Monocytopenia
-Recurrent opportunistic infections
-Vasculitis

Hairy Cell Leukemia

Cytological Features:

-Small to medium-sized
-Indented (bean-shaped) nucleus
-Homogeneous, spongy, ground-glass chromatin
-Absent or inconspicuous nucleoli
-Cytoplasm: abundant, pale blue, with circumferential "hairy" projections
-Occasional vacuoles or rod-shaped inclusions (Ribosome lamellar complexes)

Hairy Cell Leukemia



Hairy Cell Leukemia: EM

Ribosome lamellar complexes

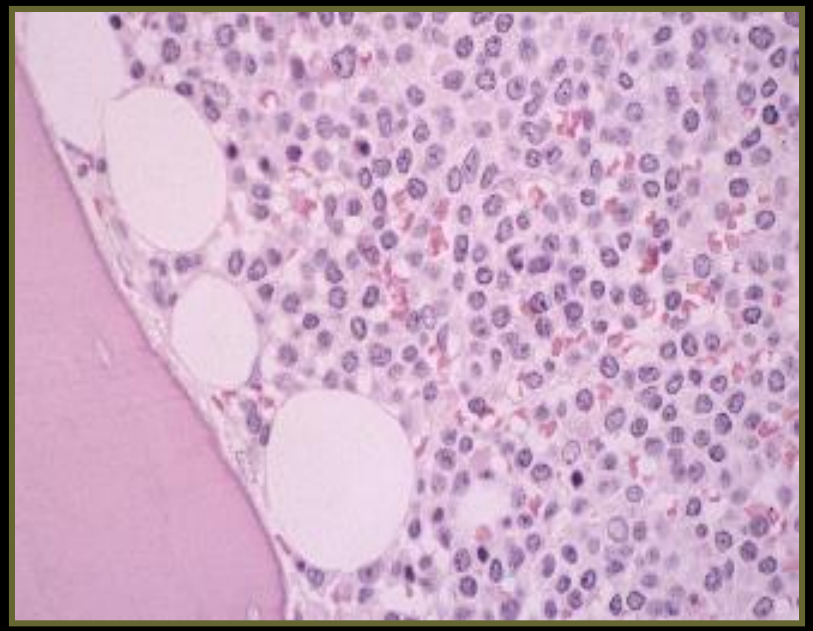
Hairy Cell Leukemia

Morphology:

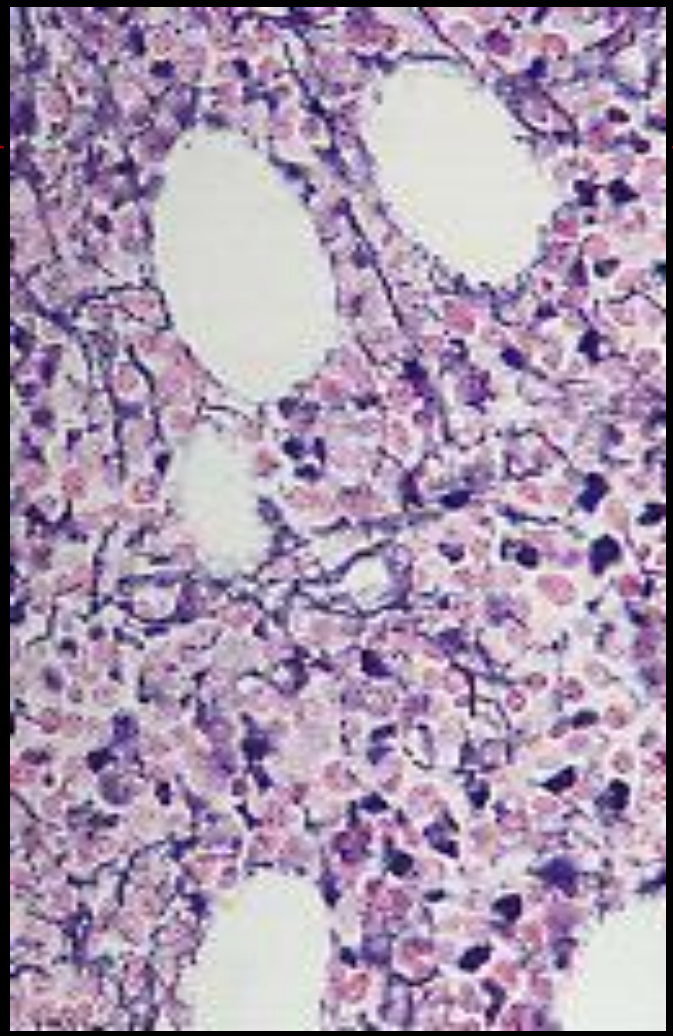
BM:

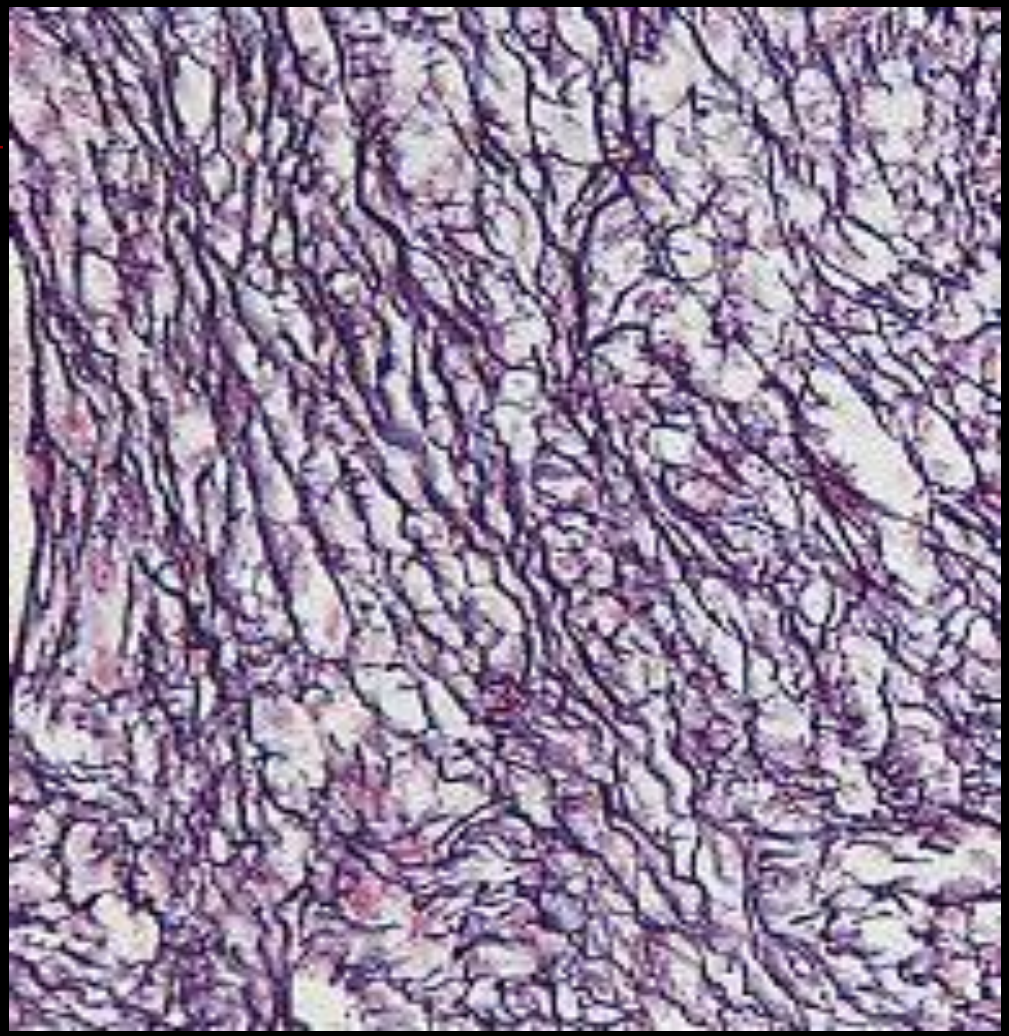
-Interstitial and patchy infiltrate
-Characteristic “fried-egg” appearance
-Variable degrees of reticulin fibrosis
-Granulocytic hypoplasia
    -Myelosuppressive cytokine production
    -Decreased growth factors

Hairy Cell Leukemia



Hairy Cell Leukemia Reticulin





Hairy Cell Leukemia

Morphology:

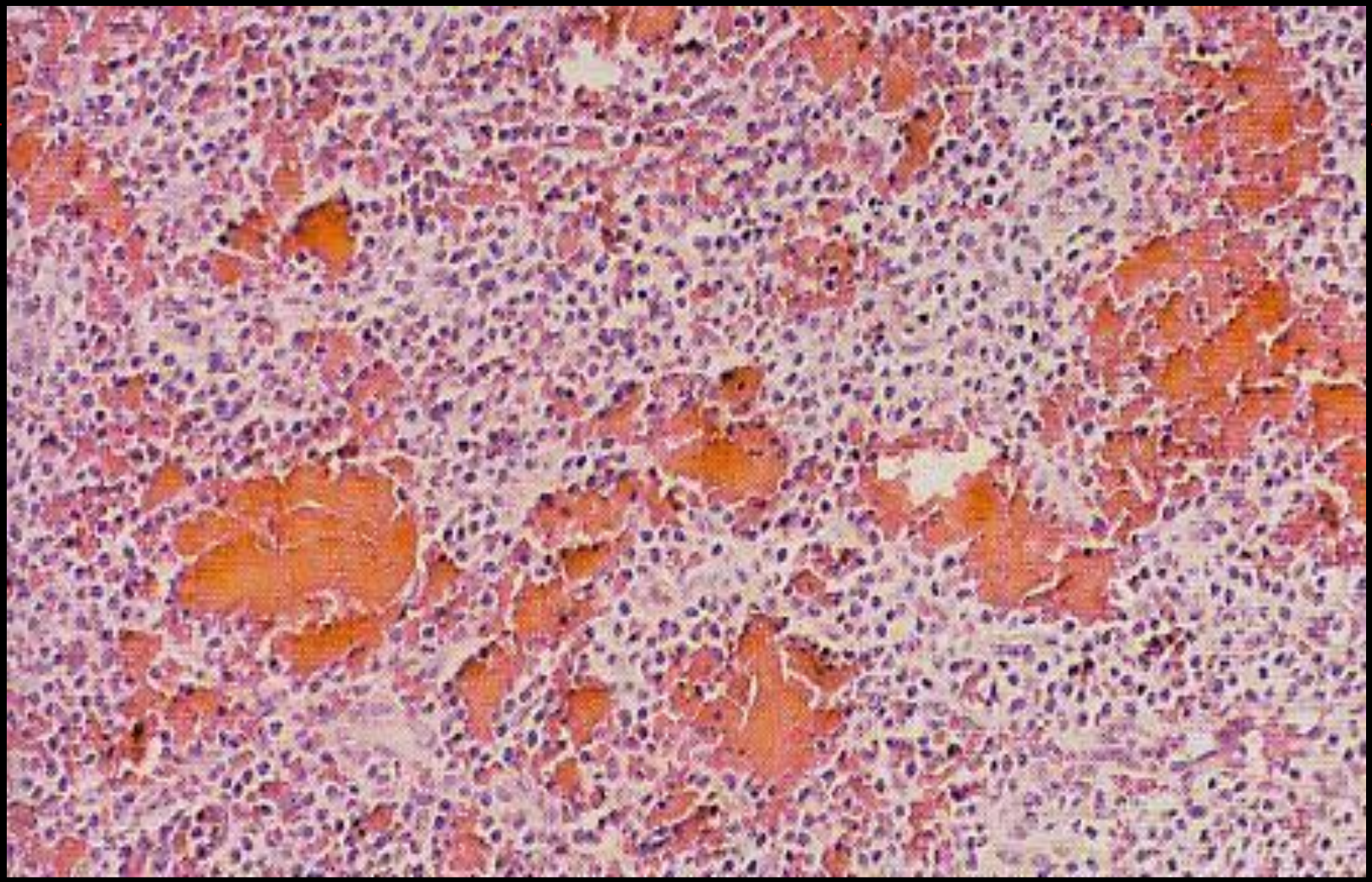
-Spleen:
- Infiltrate red pulp cord
- White pulp atrophic
- RBC lakes

-Liver: sinusoidal and portal infiltrates

-LN: paracortical, sparing of follicles

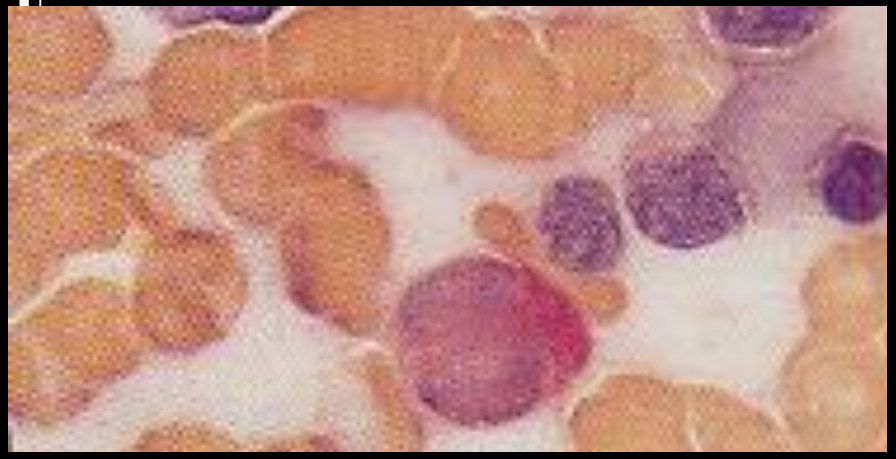
Hairy Cell Leukemia

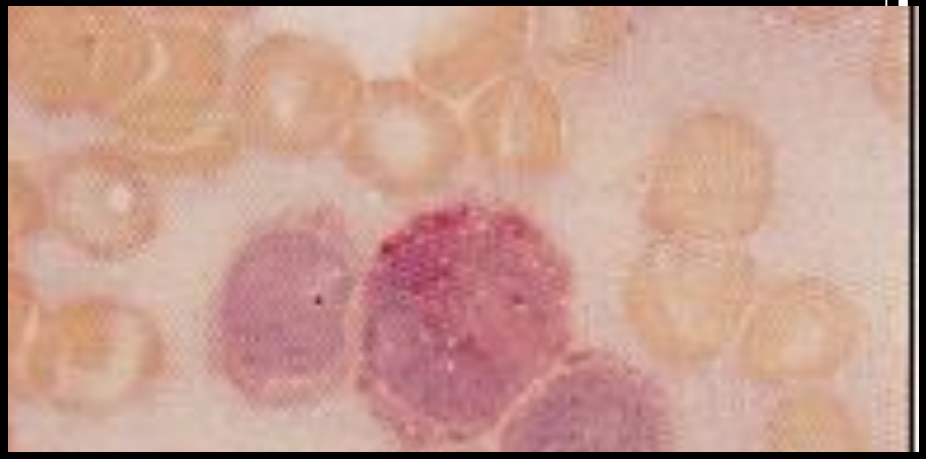
Spleen: red cell lakes

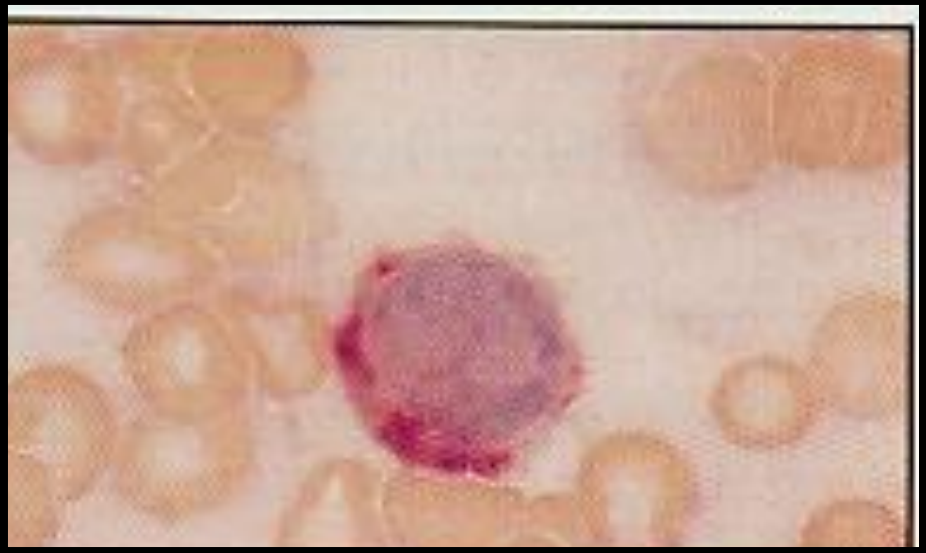


Hairy Cell Leukemia

Tartrate-resistant acid phosphatase (TRAP)







Hairy Cell Leukemia

Immunophenotype:

Positive:

-Surface sIg: M, +/- D, G, A

-CD19, CD20, CD79a, CD22

-CD11c, CD22, CD25, CD103, FMC7

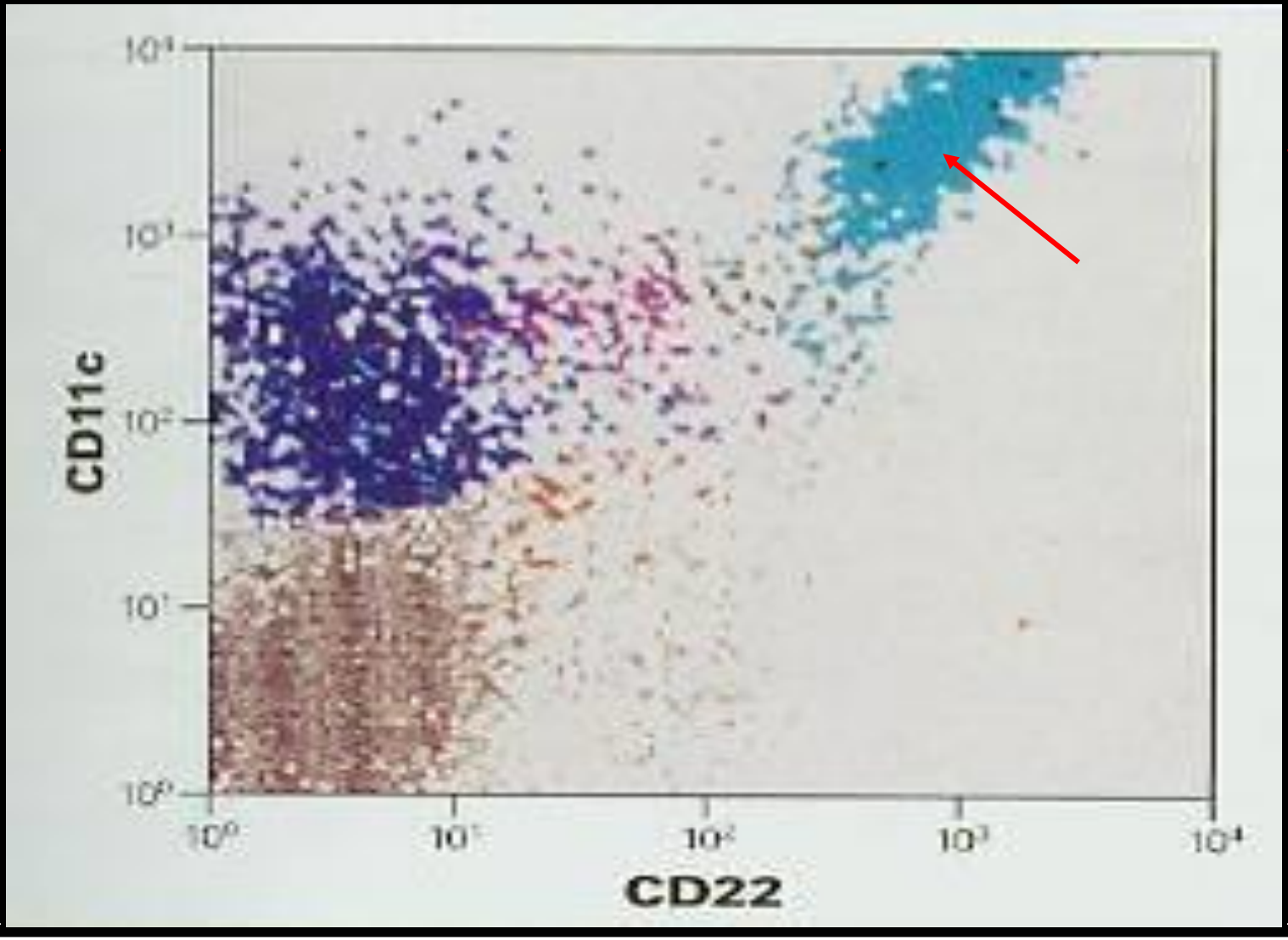
Tissue sections: DBA.44: strong (nonspecific)

Negative:

-CD5, CD10,CD23,CD79b

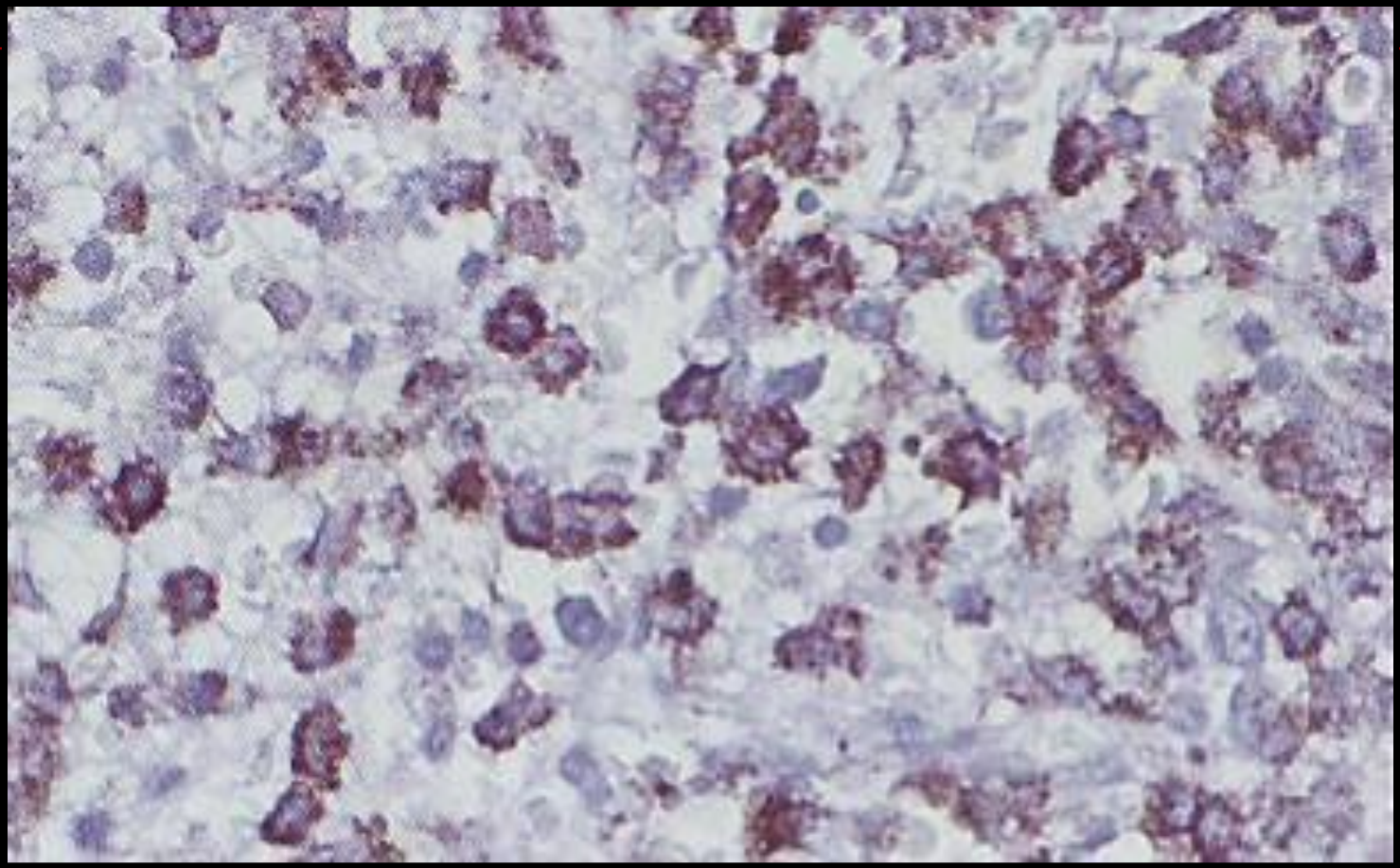
Hairy Cell Leukemia

Flow



Hairy Cell Leukemia

DBA.44



Hairy Cell Leukemia

Cytogenetics and oncogenes:

-No specific cytogenetic abnormality
-Cyclin D1 overexpressed 50-70%
-No t(11;14) or bcl1 rearrangement

Hairy Cell Leukemia

Prognosis and predictive factors:

-Cause of death: infection, rare transformation

-Treatment :

-Purine nucleoside analogues: treatment of choice
CR 75-90%,
4 year survival: 80%

-Deoxycoformycin (Pentostatin)

-2-Chlorodeoxyadenosine (2 CdA)

-Splenectomy: only if symptomatic

-Interferon-alfa 2b: CR 5-30%

WHO 2016: Hairy Cell Leukemia

- Almost all cases of hairy cell leukemia (HCL) have BRAF V600E mutations
- HCL without BRAF V600E mutations and half of HCL-variant (HCL-v): have mutations in MAP2K1 which encodes MEK1 (which is downstream of BRAF)

Plasma Cell Myeloma

WHO criteria for the diagnosis of Symptomatic Plasma Cell Myeloma

- Bone marrow clonal plasma cells (usu >10%) or plasmacytoma on biopsy
- Presence of a monoclonal protein (M-component) in serum or urine; usu IgG>30 g/L (3 g/dL), IgA >25 g/L (2.5 g/dL) or urine light chain >1 g/24 hr
- Related organ or tissue impairment (CRAB: hypercalcemia, renal insufficiency, anemia, bone lesions)

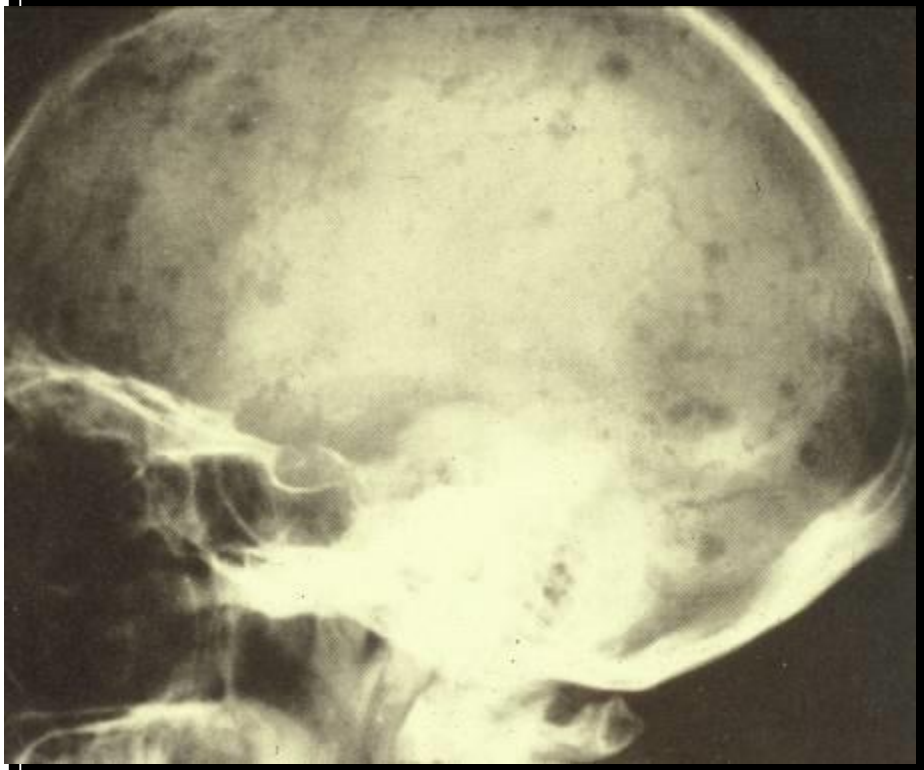
WHO criteria for the diagnosis of Asymptomatic (smoldering) myeloma:

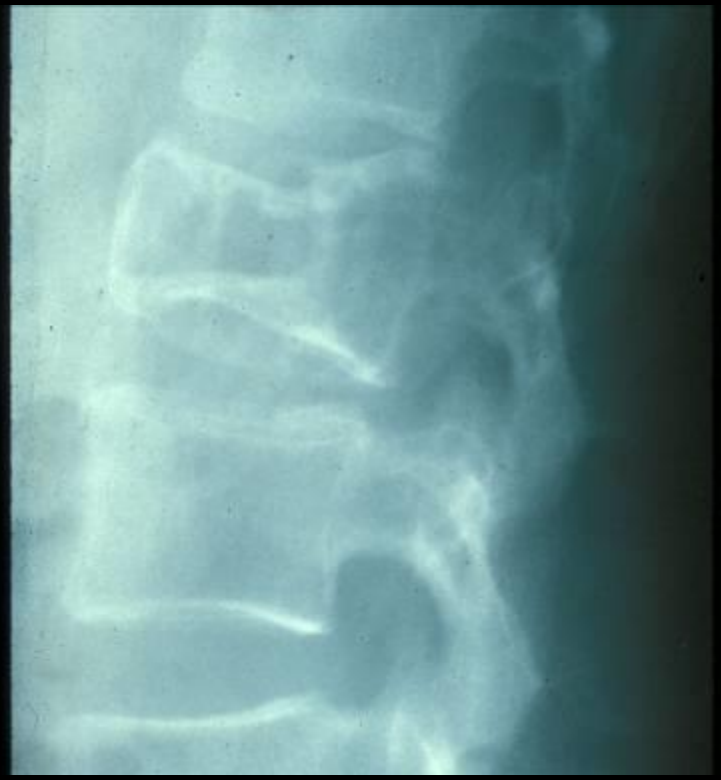
- Presence of a monoclonal protein (M-component) in serum
  IgG>30 g/L, IgA >25 g/L

  AND/OR: Clonal plasma cells in BM >10%

- No related organ impairment (no CRAB)

Lytic lesions (punched out lesions) on X Ray

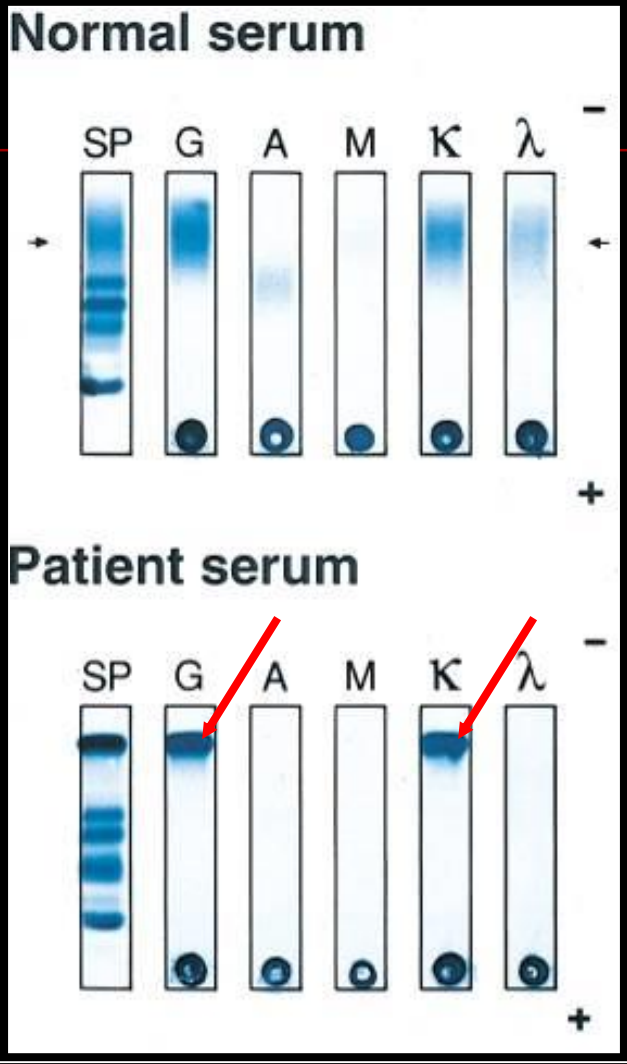




Clinical features

- Monoclonal IgG accounts for 50% and IgA for 20% of cases.
- A monoclonal light chain (Bence-Jones protein) is found in the serum of 15% of patients.
- IgD accounts for 2% of cases while bi-clonal gammopathies are found in 1% of cases.

Serum Protein Immunofixation



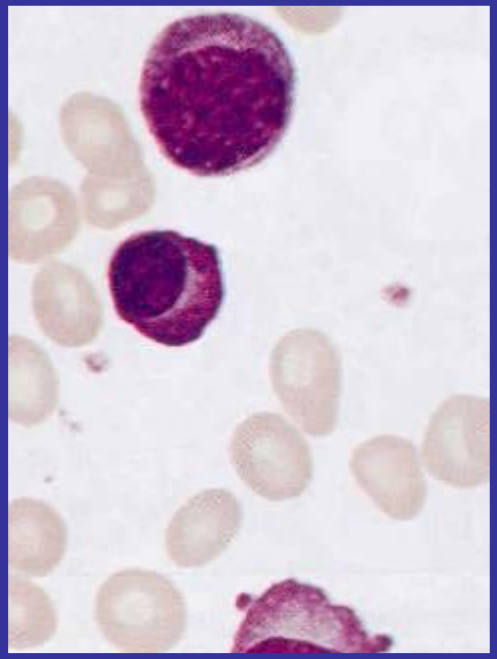
Clinical variants

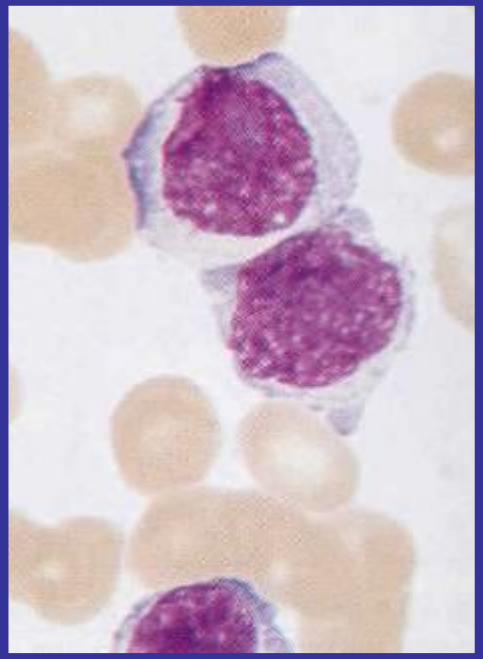
- Non-secretory myeloma:
  - May have a lower level of plasmacytosis and less depression of normal Ig.
  - Due to the lack of serum or urine monoclonal Ig, diagnosis can be missed, unless one performs
    - IHC analysis of BM biopsy with cytoplasmic K/L or other markers of plasma cells.
    - Flow cytometry analysis of aspirate with cytoplasmic K/L

Clinical features

- Plasma cell leukemia (PCL):
  - PB involvement occurs rarely in plasma cell myeloma (2%) and is defined as circulating PB plasma cells (and plasmacytoid cells) $>2x10^3$/ml or 20% of PB leukocytes.
  - It may occur at the time of diagnosis (primary PCL) or evolve as a terminal complication during the course of a plasma cell myeloma (secondary PCL).

Plasma cell leukemia

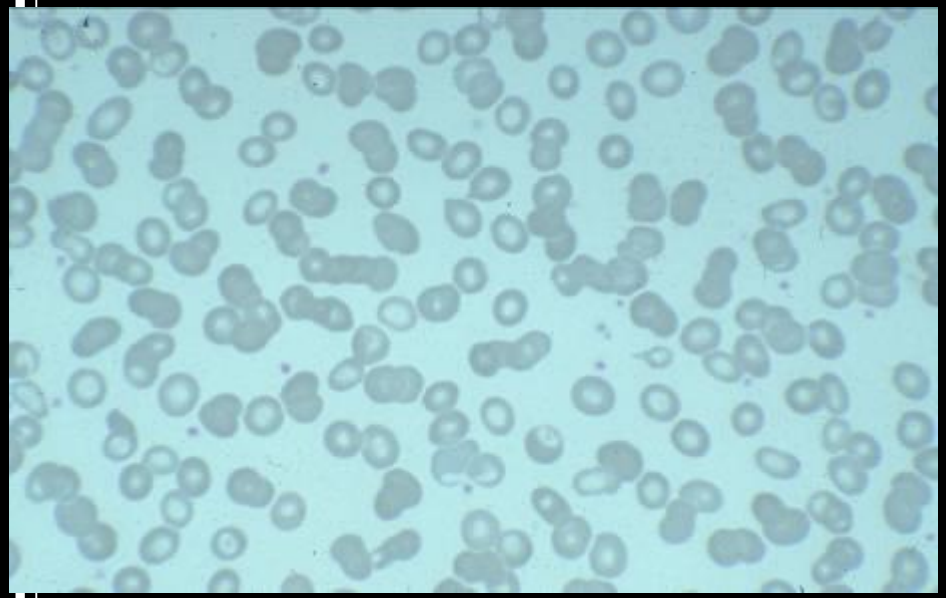


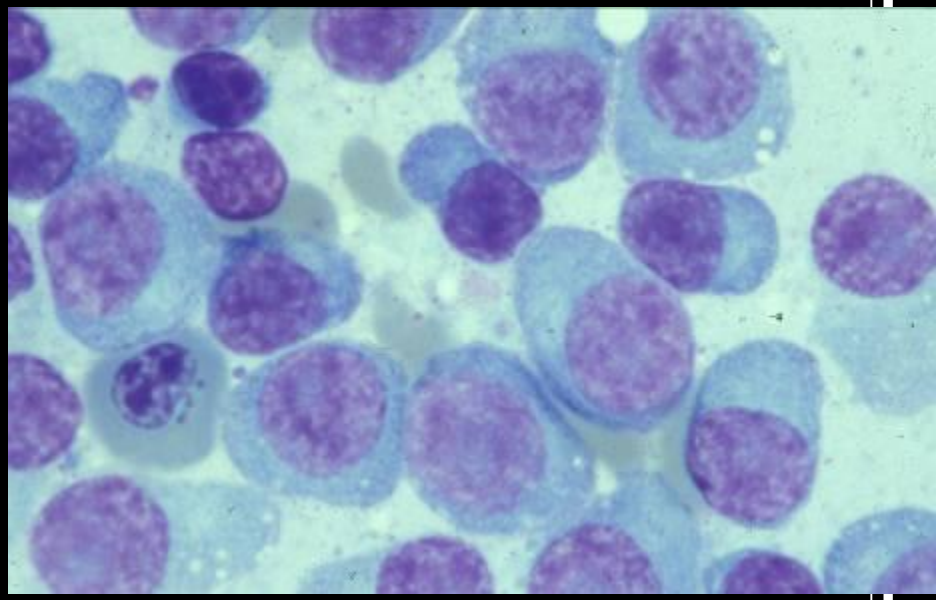


Morphology

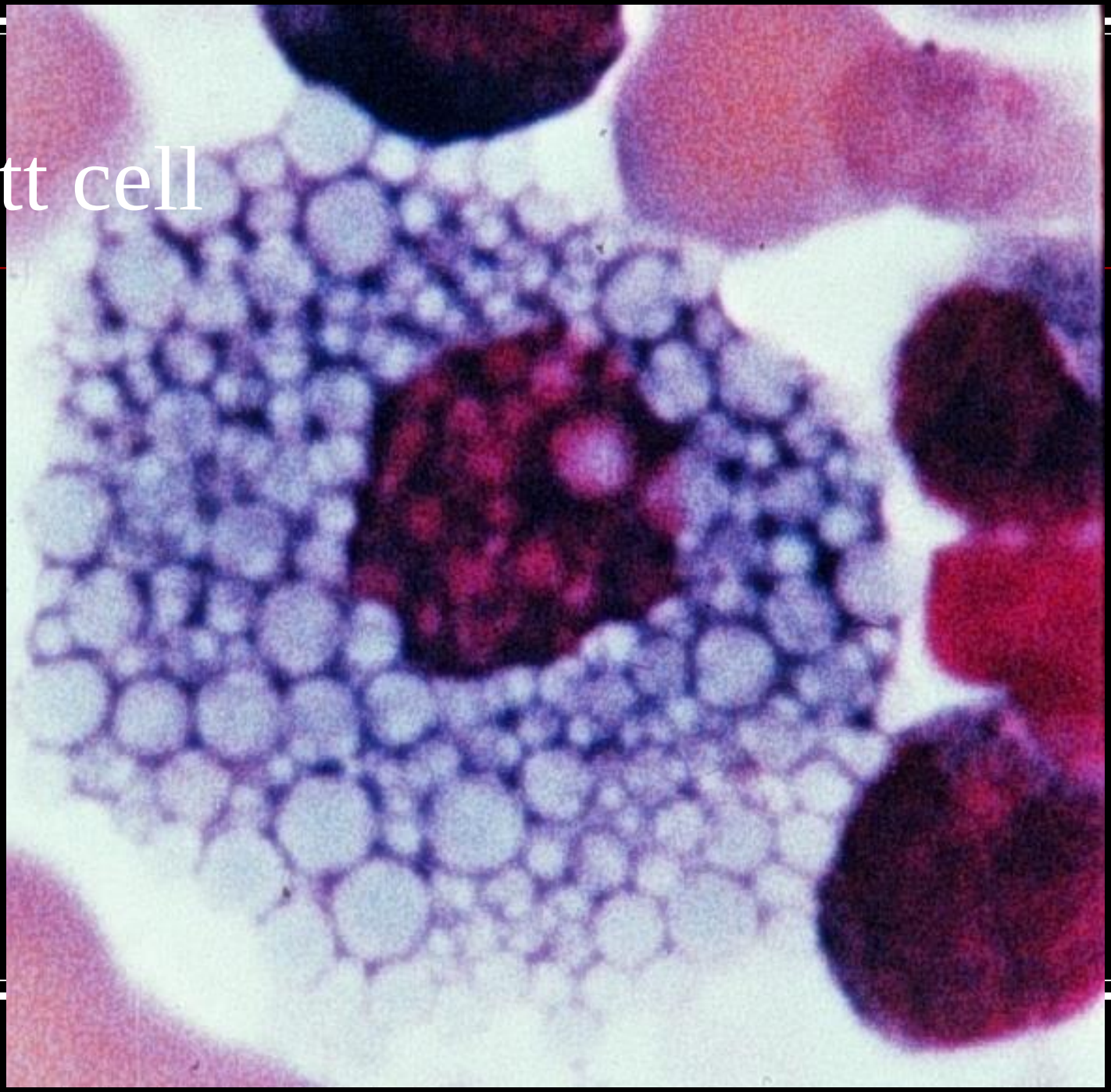
- BM aspiration:
  - Myeloma plasma cells vary from mature to immature, pleomorphic or anaplastic forms.
  - The mature plasma cells are usually oval, with a round eccentric nucleus with “spoke-wheel” or “clock-face” chromatin without nucleoli, with abundant basophilic cytoplasm and marked perinuclear hof.
  - Multinucleated, polylobated, pleomorphic plasma cells also occur.

Multiple Myeloma

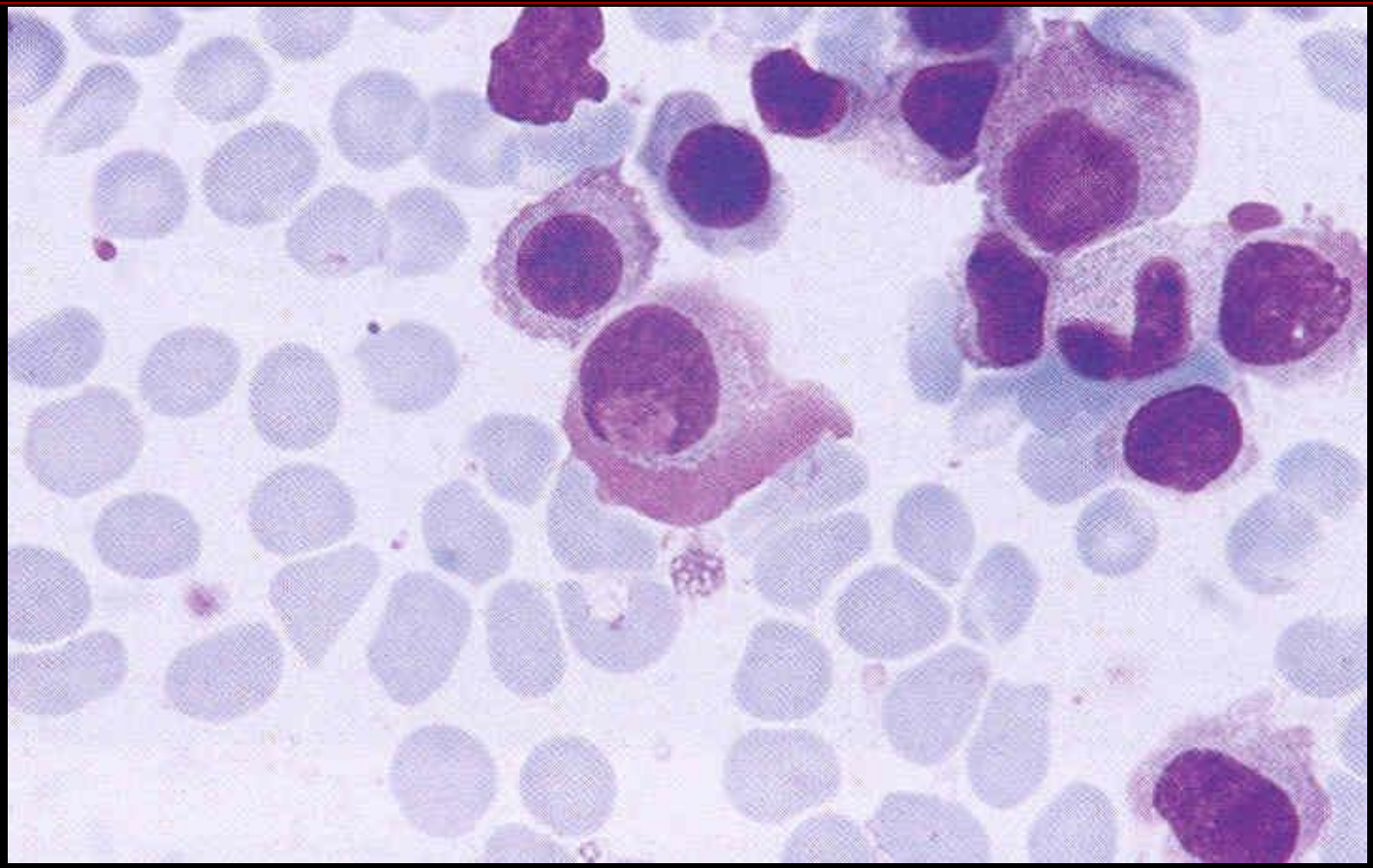




Mott cell

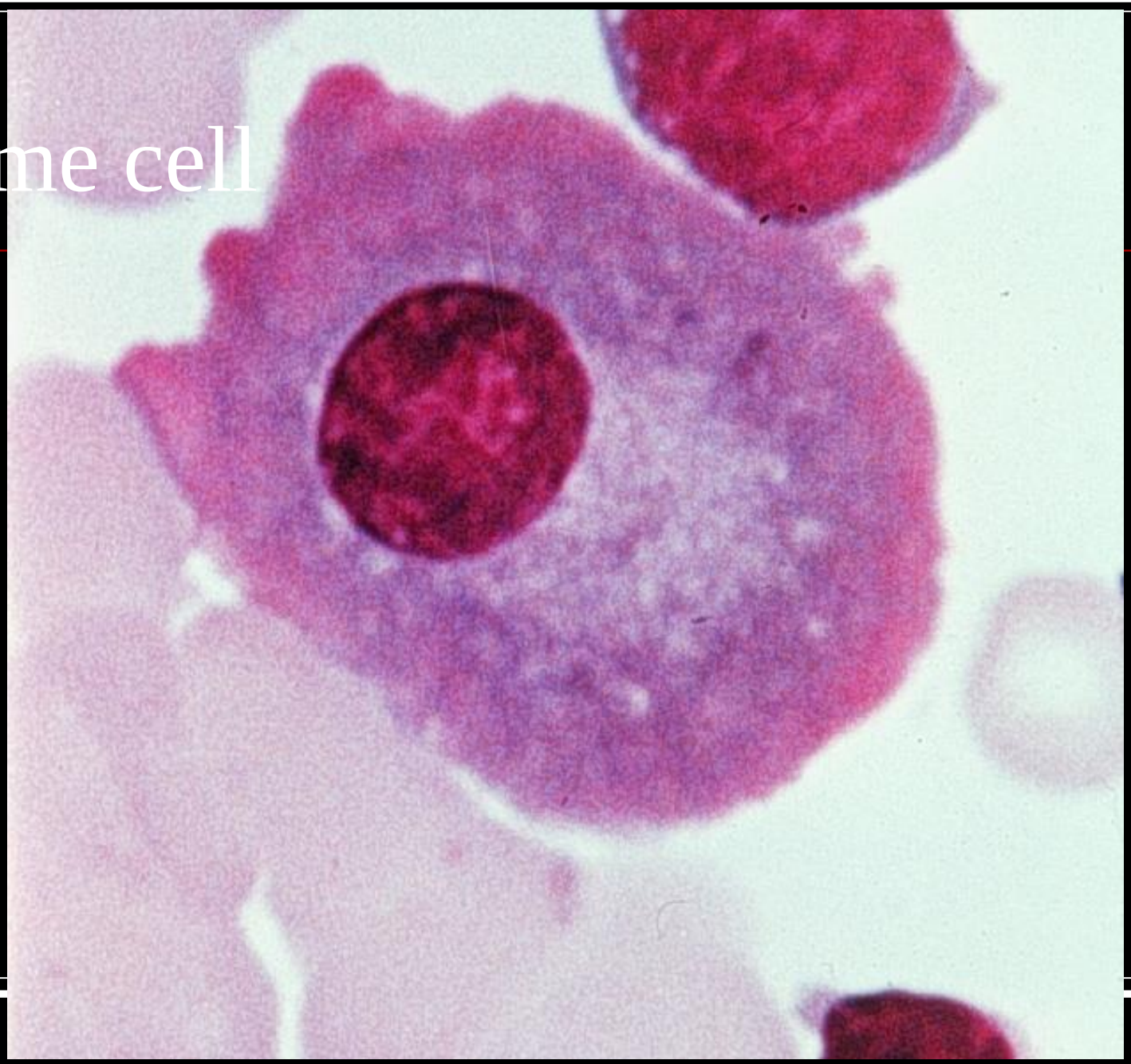


Dutcher bodies



Intranuclear inclusions

Flame cell



Immunophenotype

- Malignant plasma cells express monotypic cytoplasmic Ig and lack surface Ig. The Ig is most commonly IgG, occassionally IgA, and rarely IgD, IgE, or IgM. In 85% of cases, both heavy and light chains are produced; in 15% light chain only (Bence-Jones myeloma).
- Most but not all lack CD19 and CD20.
- CD38 and CD79a expressed in the majority of cases.

Immunophenotype

- In contrast with normal plasma cells that express CD19 and lack CD56/58, myeloma cells lack CD19 and express CD56/58.
- Collagen-1 binding proteoglycan syndecan-1 (CD138) is found in most cases of myeloma.
- VS38c is typically expressed.

Genetics: Summary on Prognosis

- Unfavorable:
  -Hypoploidy
  -del 13, del 17p
  -t(4;14), t(14;16), t(14;20)
- Favorable:
  -Hyperploidy
  -t(11;14), t(6;14)

Prognosis and predictive factors

- Plasma cell myeloma is usually incurable, with a median survival of 3-4 years, and 10% survival at 10 years and more .
- Myeloma pts with normal renal function experienced a 37-month median survival versus 8 months for those with renal insufficiency.
- Other prognostic factors include Hgb, calcium, lytic bone lesions, amount of the M component, and beta-2-microglobulin (B_2M).

Precursor lesion:Monoclonal gammopathy of undetermined significance (MGUS)

- MGUS denotes de presence of a M-component in persons without evidence of plasma cell myeloma, WM, primary amyloidosis (AL), or other related disorders.
- It was considered to be benign and often called benign monoclonal gammopathy. However, a proportion of pts will evolve to myeloma or amyloidosis, so MGUS is considered more appropriate.

Precursor lesion:Monoclonal gammopathy of undetermined significance (MGUS)

- Pts are asymptomatic (no CRAB). The M-component is discovered unexpectedly during serum protein electrophoresis (typ < 30 g/L).
- Prevalence of MGUS is 1% in pts >50 y/o and 3% in those >70 y/o.
- About 75% of MGUS paraproteins are IgG; 15% IgM; 10% IgA.

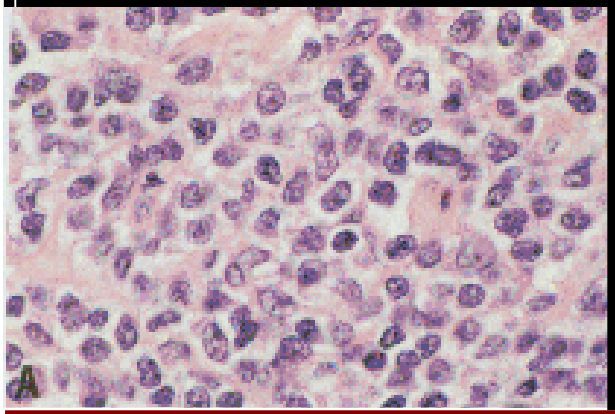
Precursor lesion:Monoclonal gammopathy of undetermined significance (MGUS)

- Approximately 25% pts with MGUS develop plasma cell myeloma, primary amyloidosis, macroglobulinemia, or other lymphoproliferative diseases after follow-up for more than 20 yrs.
- The risk for malignant transformation is unrelated to the type of of M-protein.

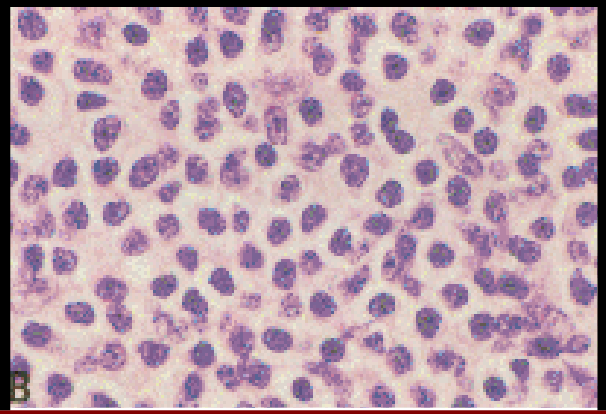
Marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

WHO MALT lymphoma

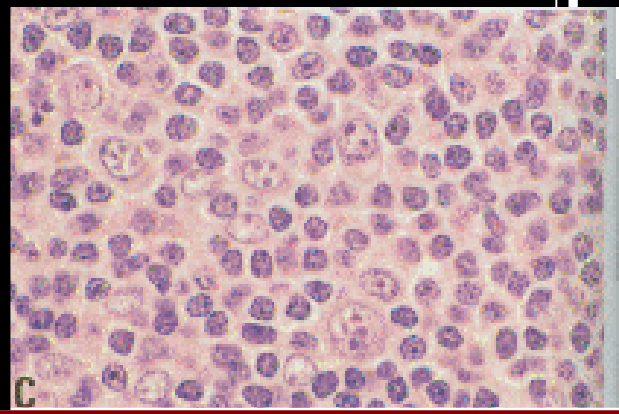
- Definition: extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is an extranodal lymphoma comprising morphologically heterogeneous small B-cells including marginal zone (centrocyte-like) cells, cells resembling monocytoid cells, small lymphocytes, and scattered immunoblasts and centroblast-like cells.



Centrocytes



Monocytoid lymphocytes



Small lymphocytes with scattered centroblasts

Precursor lesions/conditions

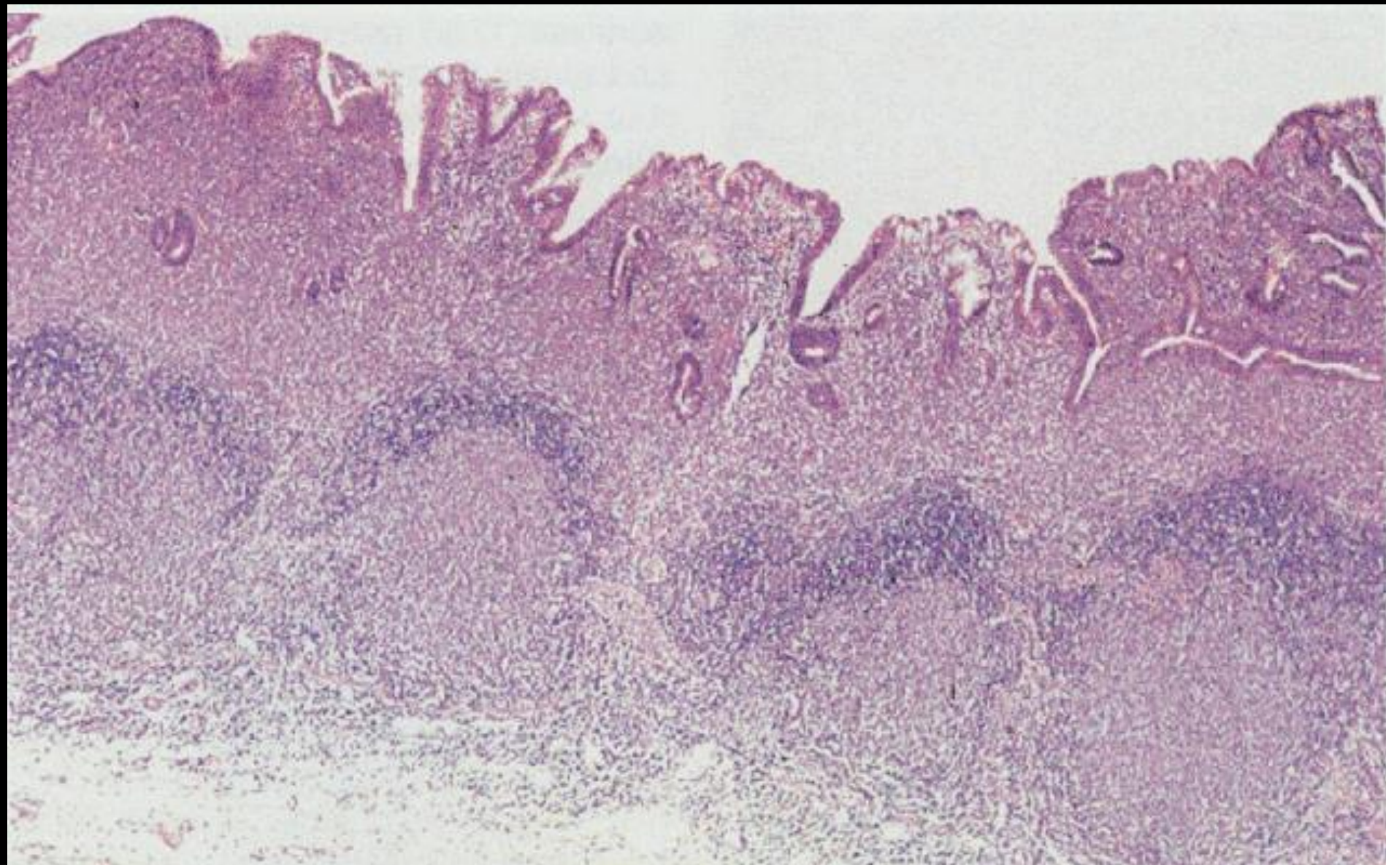
- In many cases of MALT lymphoma, there is a history of chronic inflammatory, often autoimmune disorders that result in accumulation of extranodal lymphoid tissue. Examples: H. pylori associated chronic gastritis, Sjögren syndrome or Hashimoto thyroiditis.

Sites of involvement

- The gastrointestinal (GI) tract is the most common site of MALT lymphoma, comprising 50% of all cases, and within the GI tract, the stomach is the most common location (85%). The small intestine and colon are typically involved in pts. with immunoproliferative small intestinal disease (IPSID).

Morphology

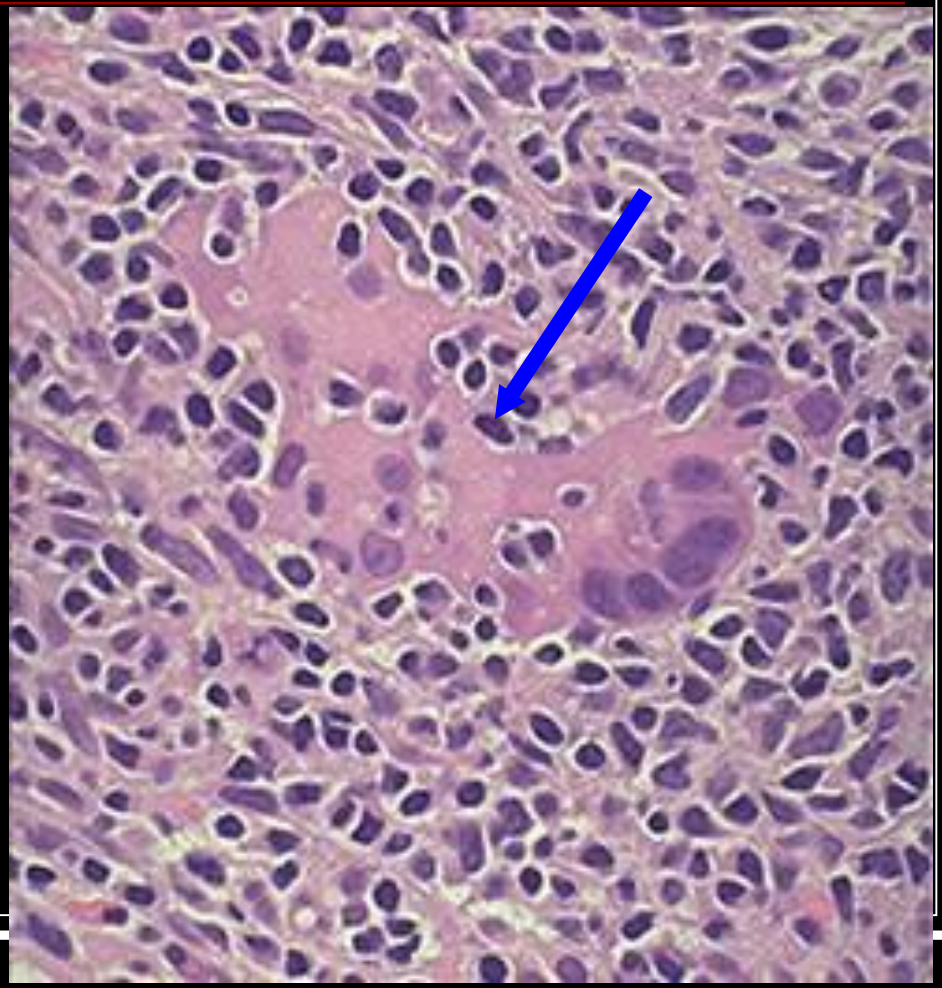
- The lymphoma cells infiltrate around reactive B-cell follicles, external to a preserved follicle mantle, in a marginal zone distribution and spread out to form larger confluent areas which eventually overrun some or most of the follicles.



Gastric MALT lymphoma, tumor cells colonize the follicles

Microscopic findings

- Lymphoepithelial lesions:
  - ≥3 marginal zone lymphocytes with distortion or distruction of epithelium



Immunophenotype

- The tumour cells are CD20+, CD79a+, CD5-, CD10-, CD23-, CD43+/-, CD11c+/- (weak).
- CD21 and CD35: staining for these antigens typically reveals expanded meshworks of FDCs corresponding to colonised follicles.

Immunophenotype

- There is no specific marker for MALT lymphoma at present.
- The demonstration of Ig light chain restriction is important in the differential diagnosis with benign lymphoid infiltrates.

Immunophenotype

- In the differential Dx with other small B-cell lymphomas, absence of the characteristic markers for those neoplasms is important:
  - Lack of CD5 is ueful in distinction from mantle cell and small lymphocytic lymphoma,
  - Lack of CD10 is ueful in distinction from FL.

Genetics

- Genetic abnormalities and oncogenes:
  - Trisomy 3 is found in 60% and t(11;18)(q21;q21) has been observed in 25-50% of the cases.
  - In contrast, t(11;18) is not found in primary large B cell gastric lymphoma. Recently, analysis of the t(11;18) breakpoint has shown fusion of the apoptosis-inhibitor gene API2 to a novel gene at 18q21, named MLT.
  - Neither t(14;18) nor t(11;14) is present.

Prognosis and predictive factors

- MALT lymphomas run an indolent natural course and are slow to disseminate.
- The tumours are sensitive to radiation therapy, and local treatment may be followed by prolonged disease-free intervals.
- In H.pylori-associated gastric MALT lymphoma, protracted remissions may be induced by antibiotic therapy for H. pylori.
- Cases with the t(11;18)(q21;q21) appear to be resistant to H.pylori eradication therapy.

Follicular Lymphoma

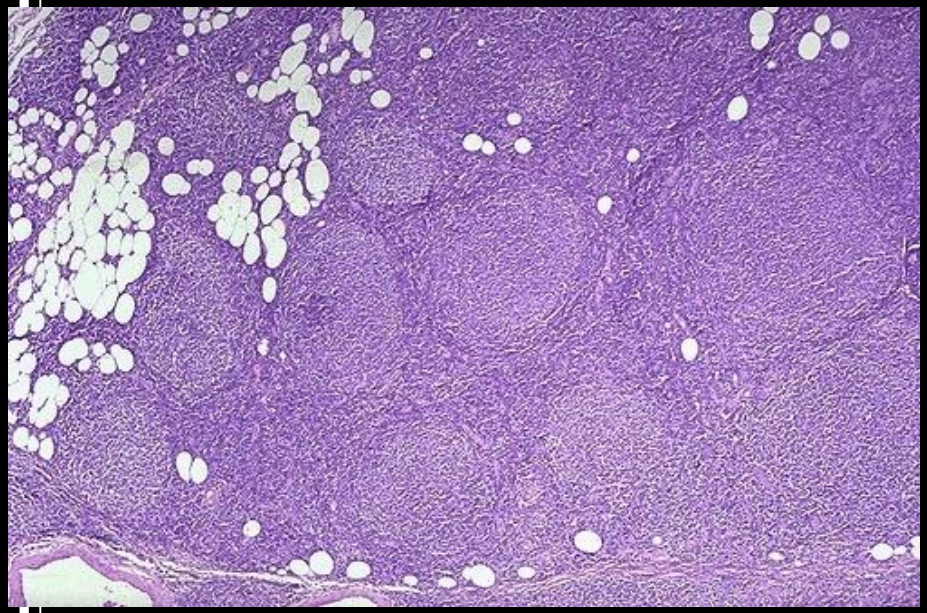
Follicular Lymphoma, Definition

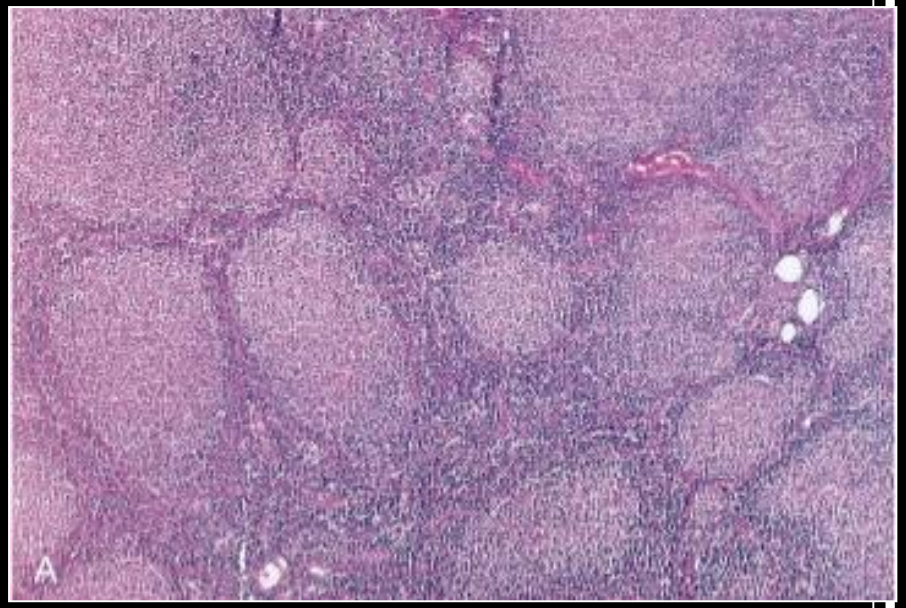
- Neoplasm of follicular centre B cells, with at least a partially follicular pattern. The lymphoma cells consist of two types: centrocytes (cleaved follicle centre B cells), and centroblasts (non-cleaved follicle centre B cells)
- Predominantly adults
- 70% of low grade lymphomas
- Most patients have widespread disease at diagnosis (bone marrow involvement in 40-50%)
- Patients are usually asymptomatic at diagnosis, except for lymph node enlargement

Follicular Lymphoma, Morphology

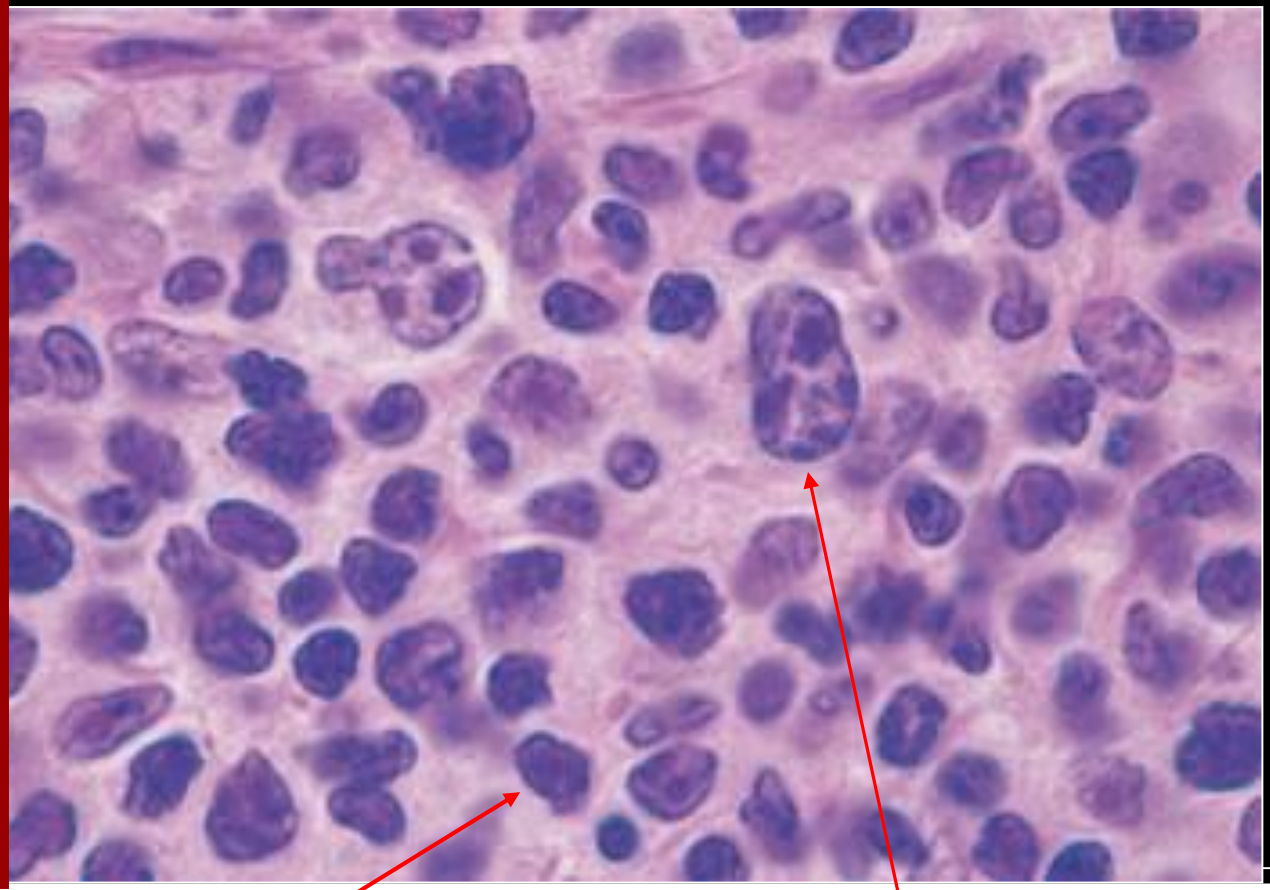
- Follicular architecture
- Neoplastic follicles are: poorly defined and closely packed, no mantle zone, no polarization, no tingible-body macrophages

Follicular Lymphoma



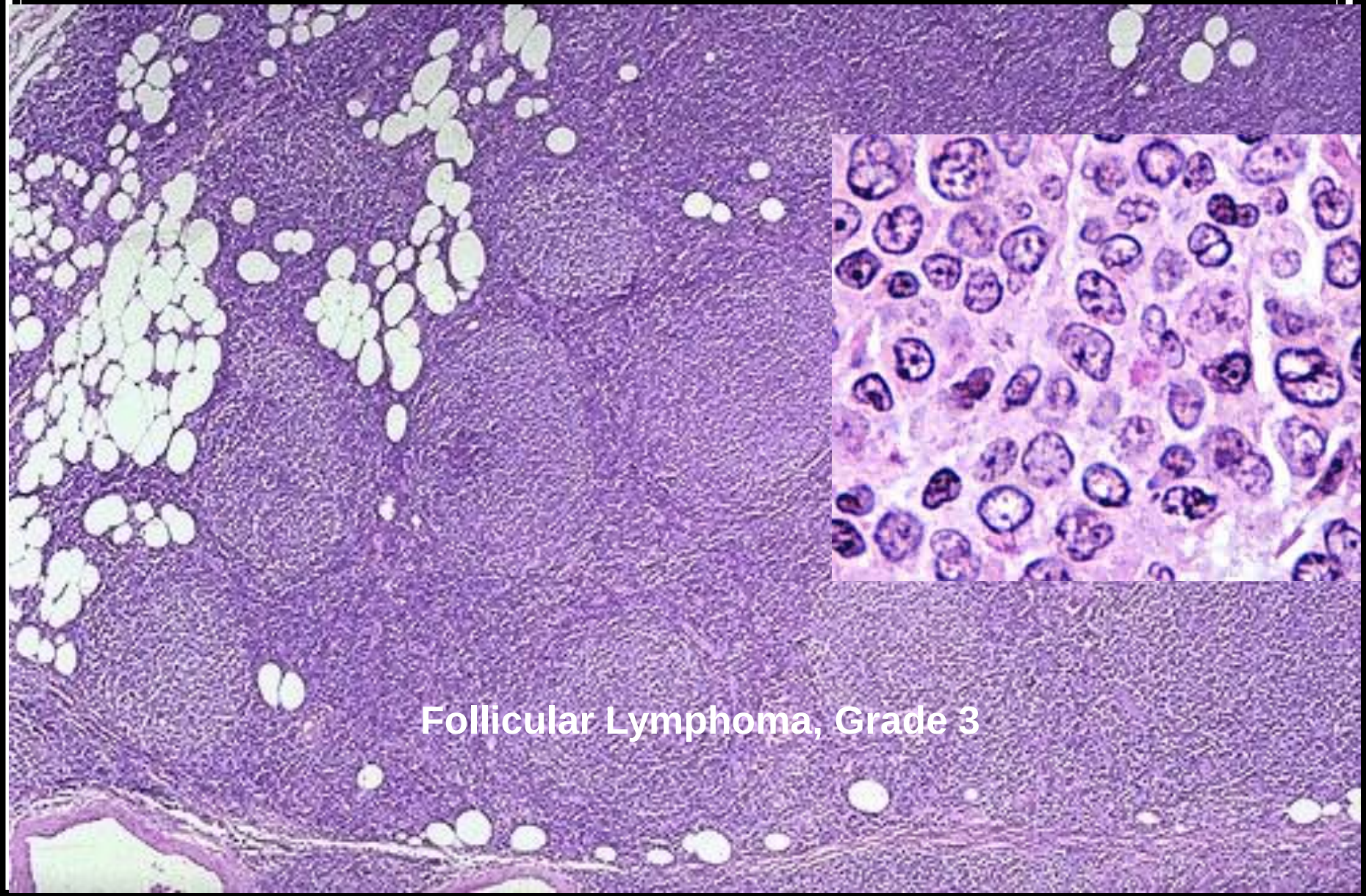


Follicular Lyphoma



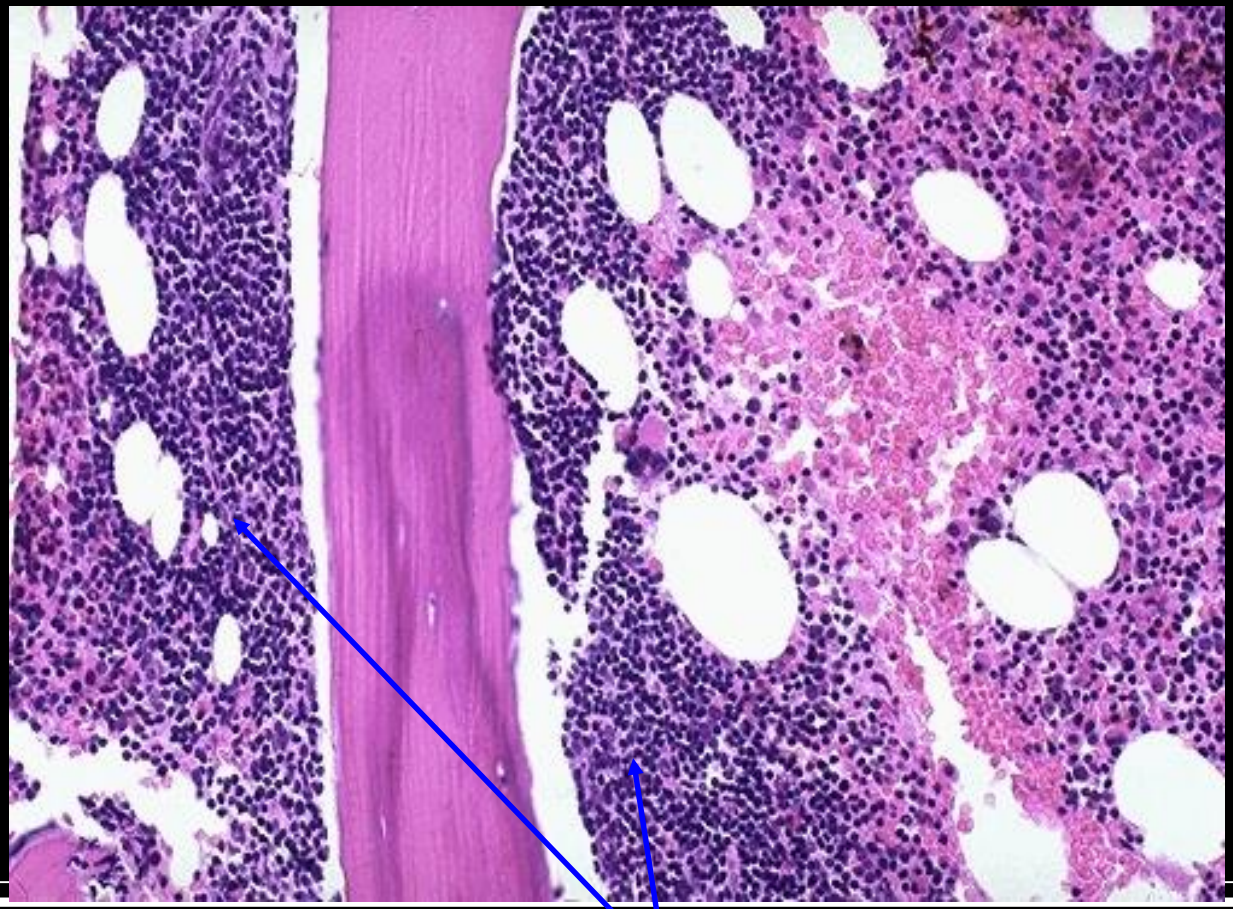
Follicular Lymphoma, Grading

- Grade 1: 0-5 centroblasts / hpf
- Grade 2: 6-15 centroblasts / hpf
- Grade 3: > 15 centroblasts / hpf
- 3a: Some centrocytes present
- 3b: Solid sheets of centroblasts



Follicular Lymphoma, Grade 3

Follicular Lymphoma in Bone Marrow

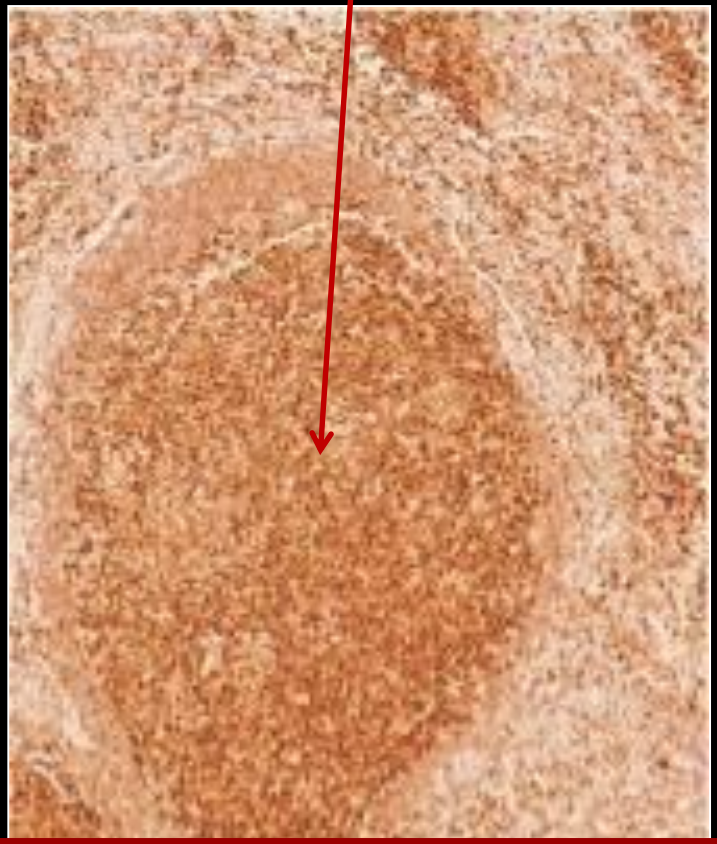


Follicular Lymphoma, Immunophenotype

- Surface Ig +
- Express B-cell antigens: CD19, CD20, CD22, CD79a
- CD 10 +
- BCL-2 + (can help distinguishing from reactive follicles; however, grade 3 and cutaneous type may be negative)
- BCL 6 +

BCL2 Staining

Use in distinguishing reactive follicular hyperplasia from follicular lymphoma



Follicular Lymphoma, Pattern

- Follicular > 75% follicular
- Follicular and diffuse 25-75% follicular
- Minimally follicular < 25% follicular

Follicular Lymphoma, Genetics

- t(14;18) (q32;q21)
- BCL 2 rearrangement, present is 70-95% cases
- Confers a survival advantage on B cells; failure to switch off BCL 2 during blast transformation may contribute to development of lymphoma by preventing apoptosis

Follicular Lymphoma, Prognosis

- Grades 1 and 2: indolent
- Grade 3: aggressive; treatment as for DLBCL, 25-33% of cases progress to DLBCL

Diffuse Large B-Cell Lymphoma

DLBCL: Definition

- Diffuse proliferation of large neoplastic B lymphoid cells
- Nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte

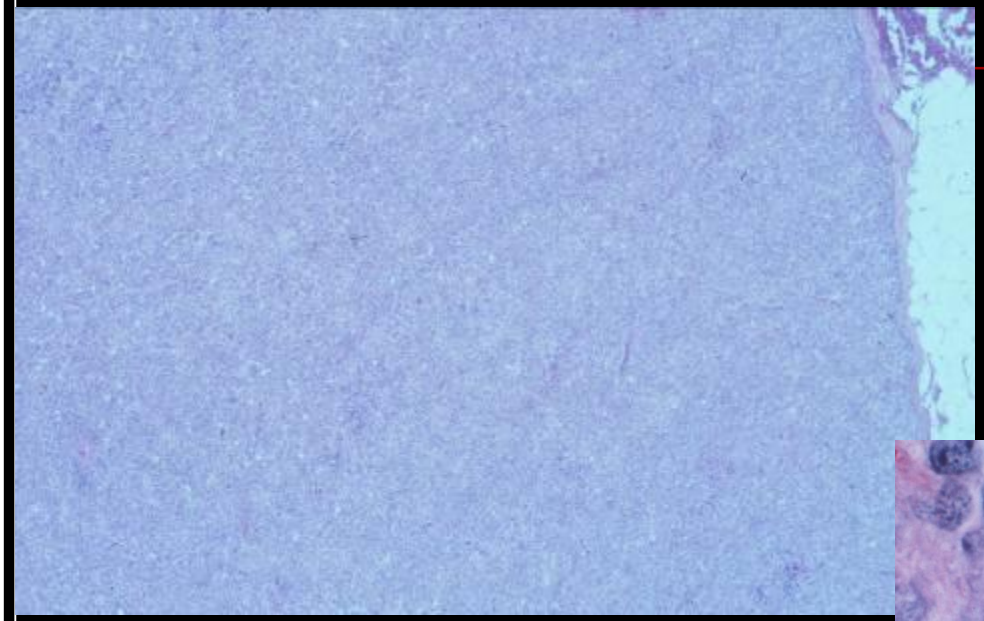
DLBCL: Epidemiology

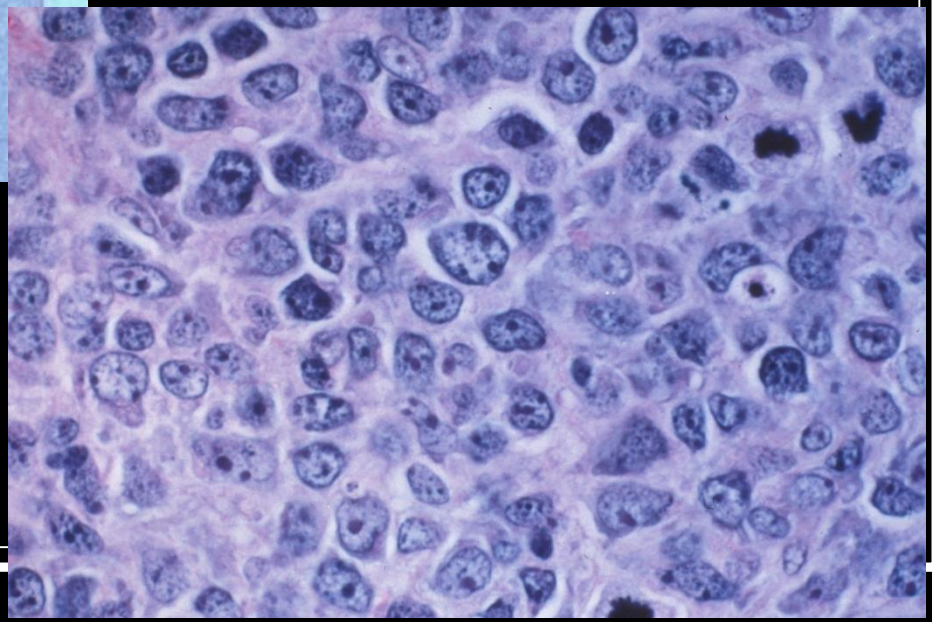
- 30-40% of adult non-Hodgkin lymphomas in western countries; higher proportion in developing countries
- Broad age range (median: 7th decade) including children
- Slightly more common in man
- Increasing incidence, independent of HIV

DLBCL: Morphology

- Typically replaces the normal architecture in a diffuse pattern
- LN involvement may be complete, partial, interfollicular, or, less commonly sinusoidal
- The perinodal soft tissue is often infiltrated; broad or fine bands of sclerosis may be observed

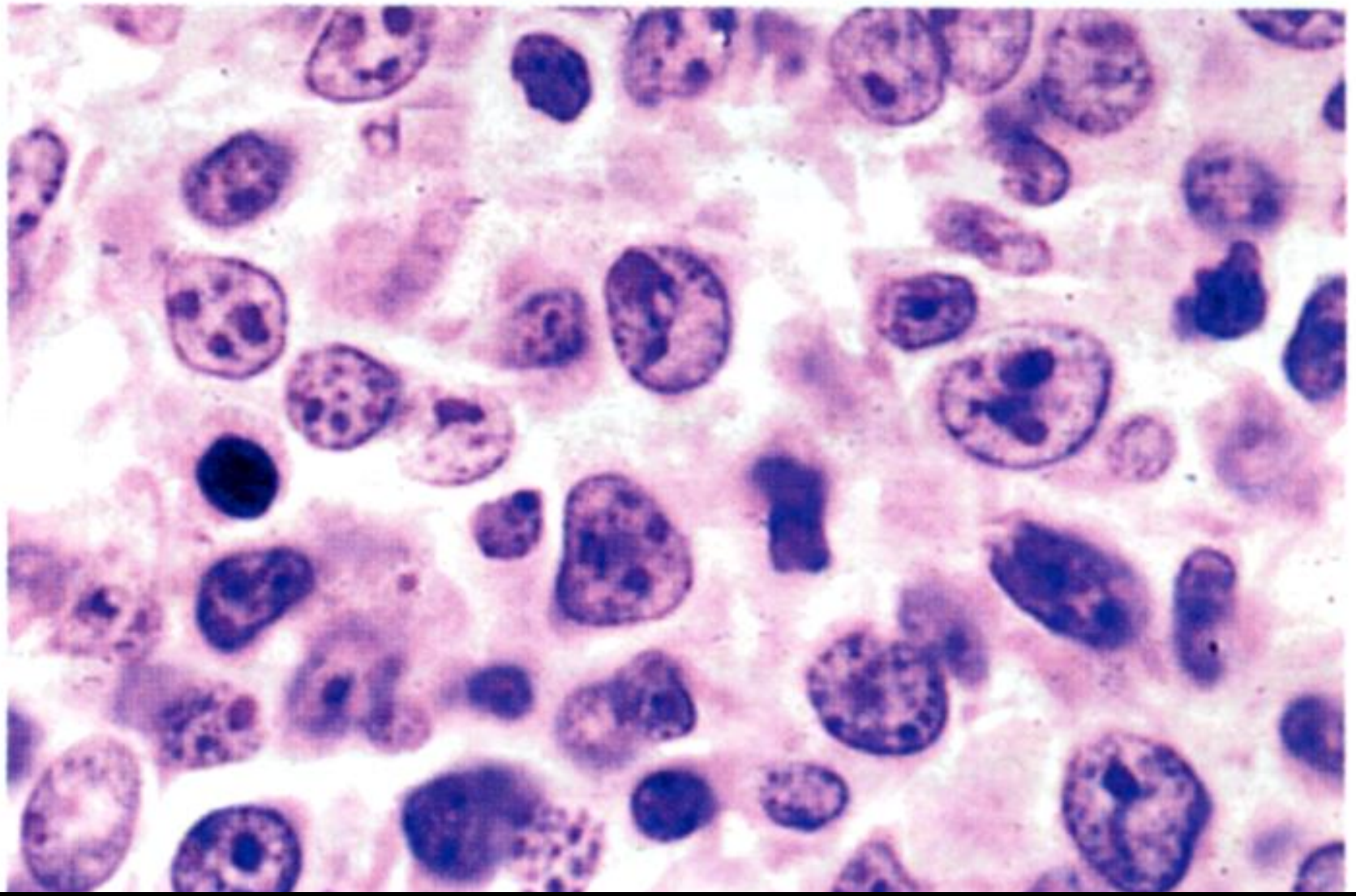
Diffuse Large Cell Lymphoma





Morphologic Variants
Centroblastic

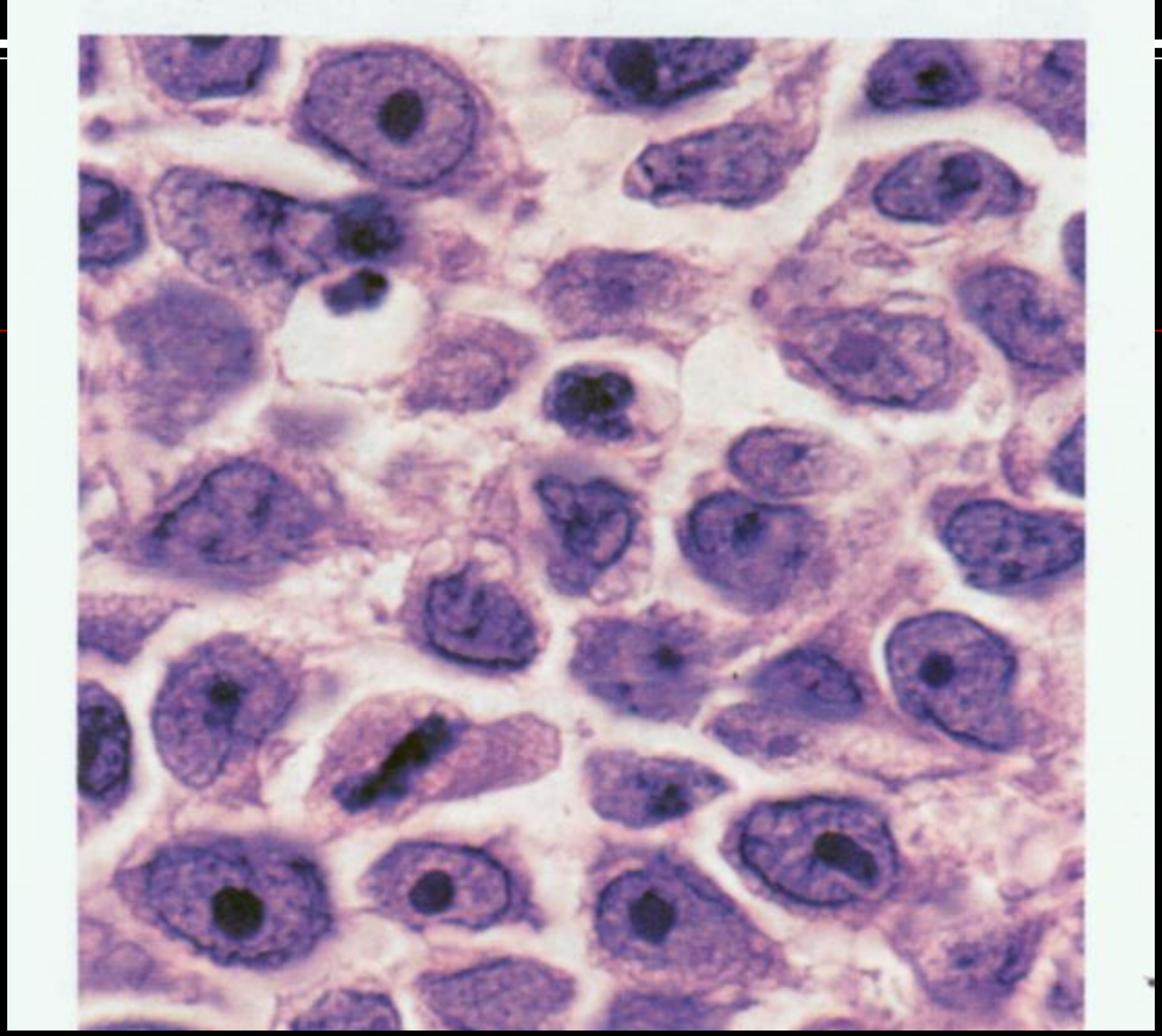
- Medium to large cells with oval to round, vesicular nuclei with fine chromatin and 2-4 nucleoli. The cytoplasm is generally scanty
- May have a monomorphic or polymorphic appearance.
- Cells may be multilobated. Centroblasts may be admixed with some immunoblasts



DLBCL, Centroblastic variant

Morphologic Variants
Immunoblastic

- Immunoblasts > 90%, with a single centrally located nucleolus and an appreciable amount of basophilic cytoplasm
- Centroblasts <10%
- Plasmacytoid differentiation may be present
- Clinical and/or immunophenotypic findings may be essential in differentiating from extra-medullary involvement by a plasmablastic variant of plasma cell myeloma



DLBCL, Immunoblastic variant

DLBCL: Immunophenotype

- Express pan-B markers (CD19, CD20, CD22, and CD79a), but may lack one or more
- Surface/cyto Ig (lgM> IgG>lgA). Cyto Ig is often seen in cases with plasmacytic differentiation
- CD30: vast majority of anaplastic LBCL and occasional non-anaplastic cases
- CD5+ in 10% and CD10+ 25-50%. CD5+ DLBCL are negative for cyclin D1 (vs blastoid MCL). CD5+ DLBCL may arise *de novo* rather than as progression of SLL/CLL

DLBCL: Immunophenotype

- BCL2+ in 30-50%
- BCL6+ in a very high proportion of cases
- P53 expression, usually associated with *TP53* mutations, in a minority of cases
- Plasma cell-associated markers such as syndecan (CD 138) in a minority of cases
- Ki-67+ is usually high (>40%) and may be greater than 90%

DLBCL: Genetics

- Most cases have rearranged Ig H and L chain genes and show somatic mutations in the variable regions
- t(14:18) occurs in 20-30%
- Up to 30% show abnormalities of the 3q27 involving BCL6
- *MYC* rearrangement is uncommon
- Many cases exhibit complex cytogenetic abnormalities
- EBV+ is more common in cases associated with immunodeficiency

DLBCL: Genetics

- DNA microarrays identified two major molecular categories with gene expression patterns suggestive of different stages of B-cell development
- One type had an expression profile characteristic of germinal center (GC) B-cells, whereas the other type had a profile similar to that of *in vitro* activated peripheral blood B-cells (ABC)

WHO 2016: DLBCL, NOS

• Distinction of germinal center (GC) vs activate B cells (ABC) type is required with use of immunohistochemical algorithm acceptable (Hans'). This may affect therapy.

	CD10	Bcl-6	MUM-1
GC	+		
GC	-	+	-
ABC	-	+	+
ABC	-	-	

• EBV(+) DLBCL, NOS : this term replaces EBV+ DLBCL of the elderly because it may occur in younger patients.

High-grade B-cell lymphoma (HGBL), with MYC and BCL2 and/or BCL6 translocations

- The old “B-cell lymphoma, unclassifiable,with features intermediate between DLBCL and Burkitt Lymphoma” (BCLU)”-> now designated HGBL,with MYC and BCL2 and/or BCL6 rearrangements (“double-/triple-hit” lymphomas)
- A consensus has not yet been reached to provide specific guidelines as to which LBCL should have fluorescence in situ hybridization studies. Some believe that all DLBCL should have genetic studies for the detection of MYC, BCL2, and BCL6 rearrangements, whereas others would limit them, for example, to cases with a GC phenotype and/or high-grade morphology or to cases with >40% MYC(+) cells

BURKITT LYMPHOMA

Epidemiology

- Endemic BL: This variant occurs in equatorial Africa representing the most common malignancy of childhood
- Peak incidence at 4 to 7 years
- Male to female ratio of 2 to 1
- BL is also endemic in Papua, New Guinea

Epidemiology

- Sporadic BL: seen throughout the world, mainly in children and young adults
- The incidence is low, 1-2% of all lymphomas in Western Europe and in USA
- BL accounts for approx. 30 to 50% of childhood lymphomas
- Median age in adult pts is 30 years
- Male to female ratio is about 3 to 1
- In some parts of the world, e.g. in South America and North Africa, the incidence is intermediate between sporadic and endemic variants

Epidemiology

- Immunodeficiency associated BL: Seen primarily associated with HIV infection
- EBV is identified in 25-40% of the cases
- BL is less often seen in other immunodeficiency states

Sites of Involvement

- Extranodal sites are most often involved
- In all three variants pts are at risk for CNS involvement
- In endemic BL, the jaws and other facial bones are the site of presentation in about 50% of the cases
- In sporadic BL, the majority of cases present with abdominal masses
- In immunodeficiency-associated BL, nodal and bone marrow involvement are common

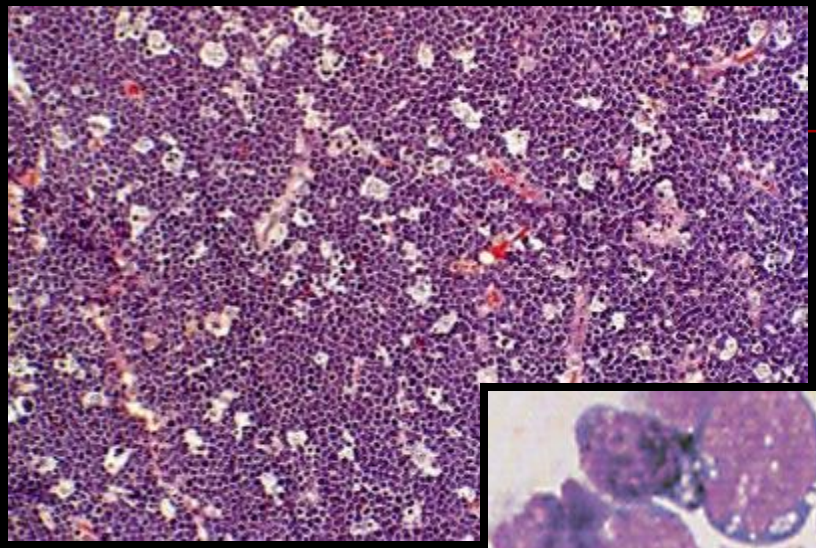
Morphology

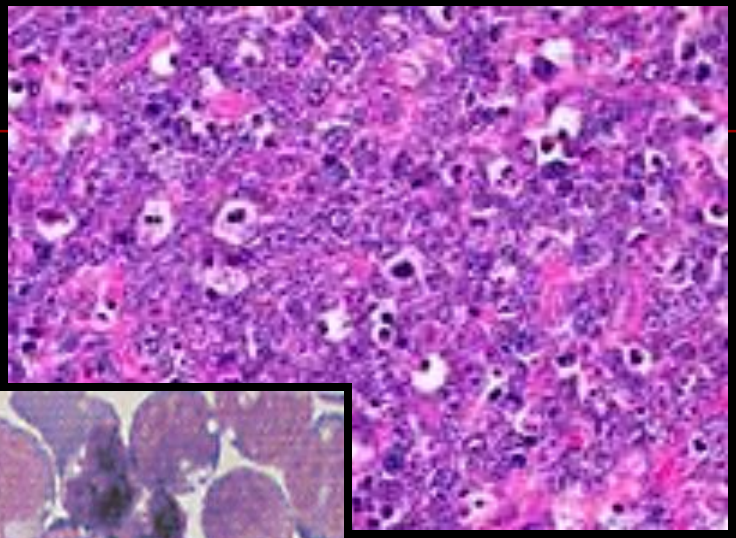
- Medium-sized cells show a diffuse monotonous pattern of infiltration
- Sometimes after fixation the cells exhibit squared off borders of retracted cytoplasm and may appear cohesive
- The nuclei is round with clumpled chromatin
- The nuclei contain multiple basophilic medium-sized, centrally located nucleoli

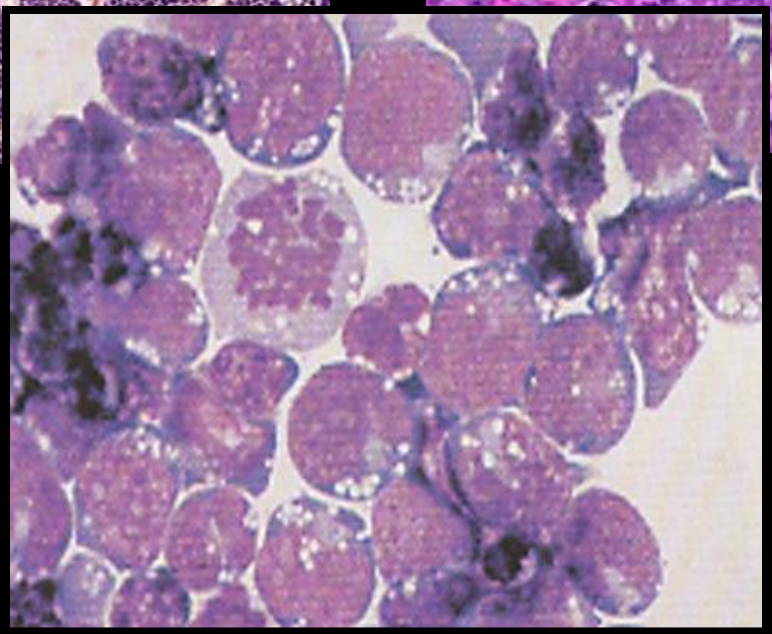
Morphology

- The cytoplasm is deeply basophilic and usually contains lipid vacuoles
- The tumor has an extremely high proliferation rate (many mitotic figures)
- High rate of spontaneous cell death
- A “starry sky” pattern is usually present
- The nuclei of the tumor cells approximate in size those of the admixed starry-sky histiocytes

Burkitt Lymphoma







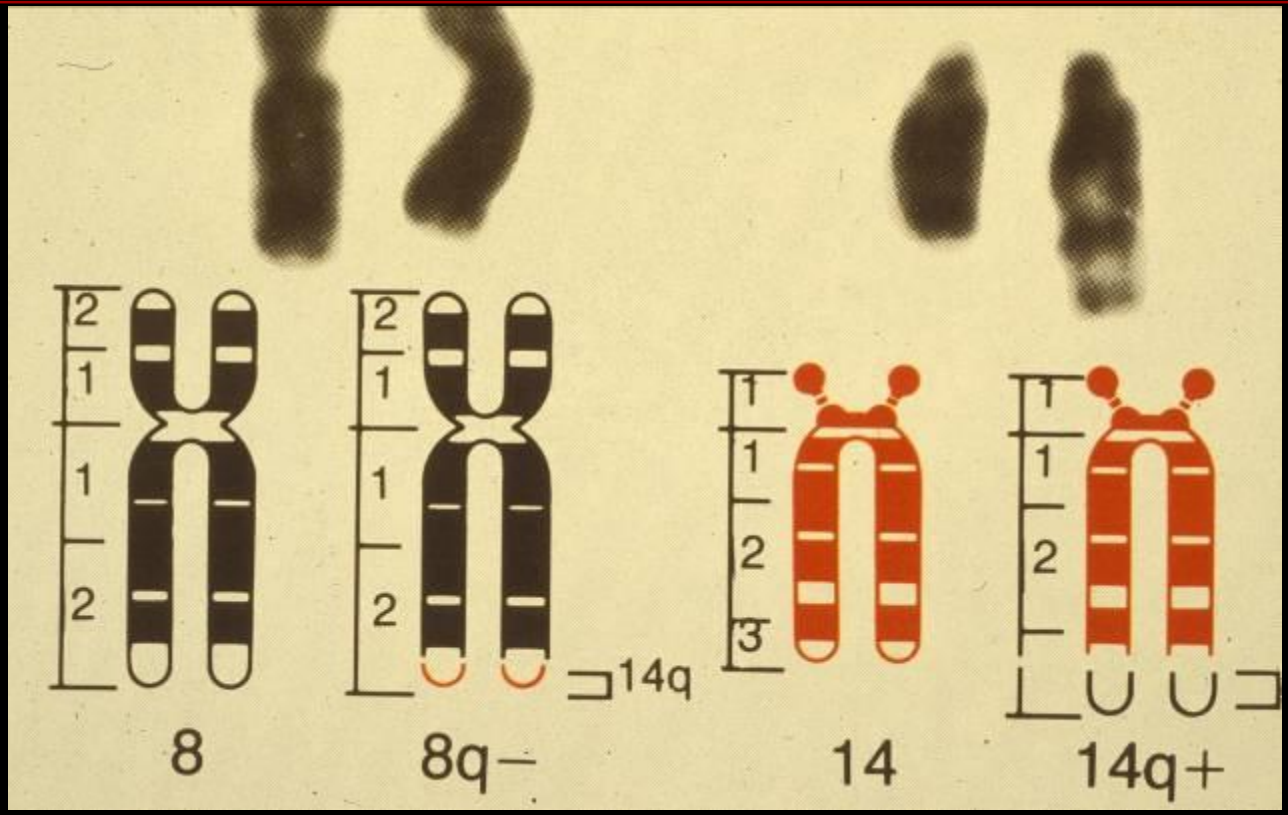
Immunophenotype

- Tumor cells express IgM with light chain restriction and B-cell associated antigens (CD19, CD20, CD22, CD10 and BCL6)
- Negative for CD5, CD23 and TdT
- BCL2 is not expressed
- The expression of CD10 and BCL6 point towards follicle center origin
- CD21 can be expressed in the endemic form
- A high growth fraction is observed: nearly 100% of tumor cells are positive for Ki-67

Genetics

- Clonal rearrangements of the Ig heavy and light chains genes
- Somatic mutations of the Ig genes are found
- All cases have the translocation of MYC at band q24 from chromosome 8 to the Ig heavy chain region on chromosome 14 [t(8;14)] at band q32
- Less commonly to a light chain loci on 2q11 [t(2;8)] or 22q11 [t(8;22)]

Burkitt Lymphoma



Prognosis

- Pts with advanced stage disease, including BM and CNS involvement may be cured with high dose tx
- Relapse, when occur is usually during the first year after dx
- Pts without relapse for 2 years can be regarded as cured
- In Burkitt leukemia, the tx consists of very intensive chemotherapy of relatively short duration and with such a tx most pts have a very good prognosis with 80-90% survival

WHO 2016: Burkitt Lymphoma

- TCF3 or ID3 mutations in up to ~70% of cases.
- Burkitt-like lymphoma with 11q aberration
  A new provisional entity that closely resembles Burkitt lymphoma, with 11q aberration but lacks MYC rearrangement

Mantle Cell Lymphoma

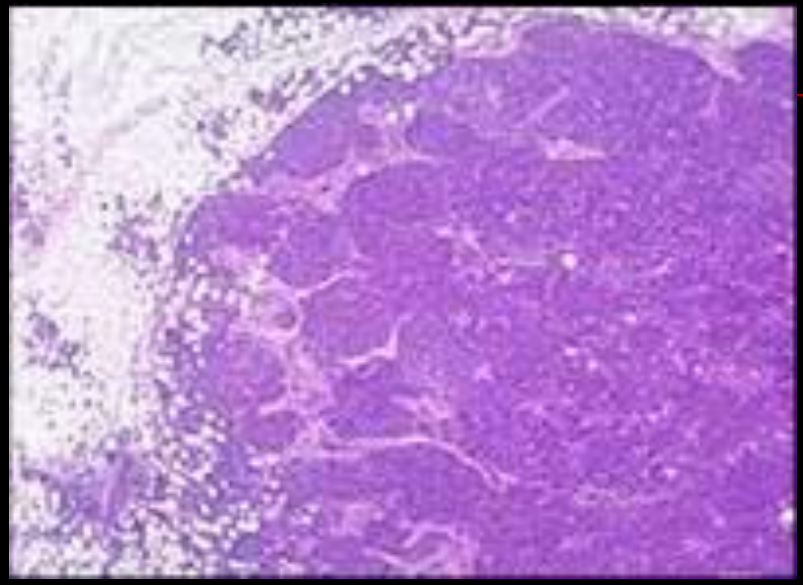
Mantle Cell Lymphoma, Definition

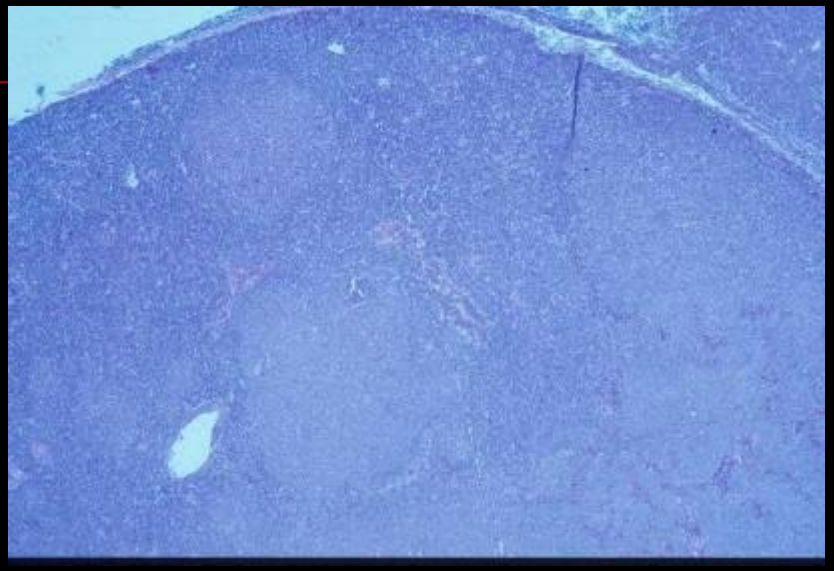
- B-cell neoplasm of monomorphous small to medium-sized cells that resemble centrocytes
- Median age: 60 yrs
- Male predominance
- Extranodal sites: bone marrow (50-60%), GI (30% with lymphomatous polyposis in large intestine), and Waldeyer's ring (pharyngeal lymphoid tissue)
- Most patients present with lymphadenopathy, hepatosplenomegaly

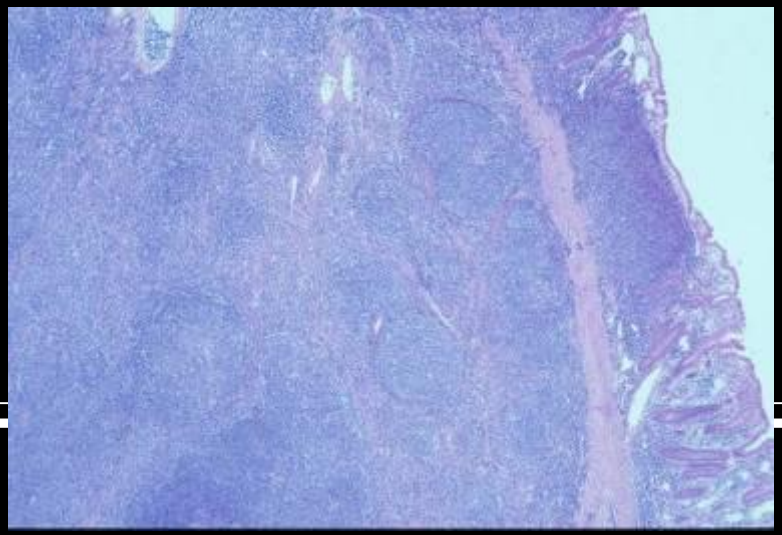
Mantle Cell Lymphoma, Morphology

- Monomorphic proliferation of small to medium-sized lymphoid cells that resemble centrocytes
- Vague nodular, or diffuse, or mantle zone growth pattern
- Hyalinized small blood vessels

Mantle Cell Lymphoma



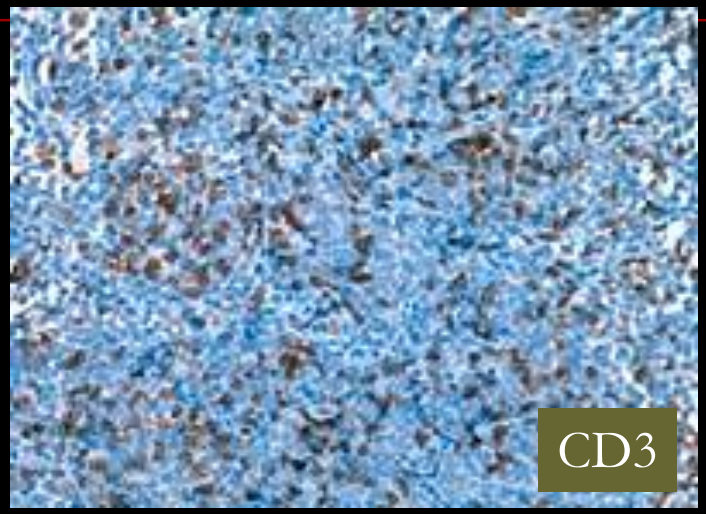


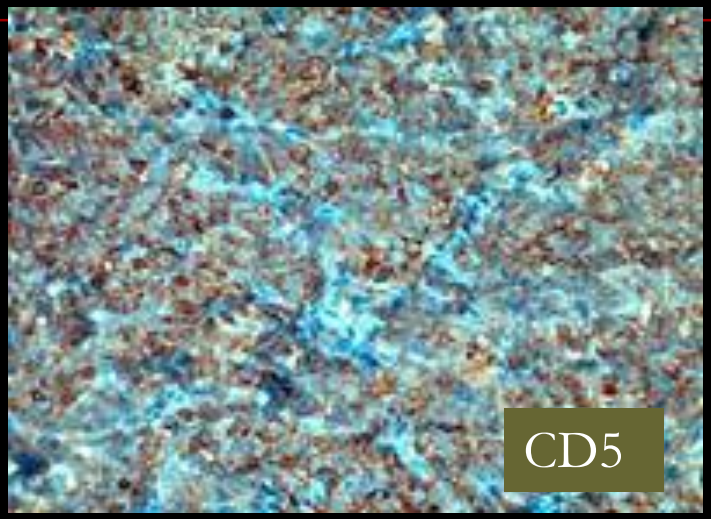


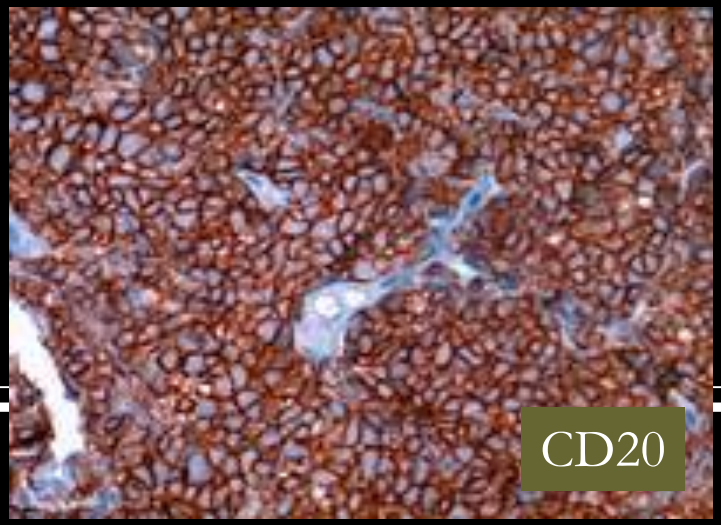
Mantle Cell Lymphoma, Immunophenotype

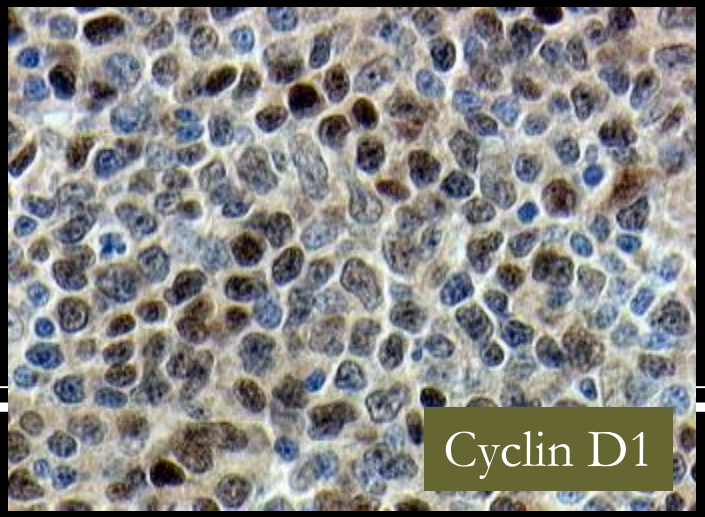
- Intense sIg (IgM +/- IgD)
- CD5 +, CD43 +, BCL2 +
- Cyclin D1 (bcl1) +
- CD10 -, BCL6 –

Mantle Cell Lymphoma





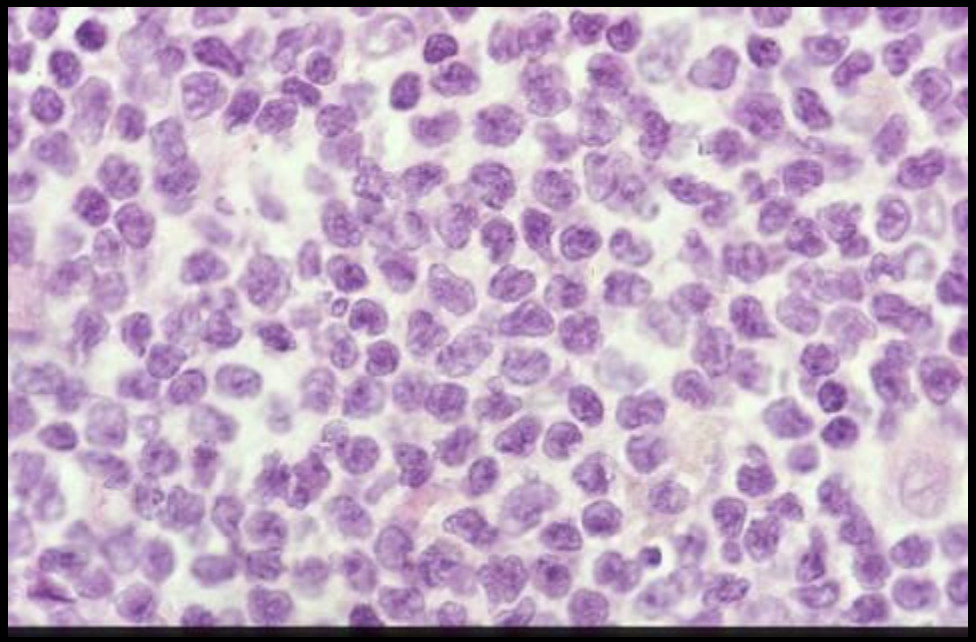




Mantle Cell Lymphoma, Genetics

- t(11;14) (q13;q32)
  chromosome 11: Cyclin D1
  chromosome 14: Ig heavy chain

Mantle Cell Lymphoma
Blastoid Variant



- Cells resemble lymphoblasts with dispersed chromatin
- High mitotic rate (>20-30/ 10 hpf)

WHO 2016: Mantle Cell Lymphoma

- Two MCL subtypes recognized: one largely with unmutated/minimally mutated IgHV and mostly SOX11(+) and the other largely with mutated IgHV and mostly SOX11(-) (indolent leukemic nonnodal MCL with PB, bone marrow , splenic involvement, may become more aggressive with secondary abnormalities, often involving TP53).

- Mutations of potential clinical importance, such as TP53, NOTCH 1/2, recognized in small proportion of cases.

- CCND2 (Cyclin D2) rearrangements in approximately half of cyclin D1(-) MCL cases.

Angioimmunoblastic T-cell lymphoma

Definition

-A subtype of peripheral T-cell lymphoma
-Systemic disease
-Polymorphous infiltrate involving LN
-Prominent proliferation of high endothelial venules
-Prominent proliferation of follicular dendritic cells

Clinical features

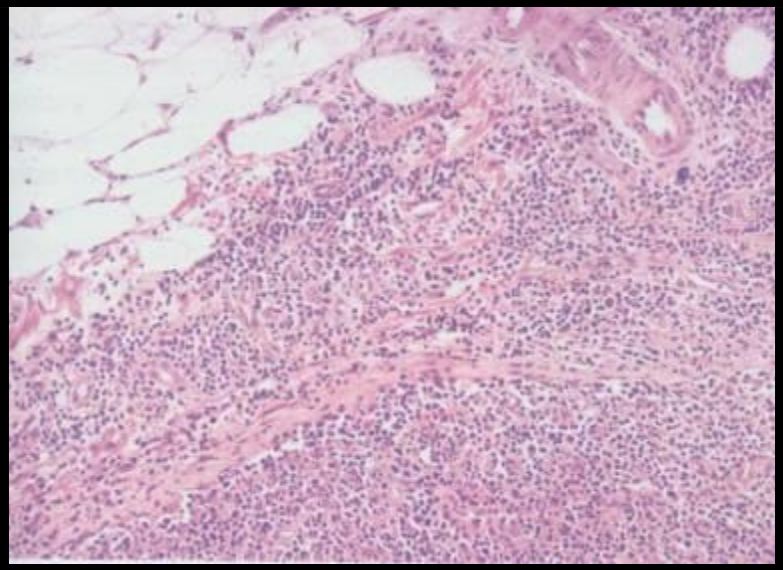
-Presents with advanced stage
-Systemic symptoms:
  Skin rash, pruritus
  Edema, pleural effusion, arthritis, ascites
-Association with drug hypersensitivity reactions (early series)
-Lab: polyclonal hypergammaglobulinemia,
  immune complexes, cold agglutinins, hemolytic anemia,
  rheumatoid factor, anti-smooth muscle Ab

Etiology

-Immunodeficiency appears to be secondary to AITCL, rather than preceding it
-EBV (75% of cases) in B-cells

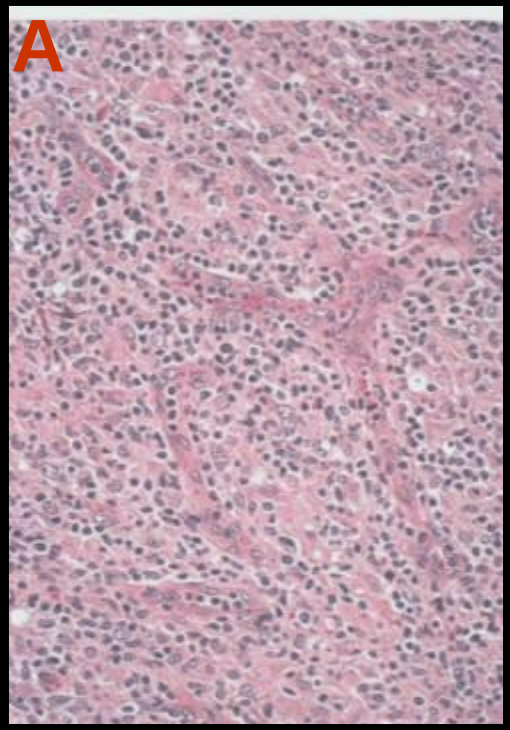
Histopathology

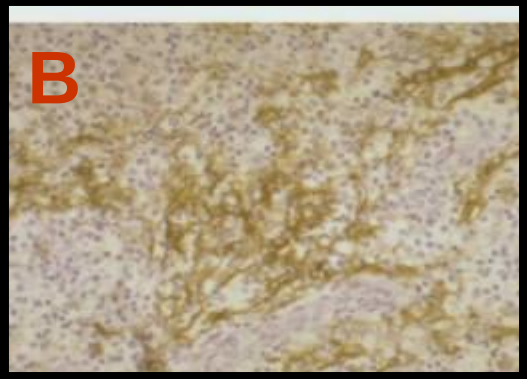
-LN architecture: partially –completely effaced
-Regressed follicles
-Paracotex: polymorphous infiltrates
Lymhoma cells: medium to large, pale cytoplasm, distinct membrane, minimal atypia
Others: small lymphocytes, plasma cells, eos, histiocytes, follicular dendritic cells, rare HRS-like cells
-Infiltrate bridges capsule; distended cortical sinus; vascular proliferation

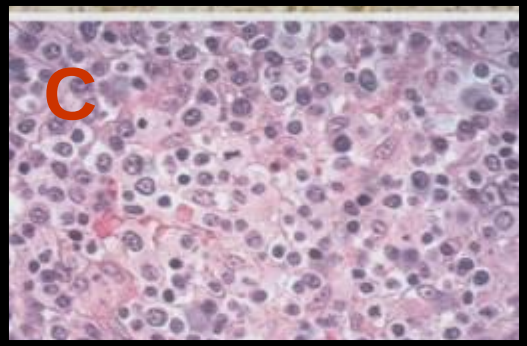


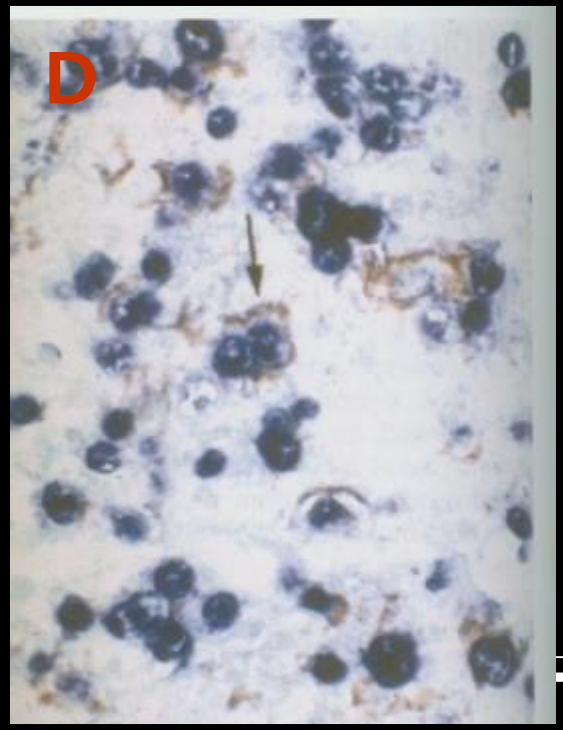
Histopathology(continued)

-A: Arborizing blood vessels
-B: Dentric cells abut and extend from venues(CD21)
-C: medium-sized lymphoytes with clear cytoplasm/distinct membrane
-D: Double staining: EBER/CD20









Immunophenotype

-Positive for CD4 (predominant), CD3, CD2, CD5
-Admixed with many reactive CD8+ cells
-Also positive for TFH cell markers: CD10, CXCL13, bcl-6, PD-1 (60-100% of cases)
-Polyclonal plasma cells
-CD21, CD23: conspicuous dendritic cells

Possible normal counterpart:
-CD4+ Follicular helper T cells (TFH) that are activated by EBV-pos B cells

Genetics

TCR gene rearrangement: 75-90%

Ig gene rearrangement: 30% (in expanded EBV-pos B cells)

Cytogenetics: trisomy 3, trisomy 5, additional X

Prognosis and predictive factors

-Aggressive
-Median survival: < 3 years
-Often succumb to infections
-Some patients may develop secondary EBV-pos DLBCL

WHO 2016: Nodal T-cell lymphomas with T-follicular helper (TFH) phenotype

- An umbrella category created to highlight the spectrum of nodal lymphomas with a TFH phenotype including angioimmunoblastic T-cell lymphoma, follicular T-cell lymphoma, and other nodal PTCL with a TFH phenotype (specific diagnoses to be used due to clinicopathologic differences).

- T follicular helper (TFH) phenotype: the neoplastic cells should express at least 2 or 3 TFH-related antigens, including CD279/PD1, CD10, BCL6, CXCL13, ICOS, SAP, and CCR5.

Peripheral T-cell Lymphoma, NOS

Peripheral T-Cell Lymphoma, NOS

- T-cell lymphomas that don’t meet the criteria for the more specific types
- About 50% of the T-cell lymphomas
- Mostly adults, but may occur in children
- Usually nodal, but may be extranodal
- Usually advanced stage at diagnosis

Peripheral T-Cell Lymphoma NOS

- Patients present with lymphadenopathy
- Constitutional symptoms often present
- Paraneoplastic features: eosinophilia, pruritus, hemophagocytic syndrome
- Aggressive clinical course
  - Patients respond poorly to treatment
  - Relapses are frequent
  - Overall 5 year survival 20-30%

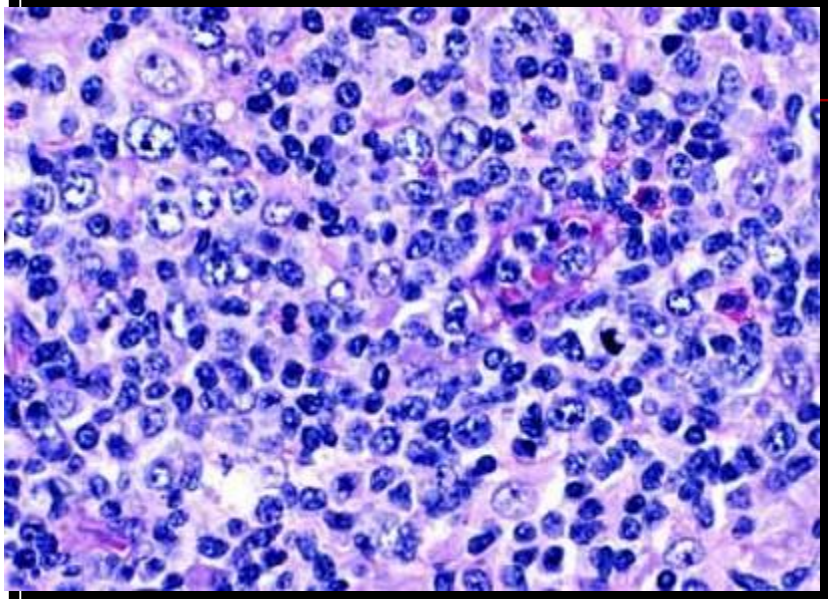
Peripheral T-Cell Lymphoma NOS

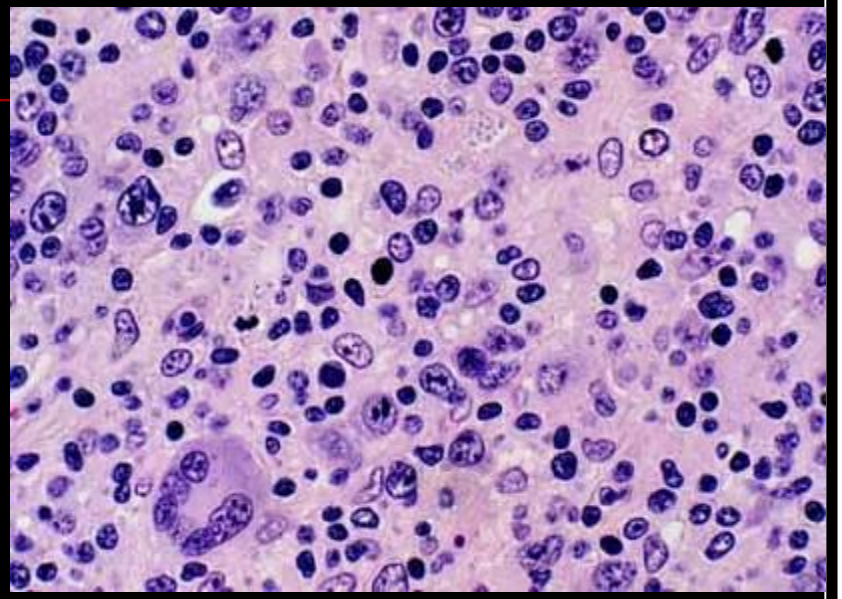
- Diffuse infiltration with effacement of lymph node architecture
- Broad cytologic spectrum: usually predominance of medium-sized or large cells with irregular nuclei
- Clear cells and Reed-Sternberg-like cells
- High endothelial venules increased
- Polymorphous inflammatory background

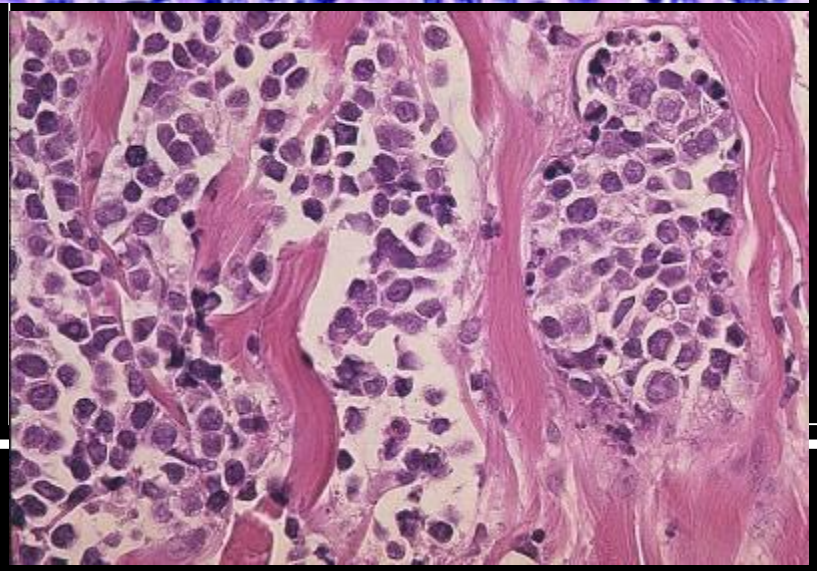
Peripheral T-Cell Lymphoma NOS

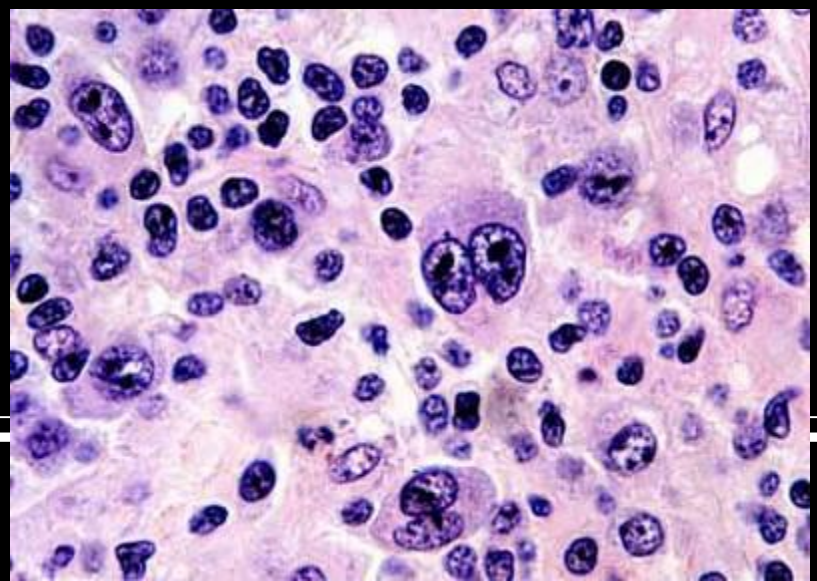
- T-zone variant
  - Interfollicular growth pattern with preserved or even hyperplastic follicles
  - Tumor cells predominantly small or medium-sized without nuclear pleomorphism
- Lymphoepithelial variant (Lennert lymphoma)
  - Diffuse or interfollicular
  - Numerous small clusters of epitheliod histiocytes

Peripheral T-Cell Lymphoma, unspecified









Peripheral T-Cell Lymphoma NOS

Immunophenotype

- T-cell associated antigens (CD3, CD5, CD7)
- Often show loss of normal antigen expression
- Most nodal cases are CD4+, CD8-
- CD30 may be positive, but not cytotoxic granule associated proteins
- Some cases may express CD56, usually extranodal with cytotoxic T-cell phenotype

Genetics

- TCR genes clonally rearranged in most cases

Anaplastic Large Cell Lymphoma (of T cell lineage)

Definition

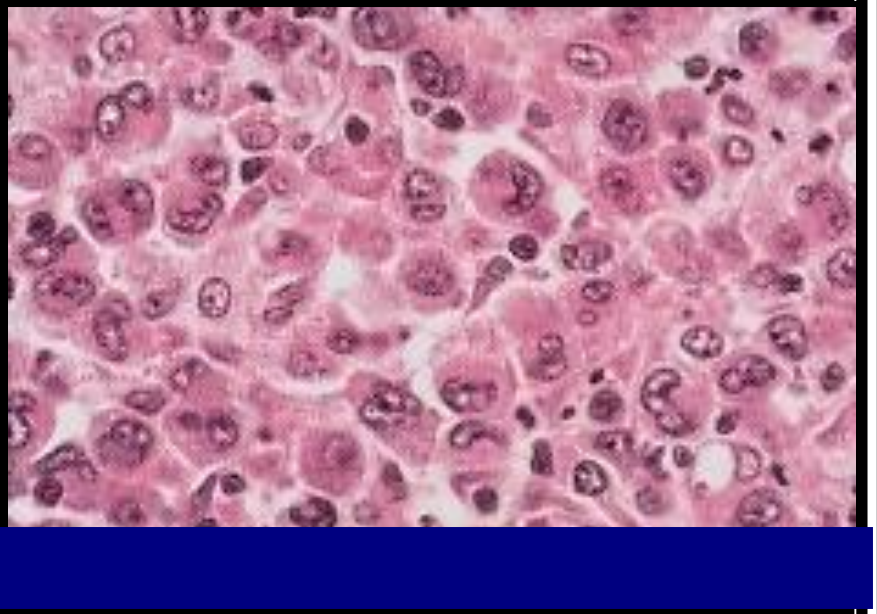
- T-cell lymphoma comprised of large cells with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei
- CD30+
- Most express cytotoxic granule-associated proteins
- Majority are positive for ALK
- Two subtypes:
  ALCL,ALK-pos, and
  ALCL, ALK-neg

Clinical Features

- 70% show advanced stage III or IV disease
  - Peripheral and/or abdominal LAD
  - Extranodal sites
  - Bone marrow involvement
- 75% B-symptoms, especially fever

Morphology

- Broad morphologic spectrum
- All cases contain a variable proportion of hallmark cells
  - Horse-shoe or kidney-shaped nuclei
  - Eosinophilic region near the indented nucleus
- Abundant cytoplasm
  - Clear, basophilic or eosinophilic
- Multinucleated wreath-like or Reed-Sternberg cells



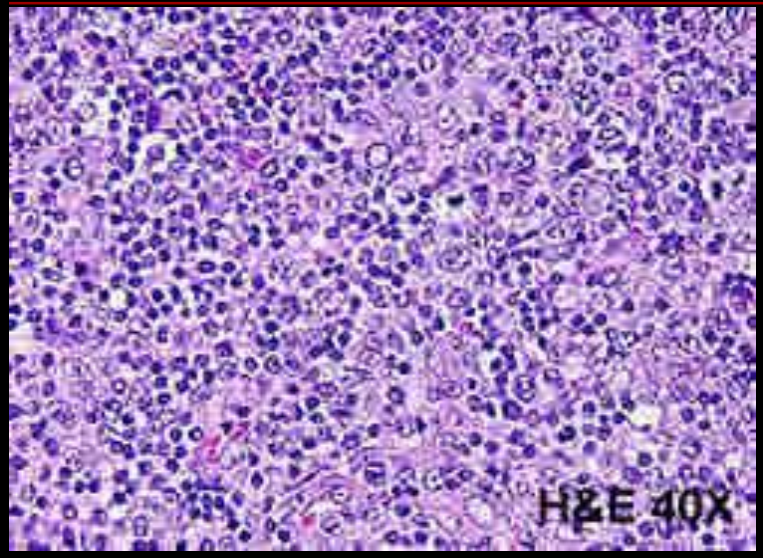
Morphology

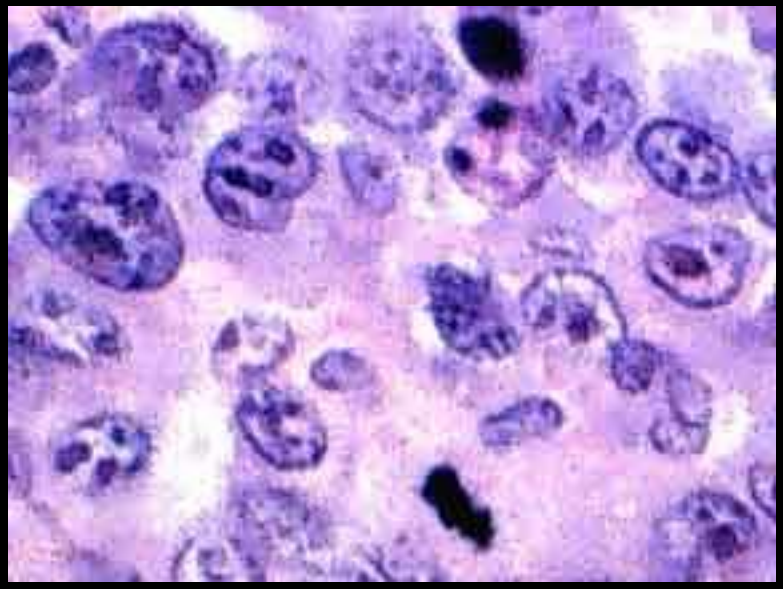
- Cytologic variants
  - Common
  - Lymphohistiocytic
  - Small cell
- 10% may have more than one variant
- Relapses may look morphologically like a different variant

ALCL, Common Variant

- 70% of cases
- Pleomorphic large cells
  - Hallmark features
- Admixed monomophic, round cells
  - May be the prominent population

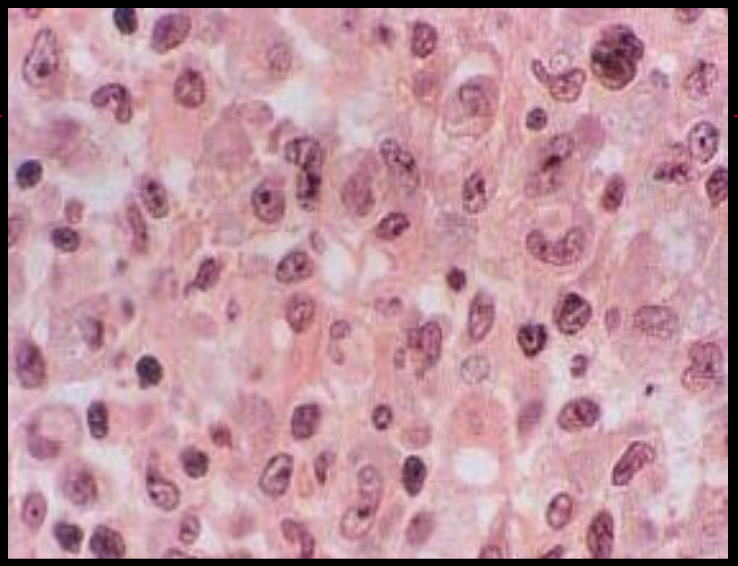
ALCL, common variant

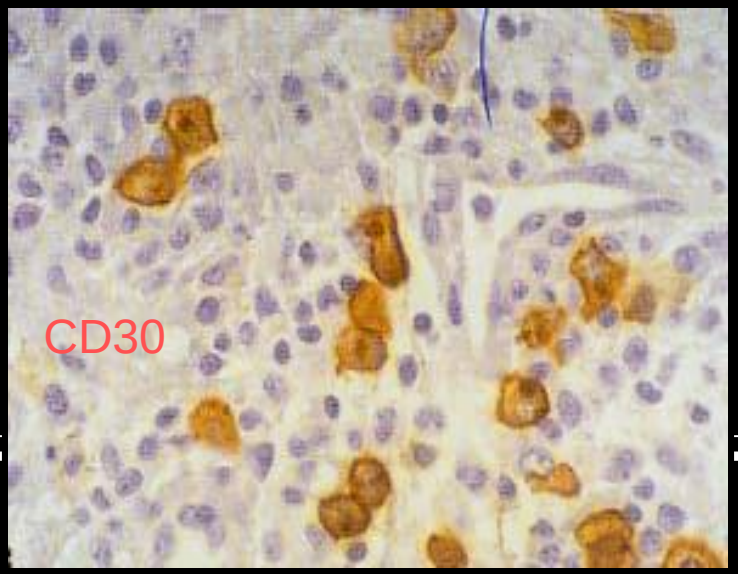




ALCL, Lymphohisitocytic variant

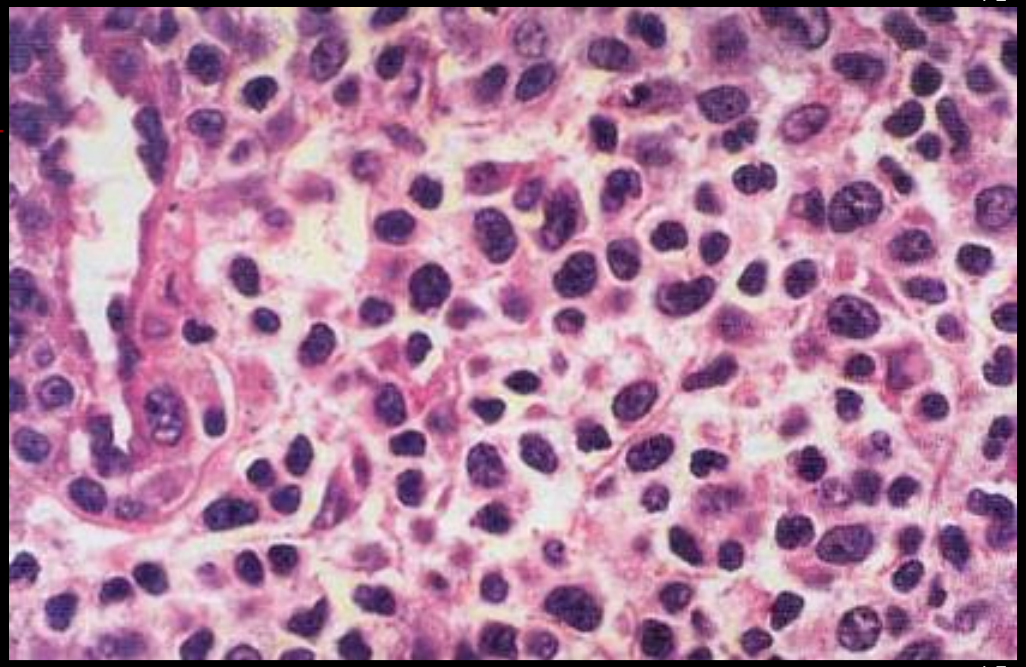
- 10% of cases
- Tumor cells admixed/masked with large numbers of histiocytes
  - Clustering of tumor cells around vessels
  - Erythrophagocytosis in some cases

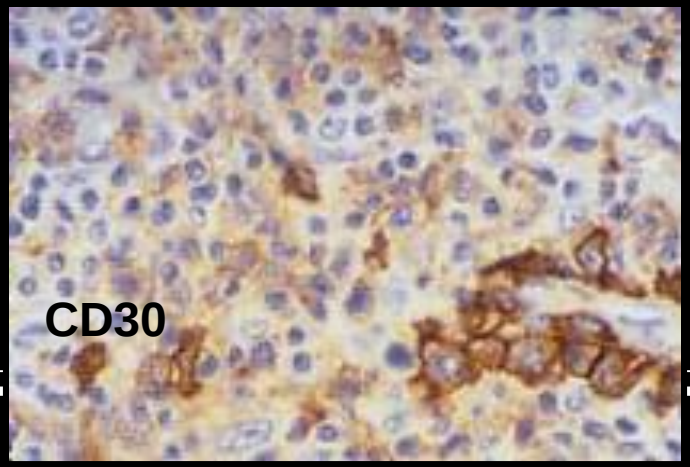




ALCL, Small Cell Variant

- 5-10% of cases
- Small to medium-sized cells with irregular nuclei
- Hallmark cells (often clustered around vessels)
- Often misdiagnosed as PTCL, NOS
- May involve peripheral blood as flower-like cells (mimicking ATCLL)

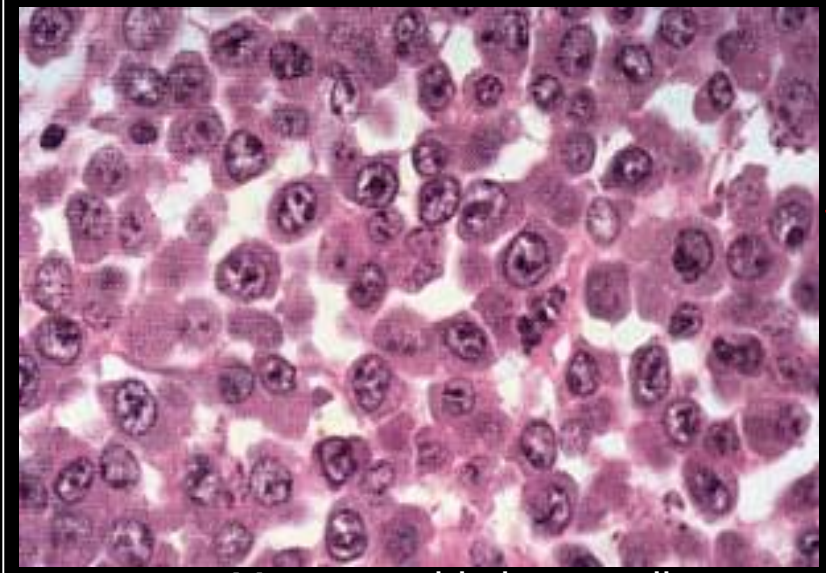




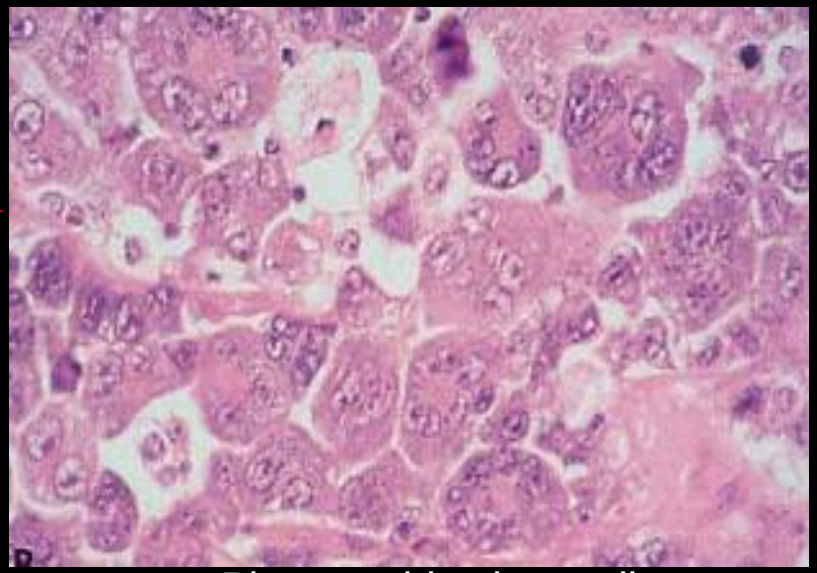
Other ALCL Variants

- Pleomorphic giant cells
- Monomorphic large cells
- Sarcomatous
- Signet ring cells
- Rare cases with myxomatous stroma and fibroblasts, or capsular thickening and nodular fibrosis (mimicking cHL, NS)

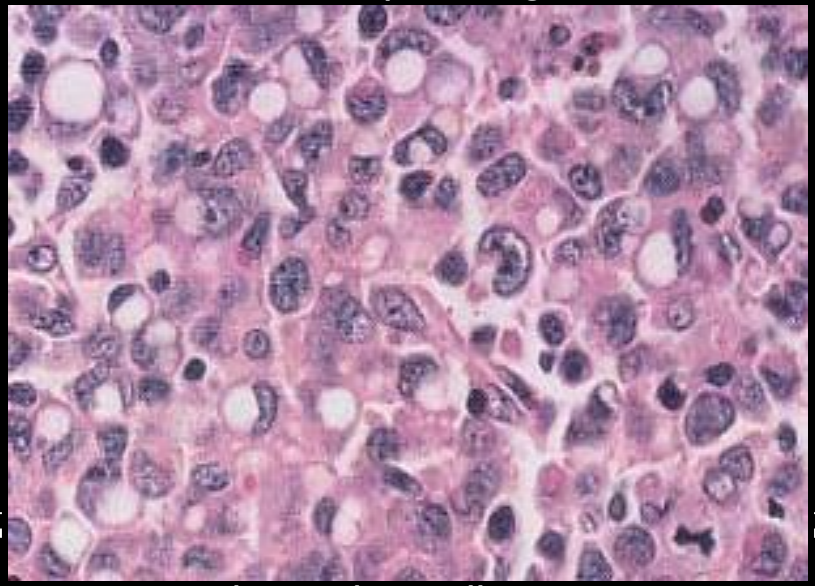
Other Histologic Patterns of ALCL



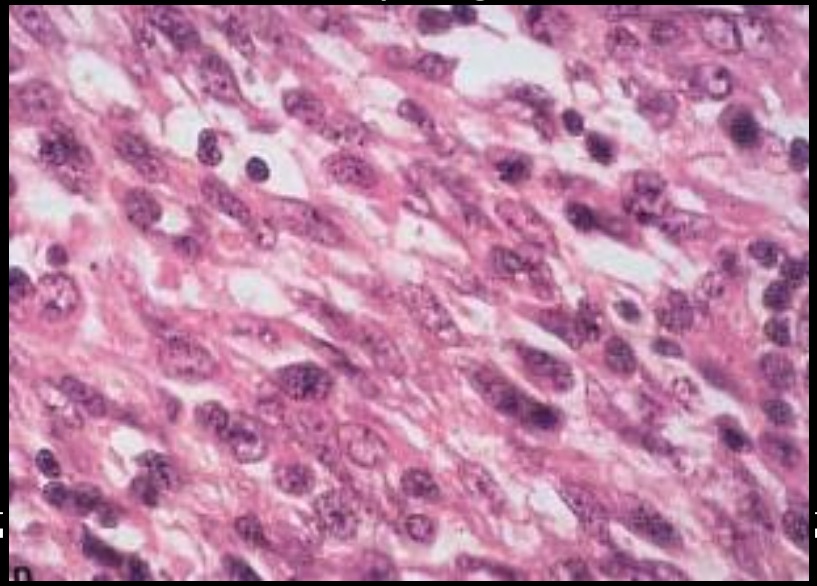
Monomorphic large cells



Pleomorphic giant cells



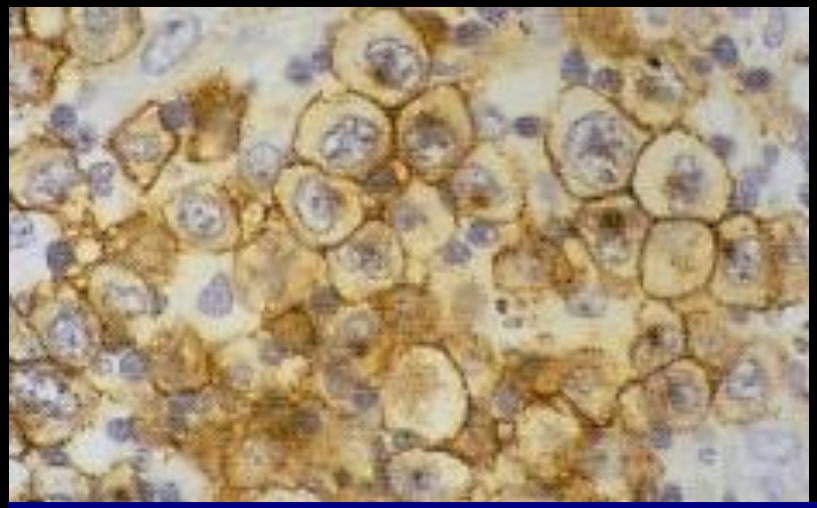
Signet-ring cells



Sarcomatous

ALCL: Immunophenotype

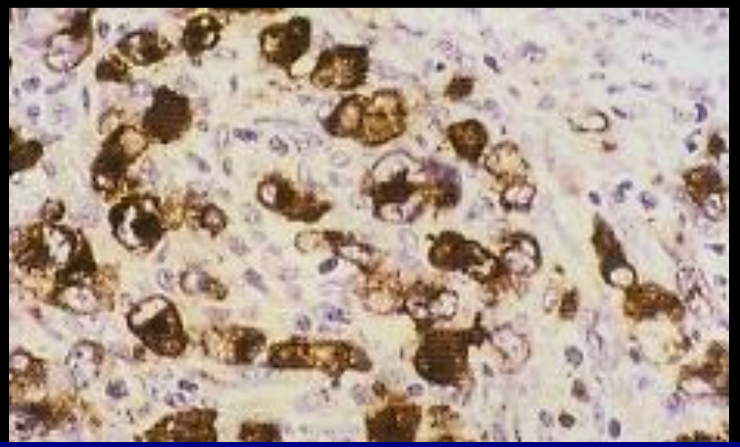
- CD30 positive
  - Membrane plus golgi
  - Strongest in largest cells
- ALK expression detected in 60-85% of cases (ALCL, ALK pos)
- EMA (+) in majority
- Positive for T-cell Antigens
  - Rarely null phenotype
    - Evidence for T-cell phenotype at molecular level
  - CD3 negative in 75% of cases
  - CD5 and CD7 more often negative
  - CD2 and CD4 more often positive
  - CD8 usually negative



CD30

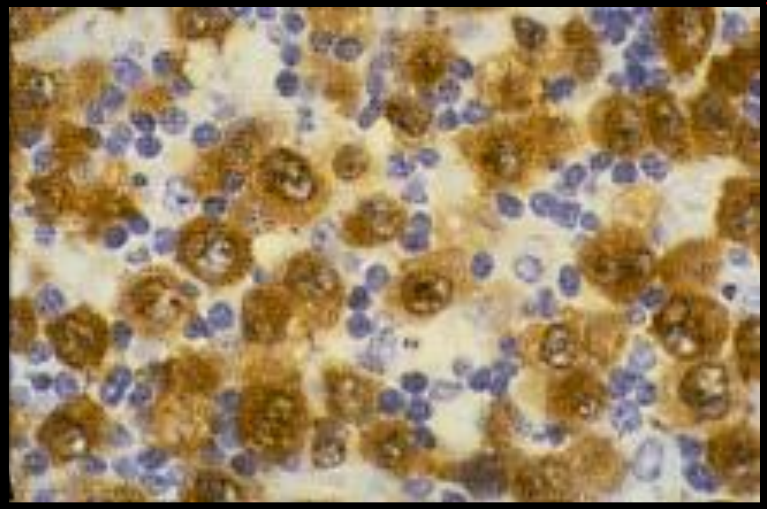
Immunophenotype (cont.)

- Most positive for TIA1, granzyme B or perforin
- CD43 in 2/3 of cases
  - Lack lineage specificity
- Variably positive for CD45
- CD15 rarely positive
  - Only in small proportion of cells
- Negative for EBV
- Clusterin pos. (absent in C-ALCL)



Granzyme B

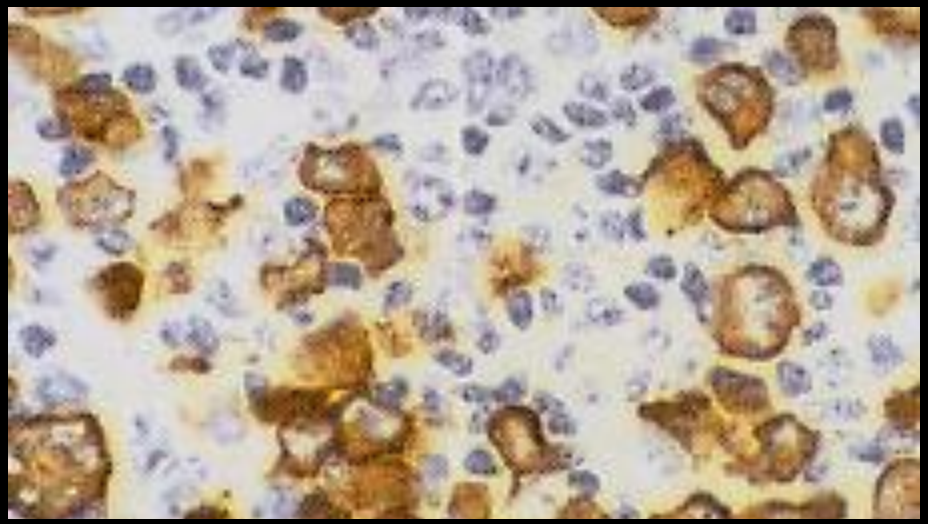
ALK Staining Patterns



- t(2;5) (p23;q35), most common
  - 70-80% of cases
  - Cytoplasmic and nuclear
  - Fusion NPM-ALK proteins
  - Results from the fusion of ALK gene (normally transmembrane) on Chr 2 with nucleophosmin (nuclear transport protein) gene on Chr 5.

ALK Staining Patterns

- t(1;2) (q25;p23)
  - Tropomyosin 3/ALK
  - 10-20%
  - Cytoplasmic



Other Translocations Involving ALK

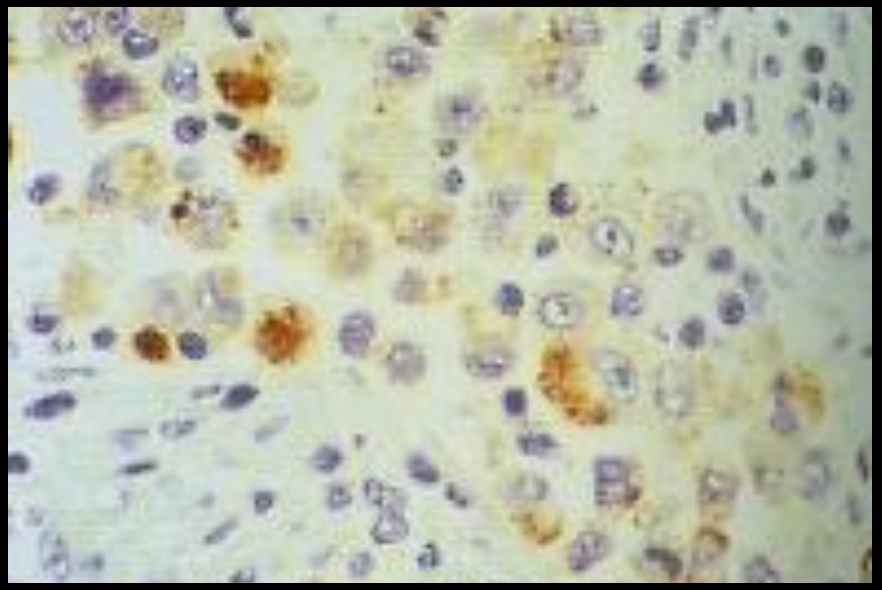
- t(2;3)(p23;q35)
  - Cytoplasmic, diffuse
  - 2-5% of cases
  - TFG/ALK

Other Translocations Involving ALK

- Inv(2)(p23 q35)
  - 2-5% of cases
  - Cytoplasmic, diffuse
  - ATIC/ALK gene
    - ATIC gene plays a role in *de novo* purine biosynthesis

Other Translocations Involving ALK

- t(2;17)
  - Cytoplasmic, granular
  - 2-5% of cases
  - CLTC/ALK
  - CLTC (clathrin heavy polypetide)
    - Structural protein of coated vesicles



ALK-negative ALCL

- Larger and more pleomorphic cells
- More prominent nucleoli
- No longer a provisional entity in WHO 2016
- CD30 must be strong, and abundant (almost all cells)
- Important to rule out primary cutaneous ALCL with clinical information

Prognosis and Predictive Factors

- IPI has some predictive value
- ALK-positivity most important for favorable prognosis (sensitivity to Adriamycin)
  - Irrespective of translocation
- Overall 5-year survival in ALK-positive ALCL is 80% except for small cell variant due to disseminated disease
- Relapses uncommon (30%)
  - Usually remaining sensitive to therapy; SCT/BMT for refractory cases
- 5-year survival in ALK-negative ALCL is 40%

WHO 2016: ALTCL

- A subset of ALK(-) ALTCL with 6p25 rearrangments at IRF4/DUSP22 locus tends to be relatively monomorphic, usually lack cytotoxic granules, and have been reported to have a superior prognosis, silmilar to that of ALK(+) ALTCL.
- A small subset with TP63 rearrangements are very aggressive
- Breast implant–associated anaplastic large cell lymphoma:
  -A new provisional entity distinguished from other ALK(-) ALCL; noninvasive disease associated with excellent outcome.

  -Presents as an accumulation of seroma fluid between the implant itself and the surrounding fibrous capsule. Both saline- and silicone-filled implants have been implicated, with a median interval from the time of the implant to the lymphoma of about 10 years. In most cases, the neoplastic cells are confined to the seroma fluid, without invasion of the capsule.

Mycosis Fungoides

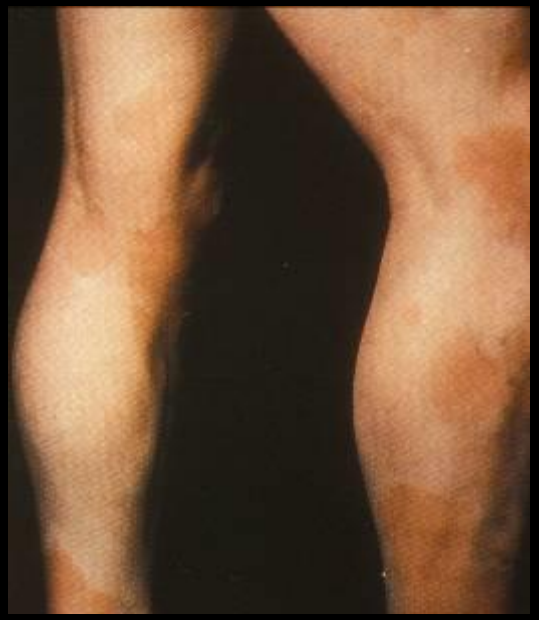
Definition

- Mature T-cell lymphoma
- Presents in skin with patches/plaques
- Characterized by epidermal and dermal infiltration of small to medium-sized T-cells with cerebriform nuclei

Clinical features

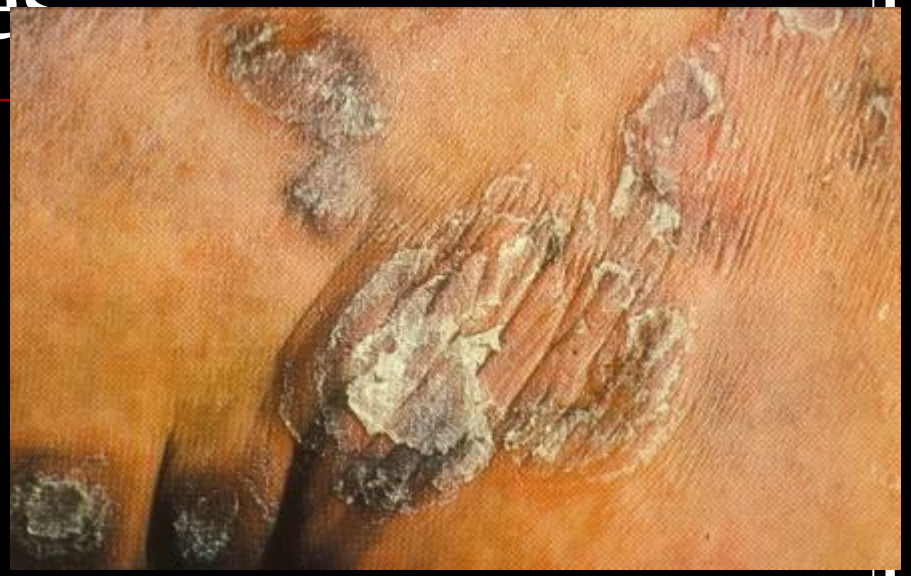
- Initial diagnostic lesions
  - Limited patches and/or plaques
    - Frequently on trunk
    - May persist for years
- Later diagnostic lesions
  - More generalized plaques
  - Tumors

Mycosis Fungoides

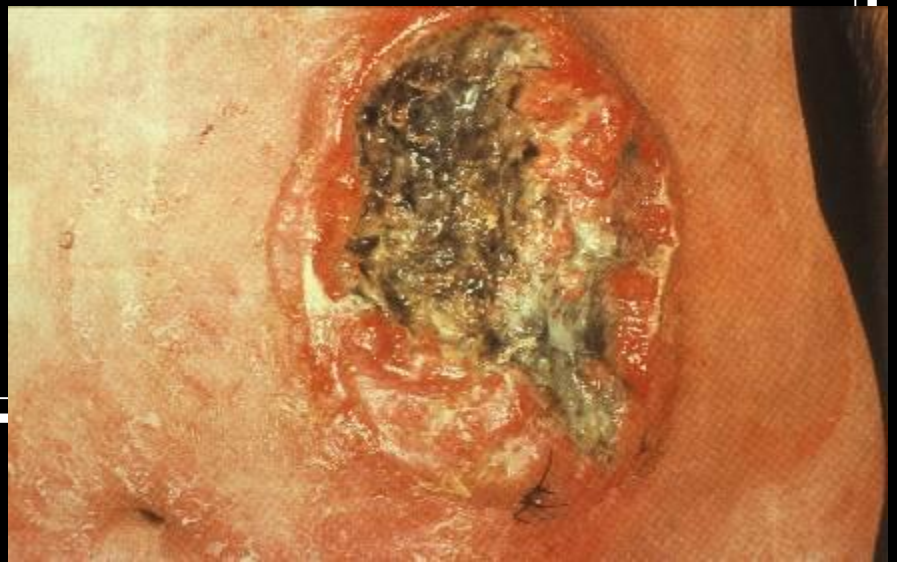


Early stage

Plaque stage

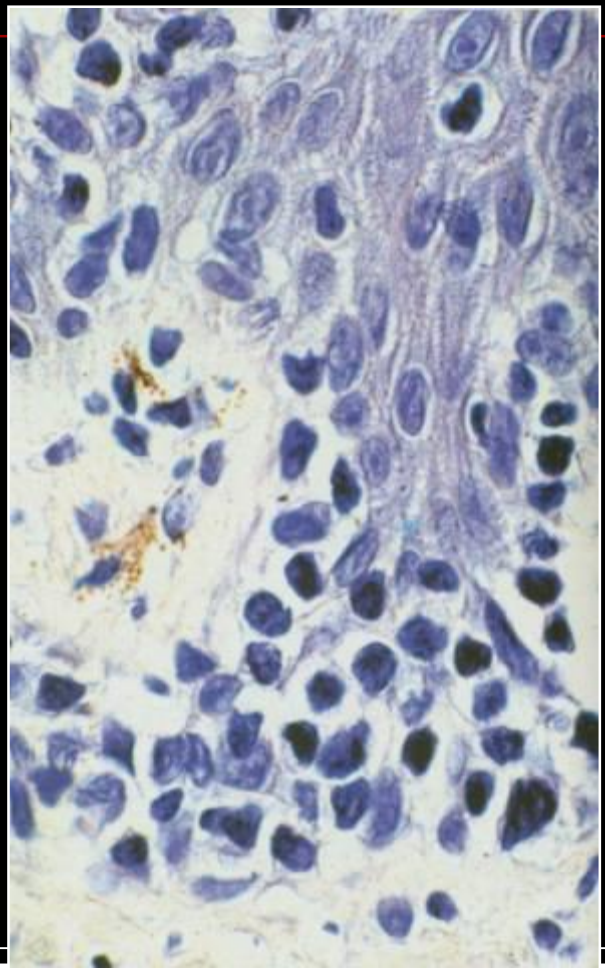


Tumor stage



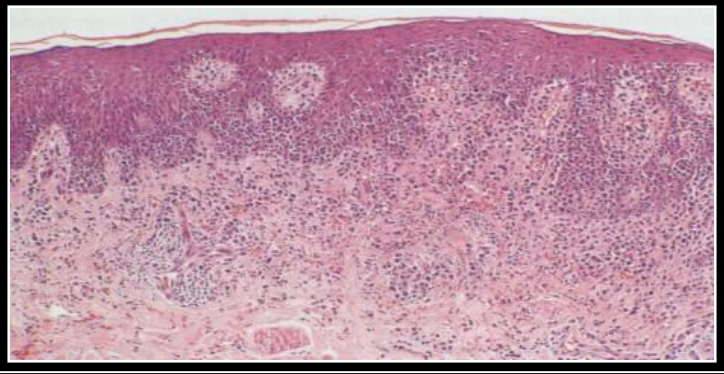
Morphology

- Epidermotropism
  - Small to medium-sized cells with irregular (cerebriform) nuclei
  - Larger cells with similar nuclei (minority)
  - Involvement with single cell or with linear distribution in basal layer is most common form of epidermotropism



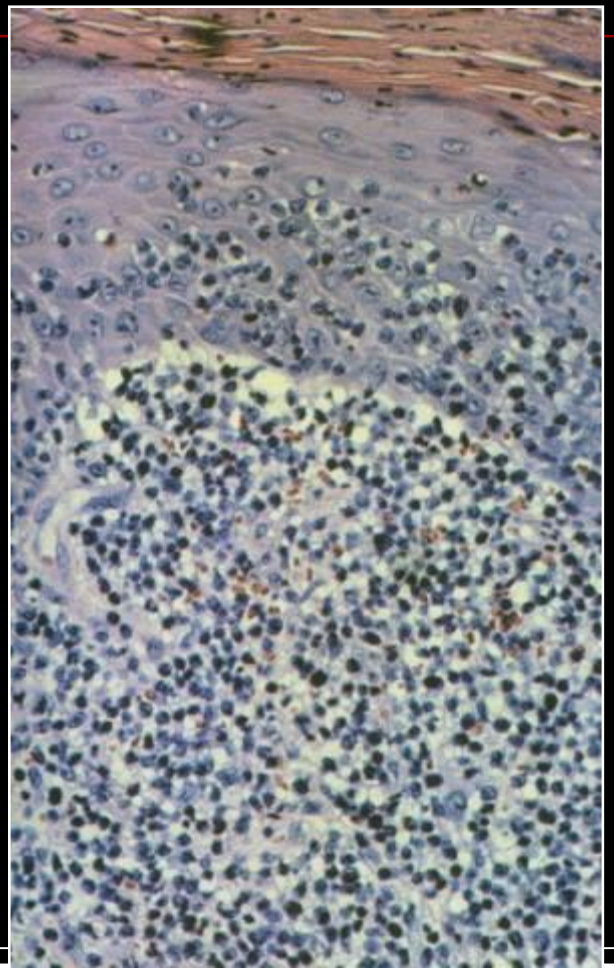
Morphology

- Plaque
  - More dense infiltrate of atypical lymphocytes that can extend around the adnexae
  - Atypical lymphocytes are more common
    - 10-30 μm in diameter
    - Prominent nuclear convolutions (cerebriform)



Morphology

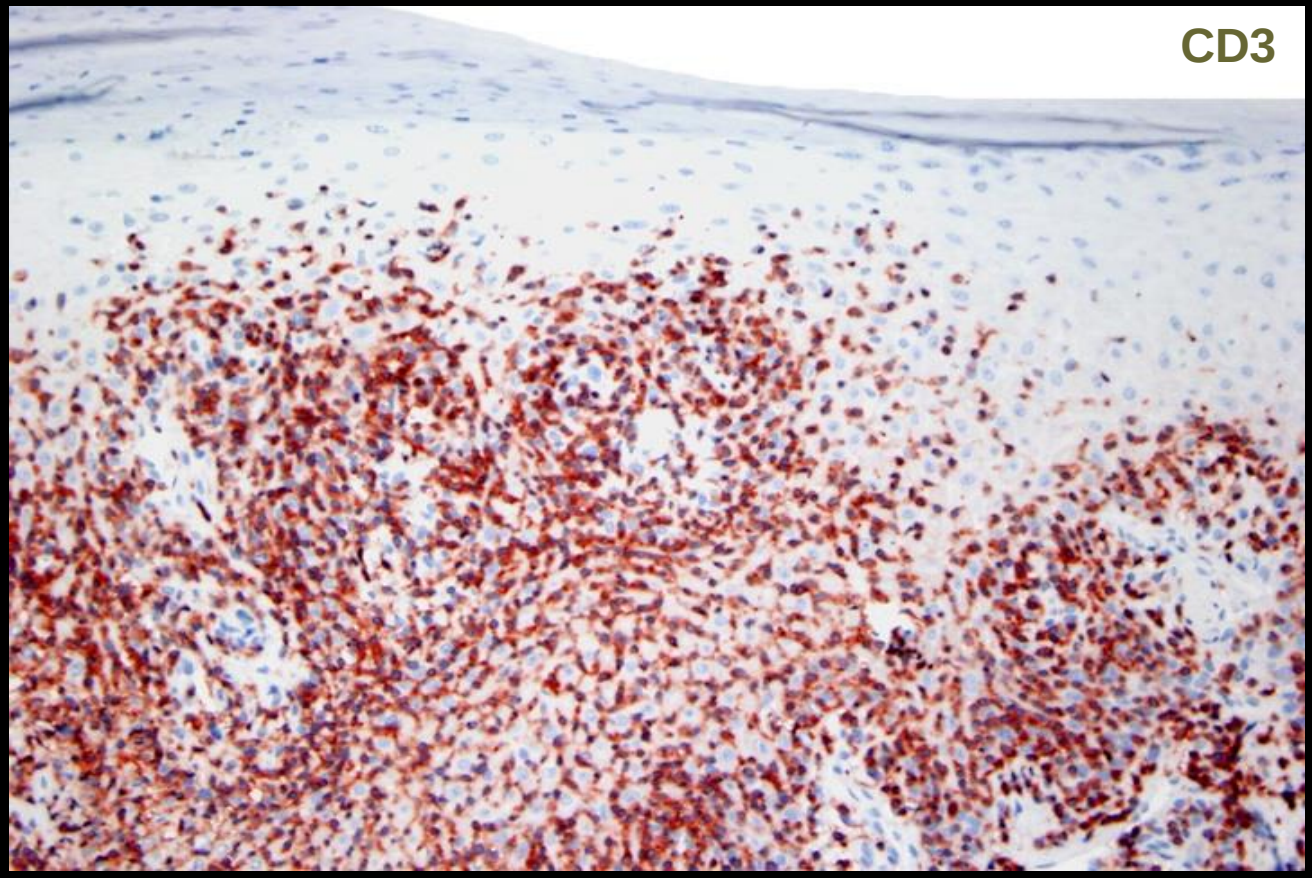
- Tumor
  - Involvement of entire dermis +/- subcutis
  - Infiltrate of larger atypical lymphocytes



Immunophenotype

- CD2/3/4/5 and TCRβ positive
- Cutanous lymphocyte antigen (CLA), associated with lymphocyte homing to skin, positive in most cases
- CD7/8 negative
- Cytotoxic granule associated proteins negative in early patch/plaque lesions

Mycosis Fungoides



Prognosis

- Most important prognostic factor is clinical stage
- Limited disease
  - Excellent prognosis
  - Survival similar to general population
- Advanced stages: poor prognosis, especially with
    - Skin tumors
    - Extracutaneous dissemination

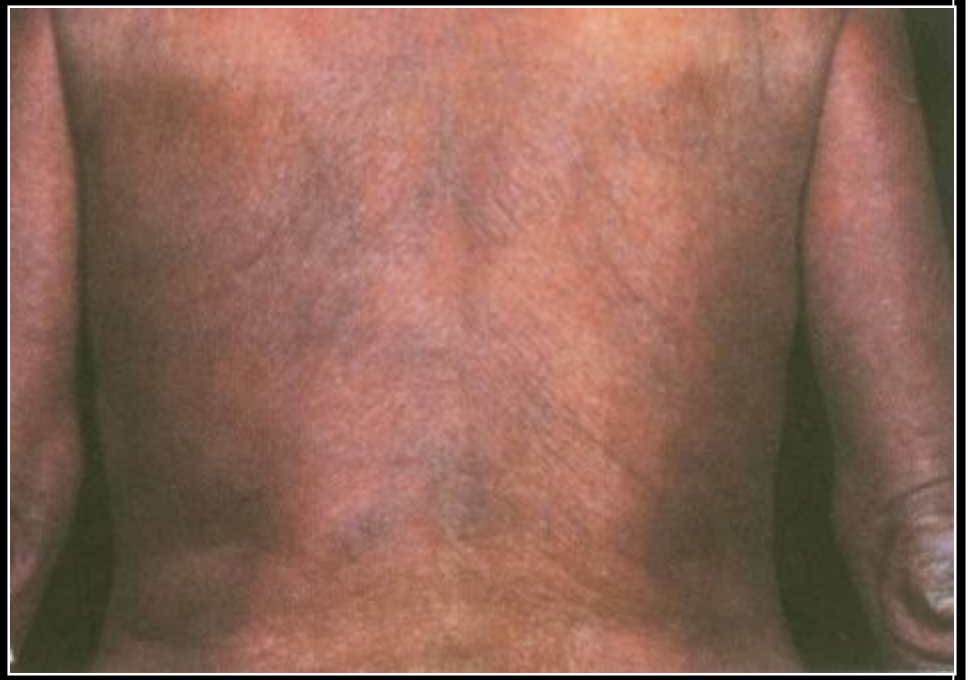
Sézary Syndrome

Definition

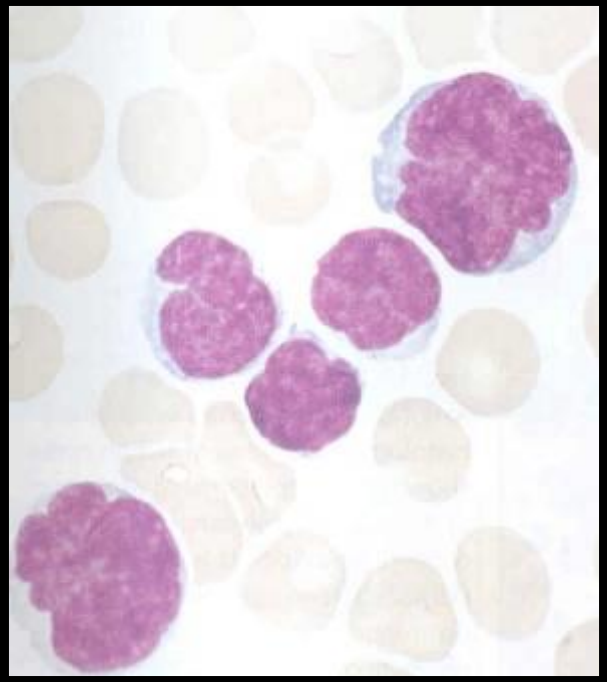
- Generalized mature T-cell lymphoma
- Characterized by
  - Erythroderma (generalized exfoliative dermatitis)
  - Lymphadenopathy
  - Neoplastic T-lymphocytes in PB (cerebriform)
- MF variant, but behavior is much more aggressive

Clinical features

- Patients present with
  - Erythroderma
  - Generalized lymphadenopathy
  - Pruritis
  - Alopecia (hair loss)
  - Palmar or plantar hyperkeratosis
  - Onychodystrophy (malformation or discoloration of nails)



Sezary syndrome



Cells with convoluted nuclei

Cebebriform nuclei (EM)

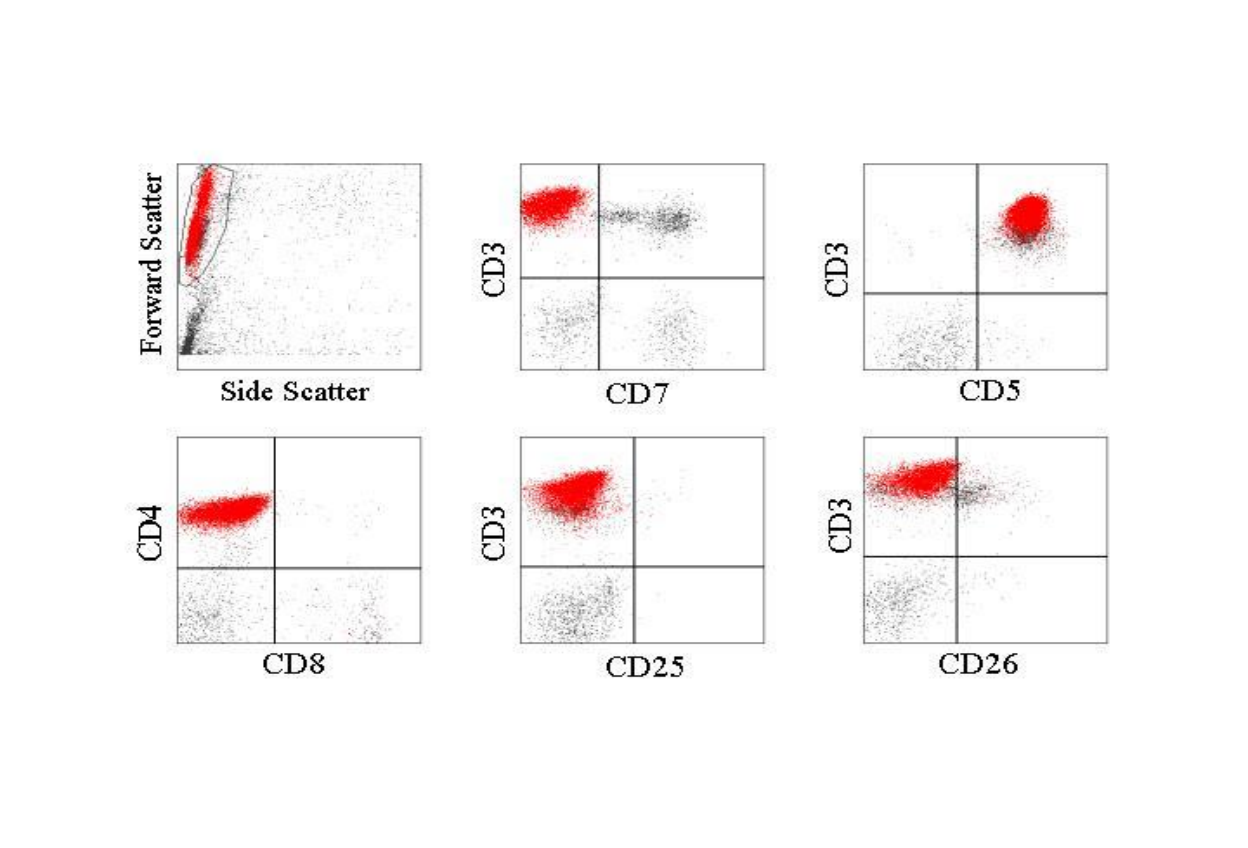
Morphology

- Neoplastic cells in PB
  - No consensus on degree of lymphocytosis
  - Most studies require ≥1,000 Sézary cells per mm^3

Immunophenotype

- CD2/3/5 and TCRβ positive
- CD4 positive in most cases
  - Elevated CD4/CD8 ratio
  - Increased proportion of CD4(+) and CD7(-) T cells
- CD8 expression is rare
- Aberrant T-cell phenotypes are common

Sezary Syndrome: Flow Cytometry



Genetics

- TCR clonally rearranged
- Complex karyotypes present in many patients
- No specific cytogenetic abnormality identified

Prognosis

- Aggressive disease
  - 10-20% 5 year survival rate
- May transform to a large T-cell lymphoma as a terminal event

Classical Hodgkin lymphoma

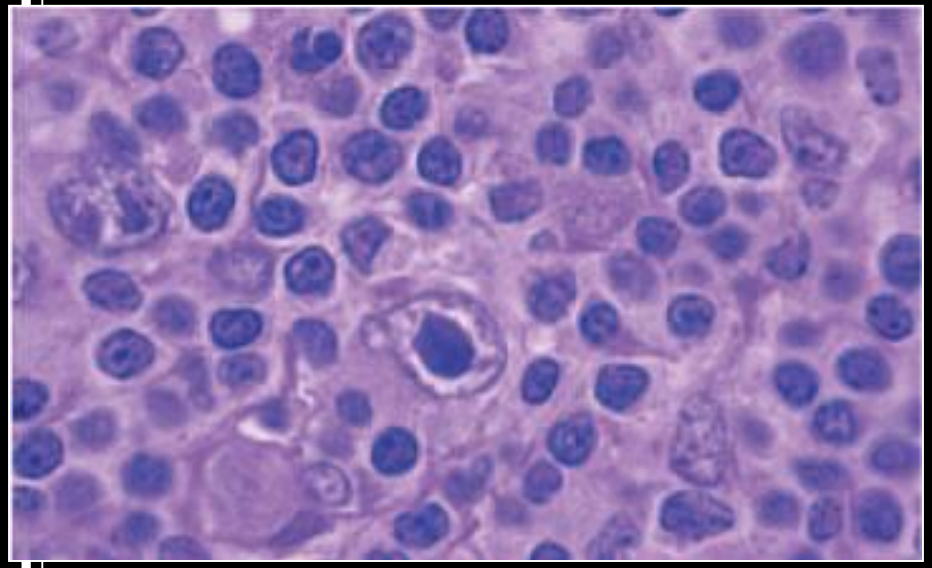
Classical Hodgkin lymphoma

- 95% of Hodgkin lymphomas
- Bimodal age distribution
- EBV has been postulated to play a role

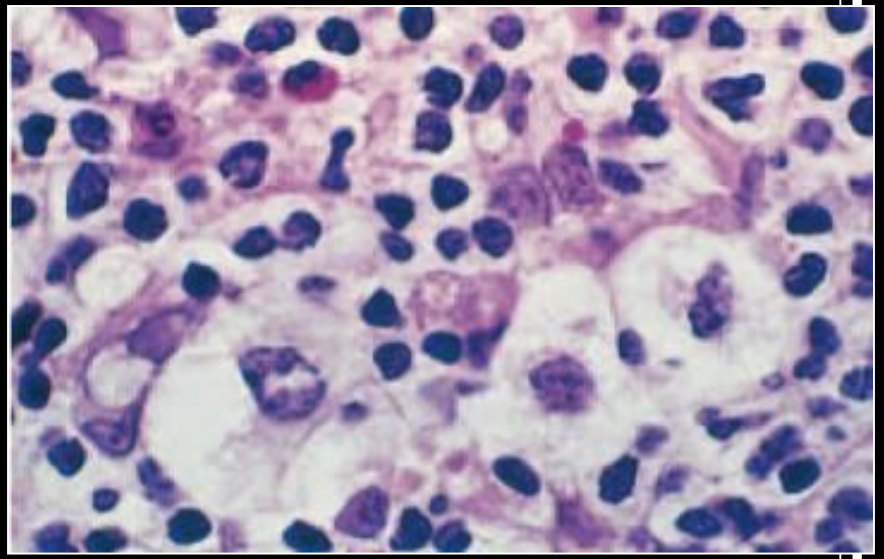
Sites of involvement

- Cervical lymph nodes
- 60% have mediastinal invlovement
- Bone marrow involvement rare (5%)
  –> stage IV disease

Hodgkin Lymphoma
Malignant Cell Variants

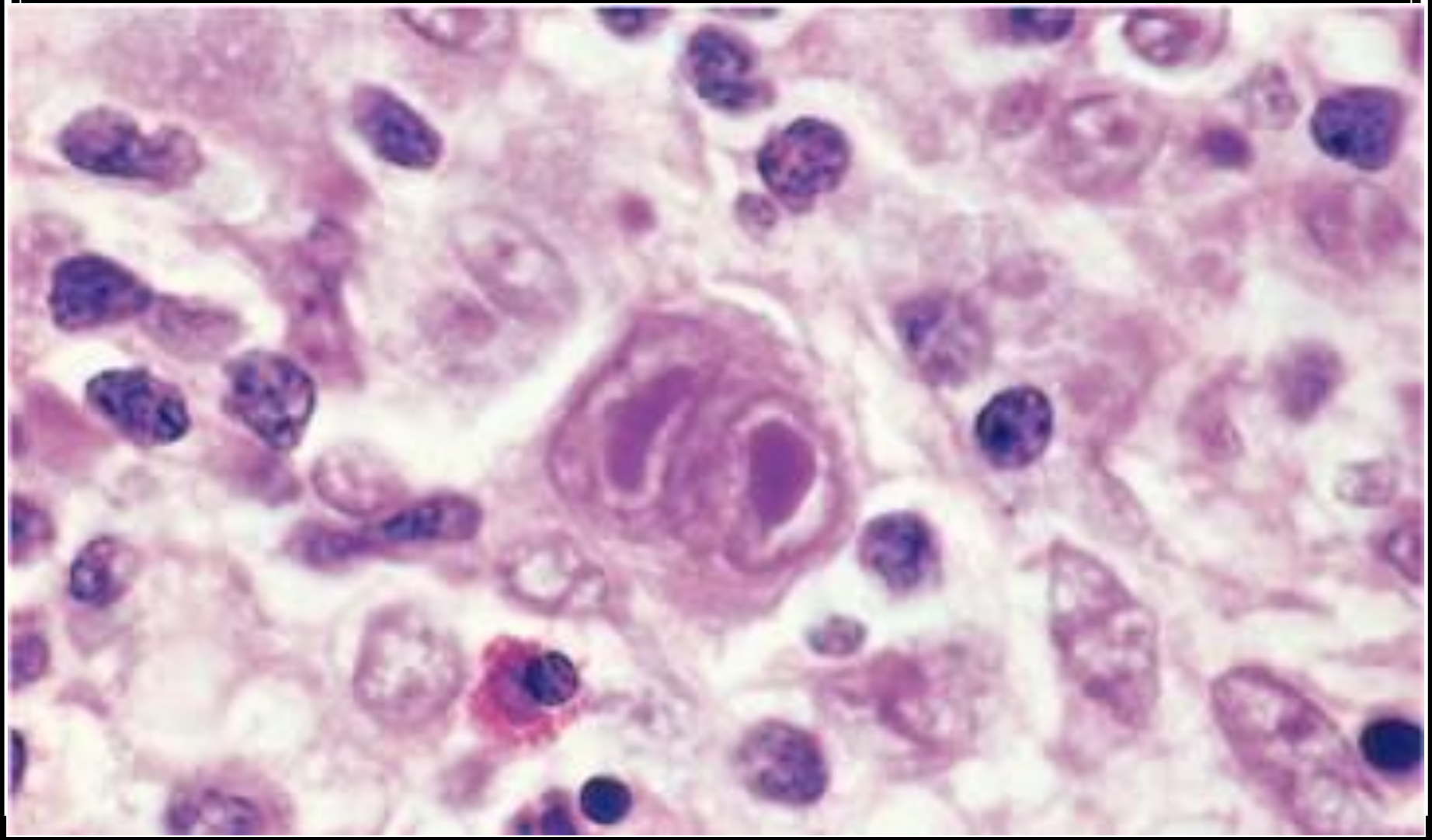


Mononuclear Hodgkin Cell



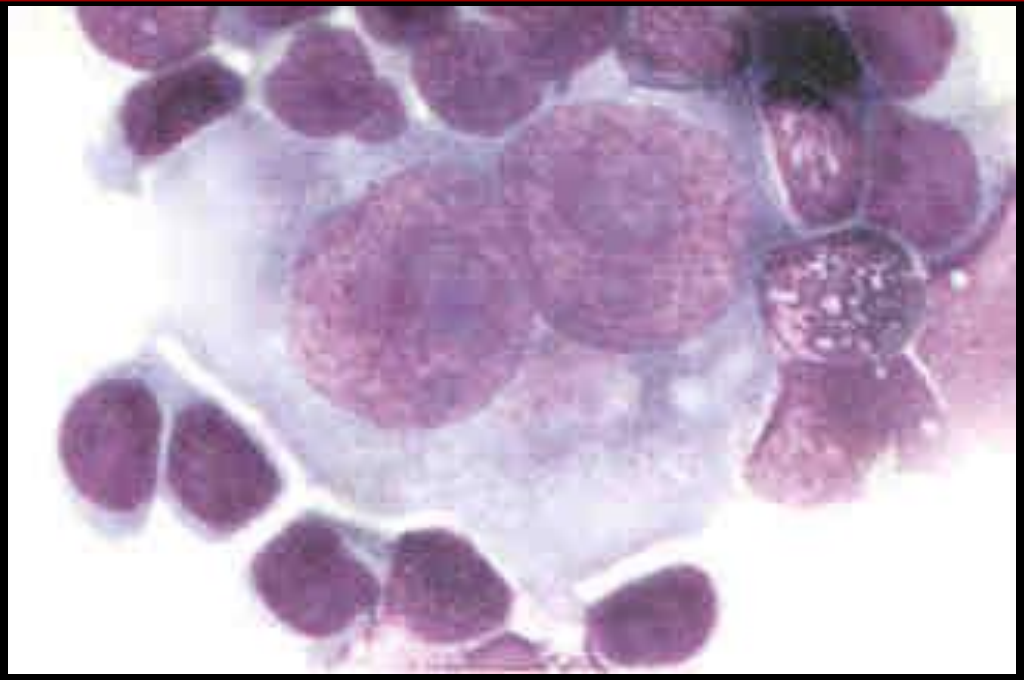
Lacunar cells seen in nodular sclerosis Hodgkin lymphoma

Hodgkin Lymphoma

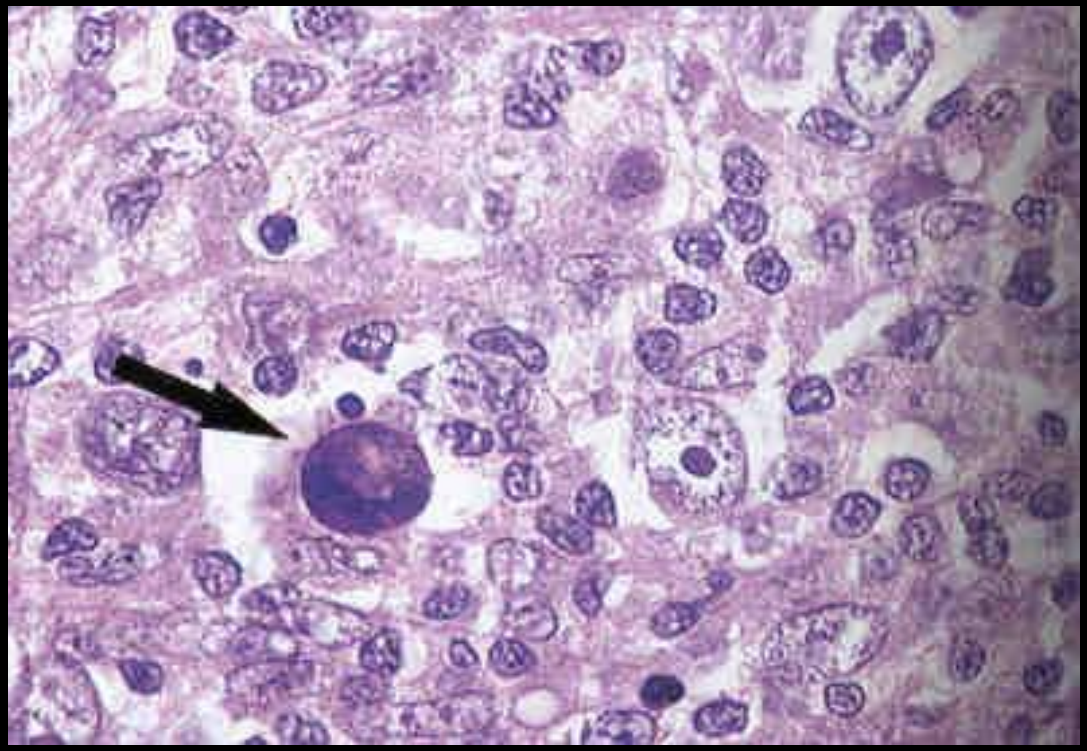


Diagnostic Reed-Sternberg cell

Reed-Sternberg cell



Mummified RS cell



Defining characteristics

- RS cells in the appropriate cellular background

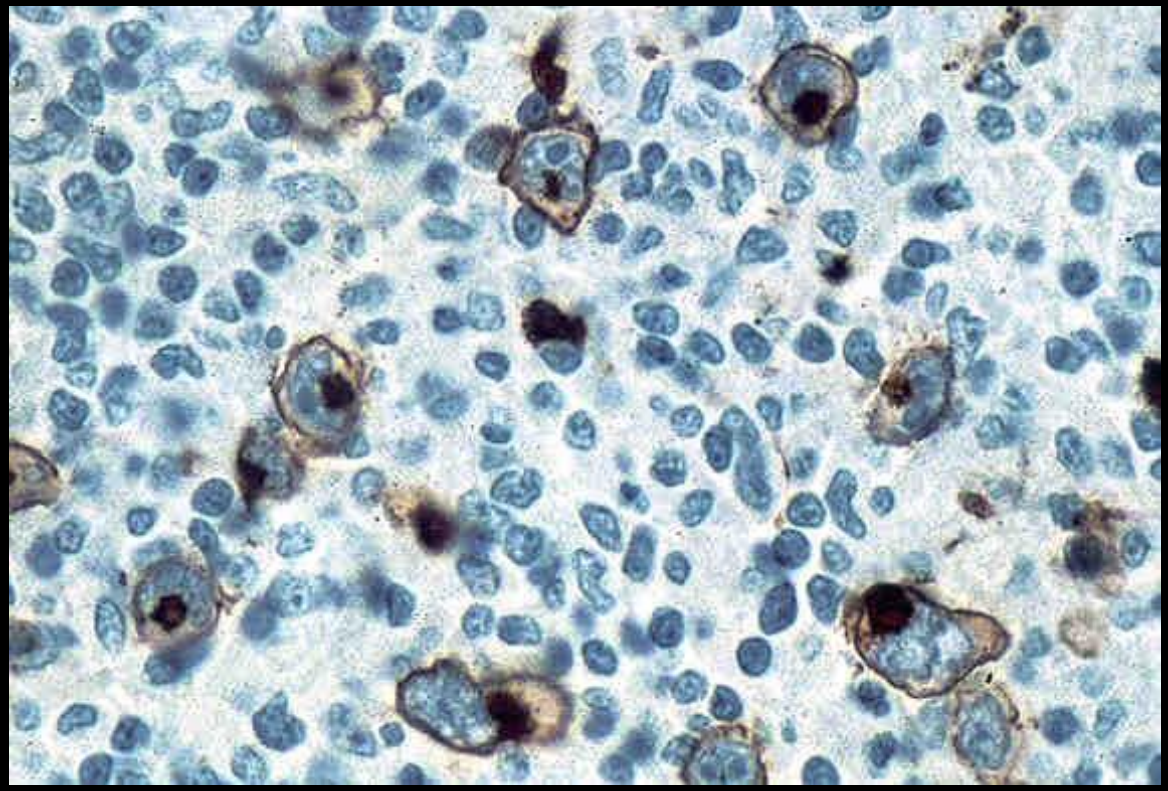
Immunophenotype

CD45- , CD15+ , CD30+, PAX5+

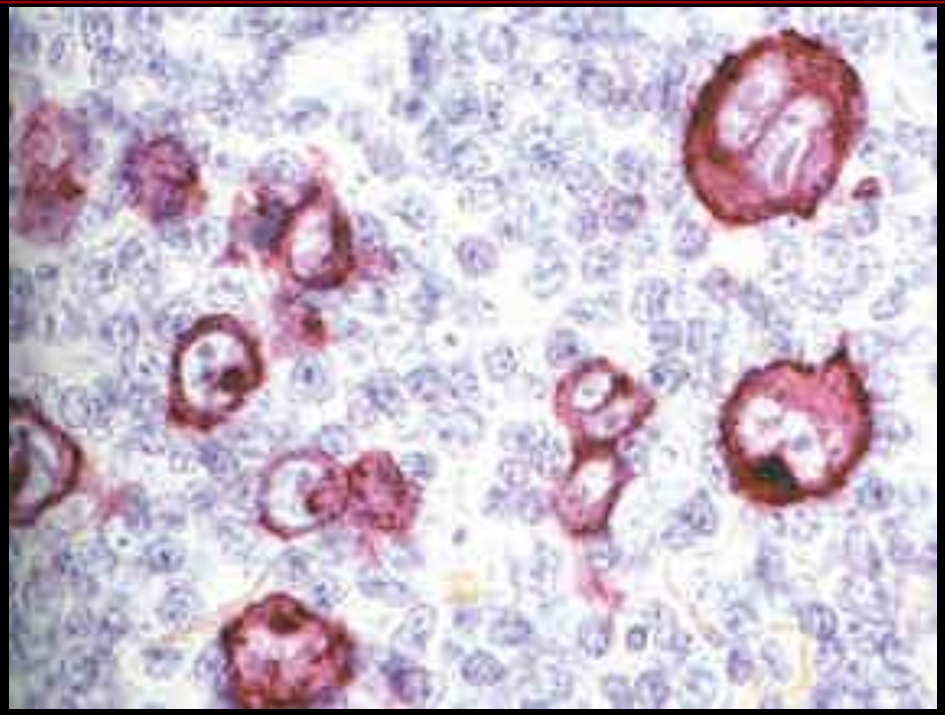
The neoplastic cells are usually not CD20 positive

The background lymphocytes are T cells (CD20 negative)

RS cells and CD15



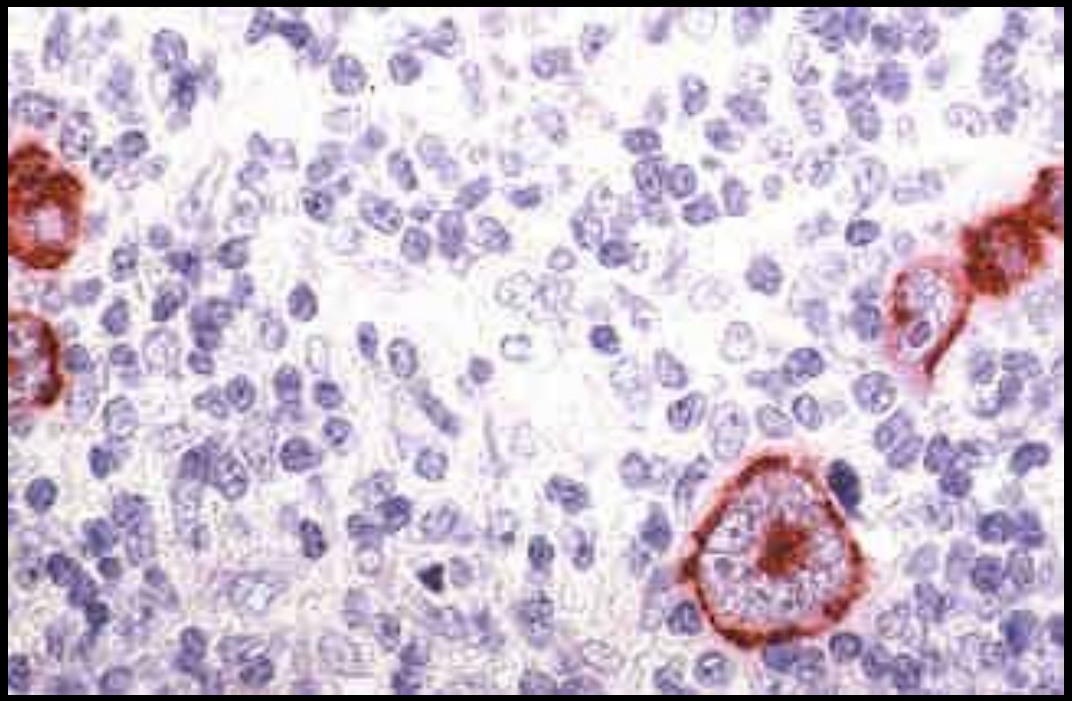
CD30



EBV

- The prevalence of EBV in RS cells varies according to the histological subtype:
  - Highest in mixed cellularity (75%)
  - Lowest in nodular sclerosis (10-40%)

EBV

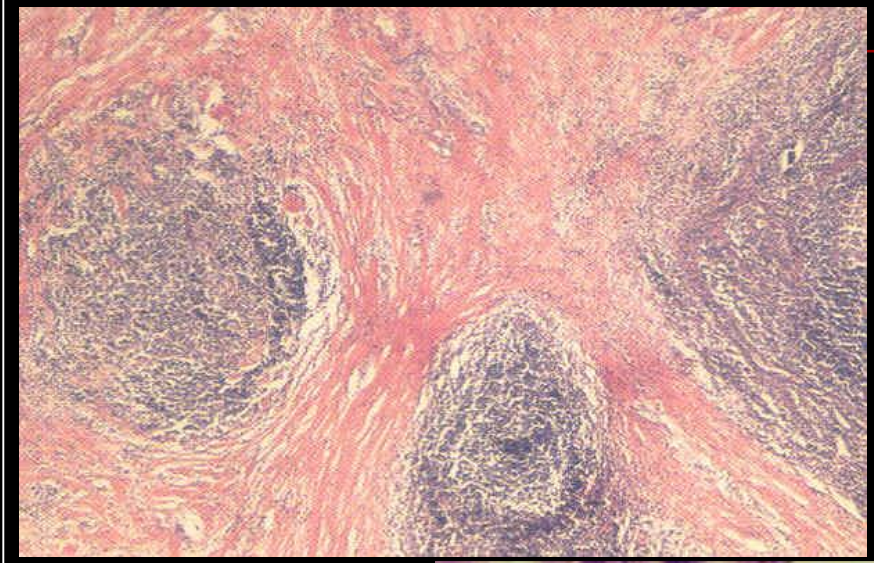


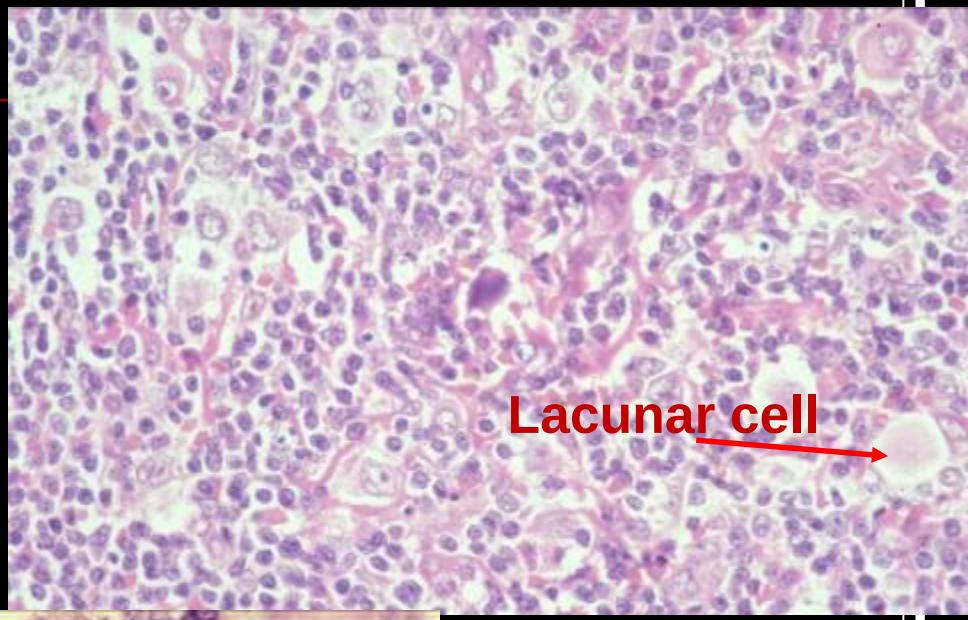
EBV-encoded Latent Membrane Protein 1 (LMP 1)

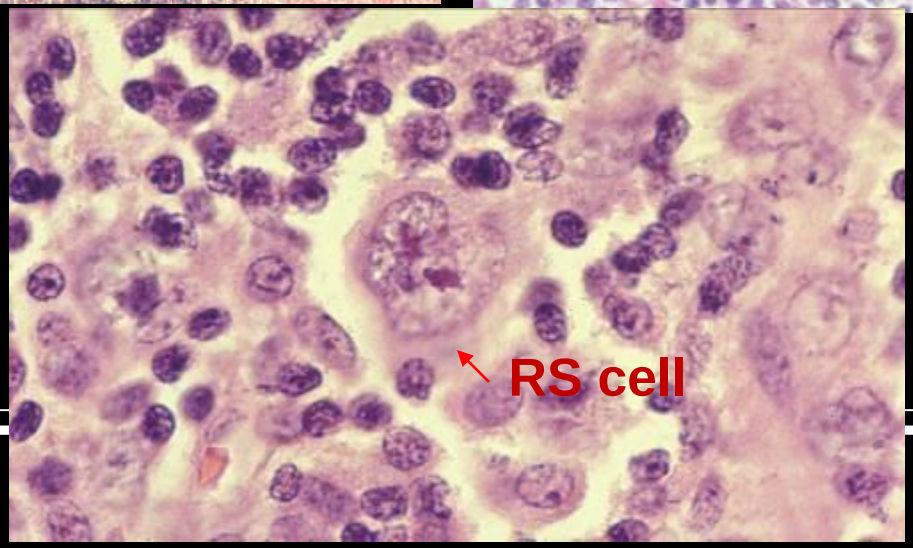
Nodular Sclerosis

- Most common type
- The only type of HL without a male predominance

Hodgkin Lymphoma
Nodular Sclerosis Type



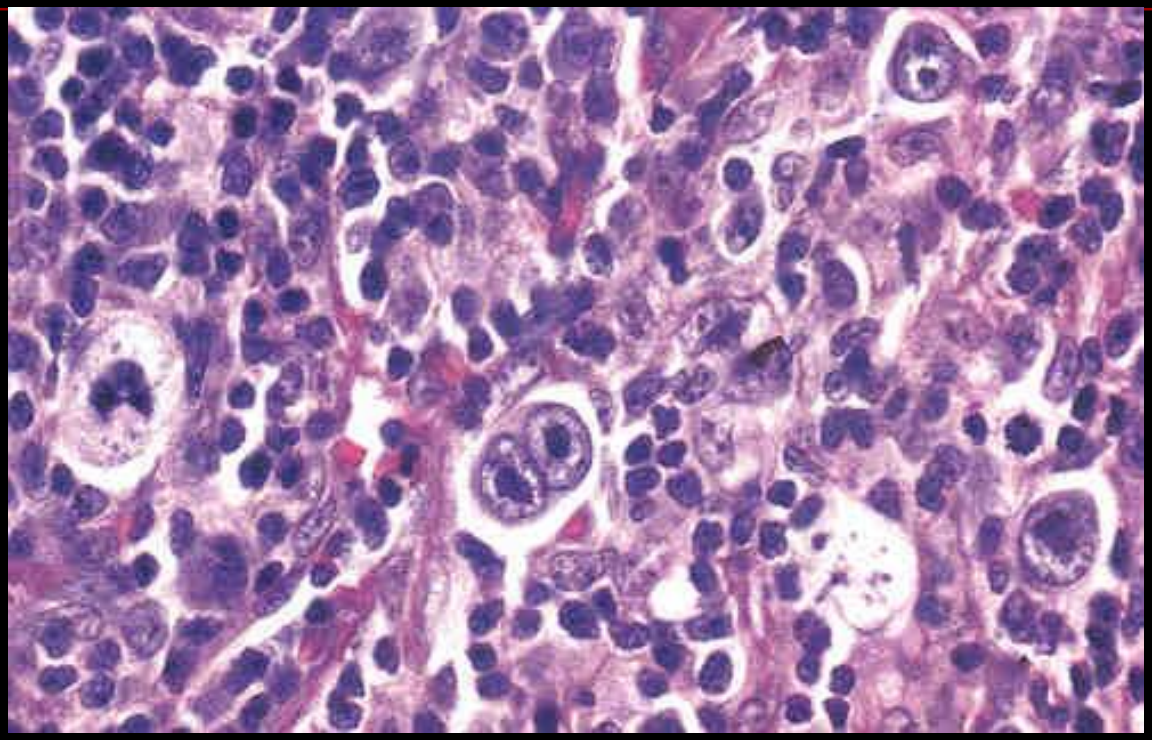




Mixed Cellularity HL

- More frequent in patients with HIV infection and in developing countries
- A bimodal age distribution is not seen

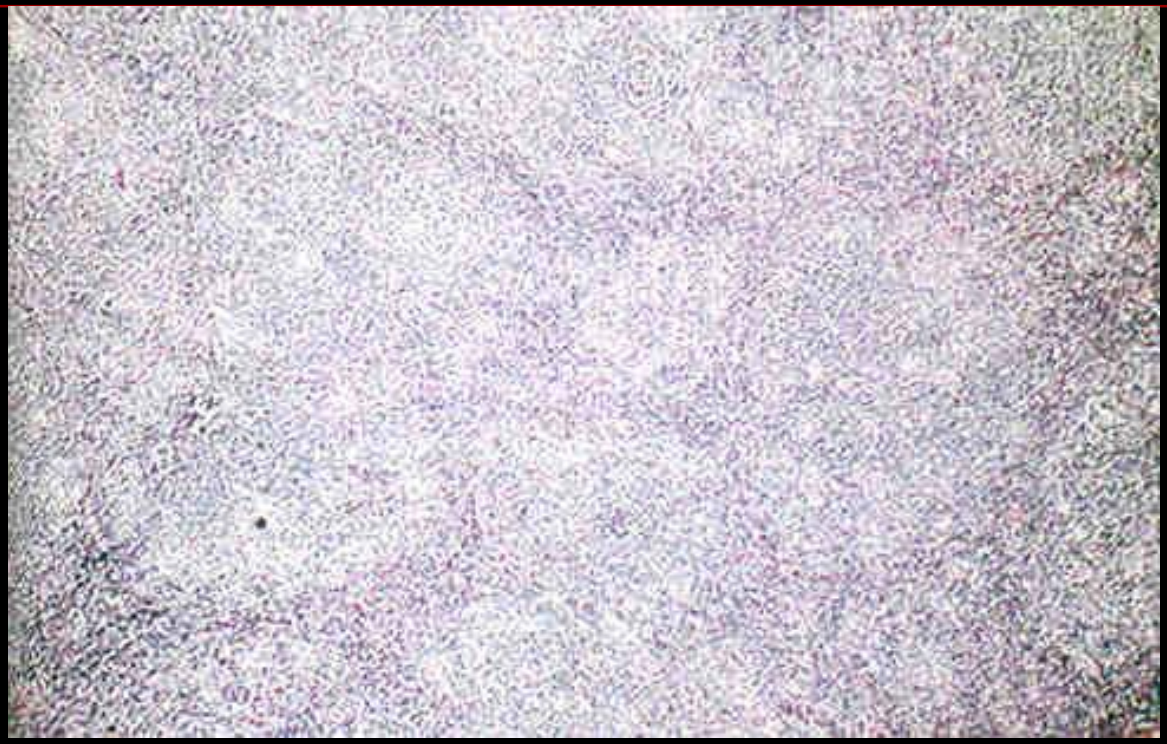
Mixed cellularity



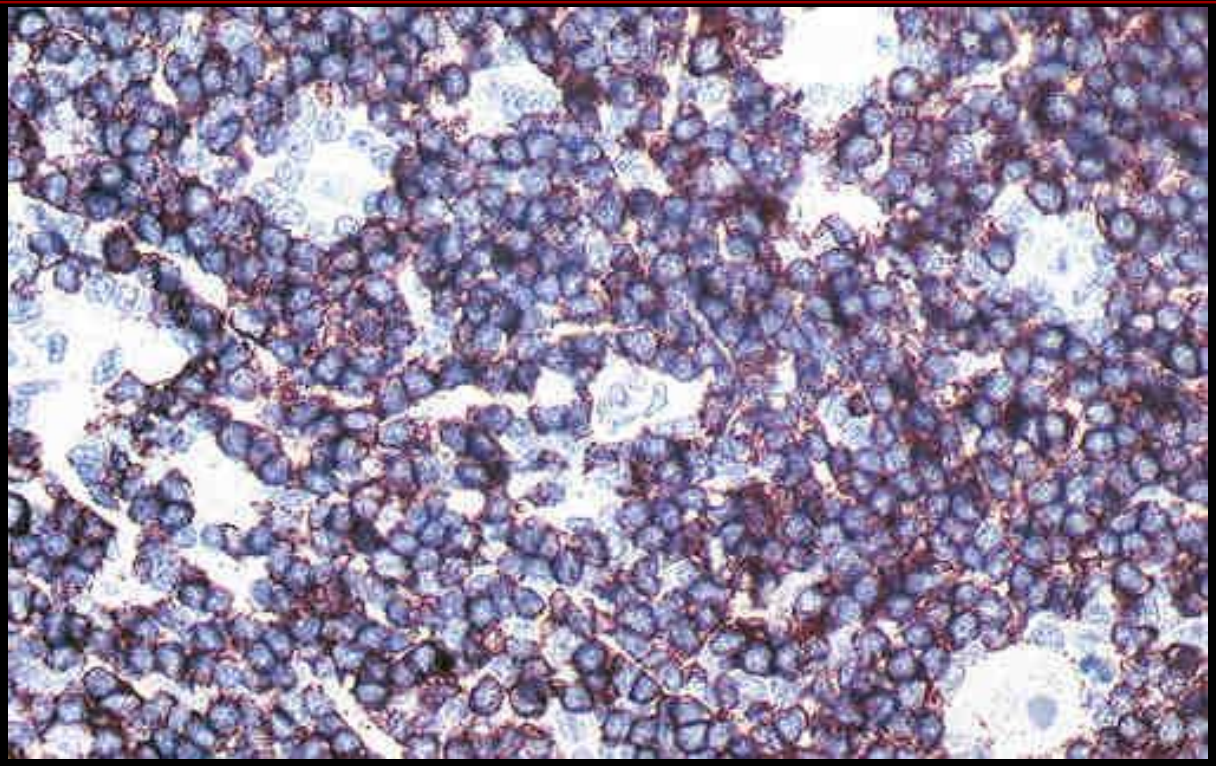
Lymphocyte rich classical Hodgkin lymphoma

- Nodular (common)
- Diffuse

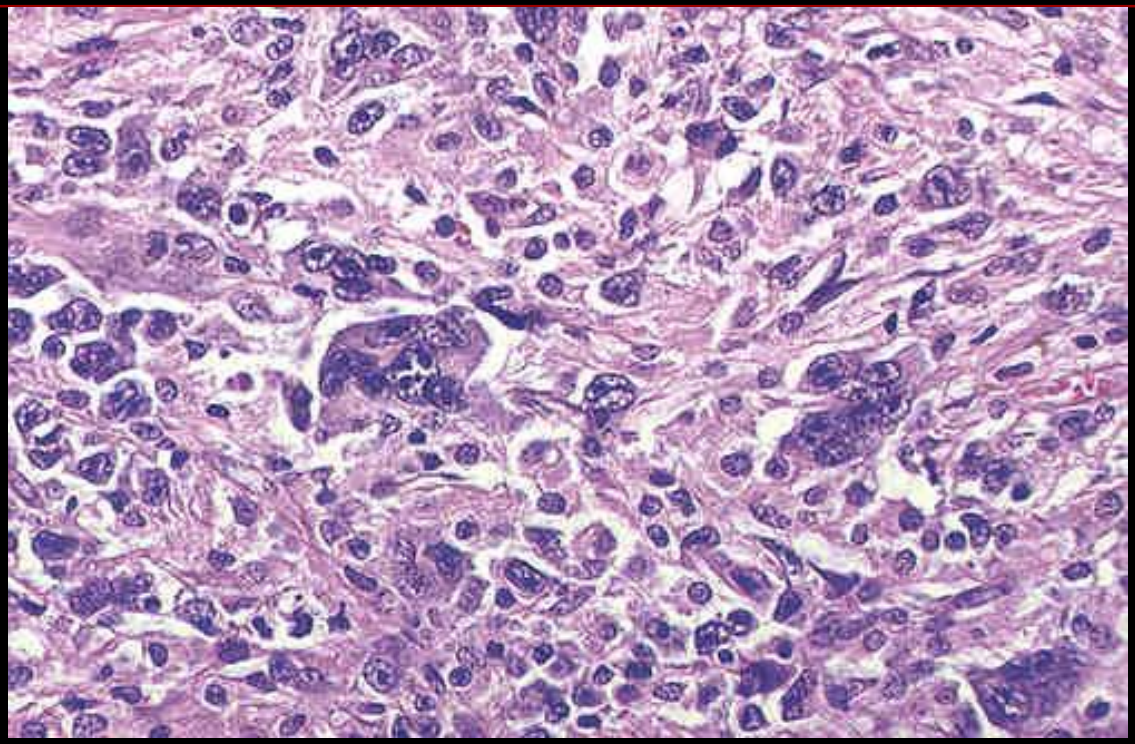
(Nodular) lymphocyte rich HL



Lymphcyte rich HL and CD20



Lymphocyte depleted HL



Classical Hodgkin : Prognosis

- Prognosis is now based on the clinical stage rather than the histological subtype.

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

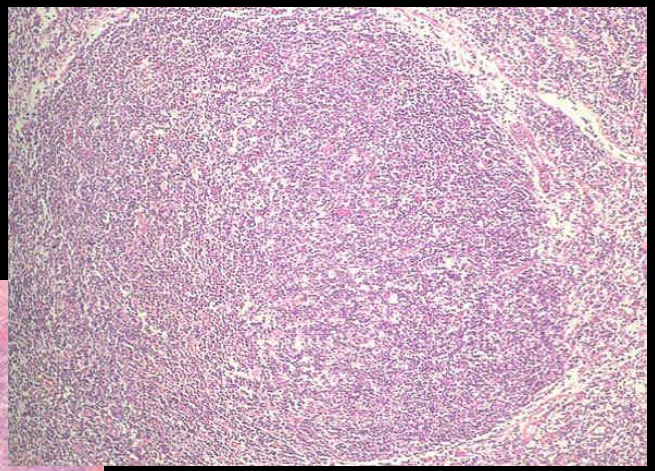
- 5% of Hodgkin lymphoma
- Male; mid 30's
- Bimodal age distribution not seen
- Most present with localized peripheral lymphadenopathy, develops slowly and is responsive to therapy
- LP (lymphocyte predominant) cells or L&H (lymphocytic and histiocytic) cells, also known as "Popcorn" cells

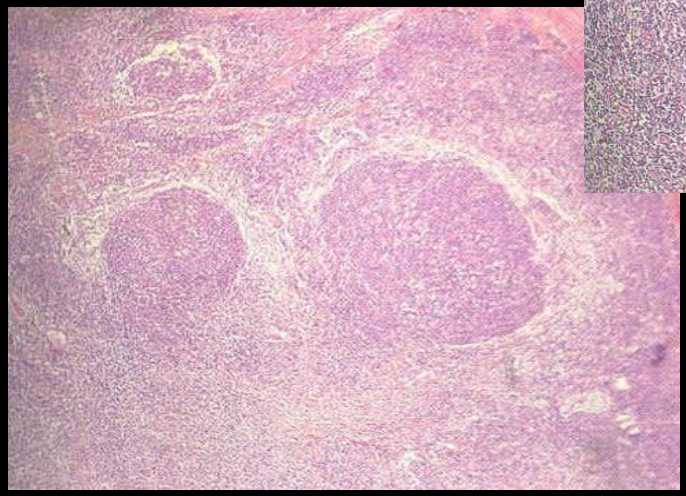
NLPHL

- Tends to spare mediastinum, spleen or BM
- Association with or progression to DLBCL (2-3%)
- Analogous to “low grade” B-cell lymphomas; but: (1) disseminated disease not usually seen, and (2) younger age.
- EBV negative

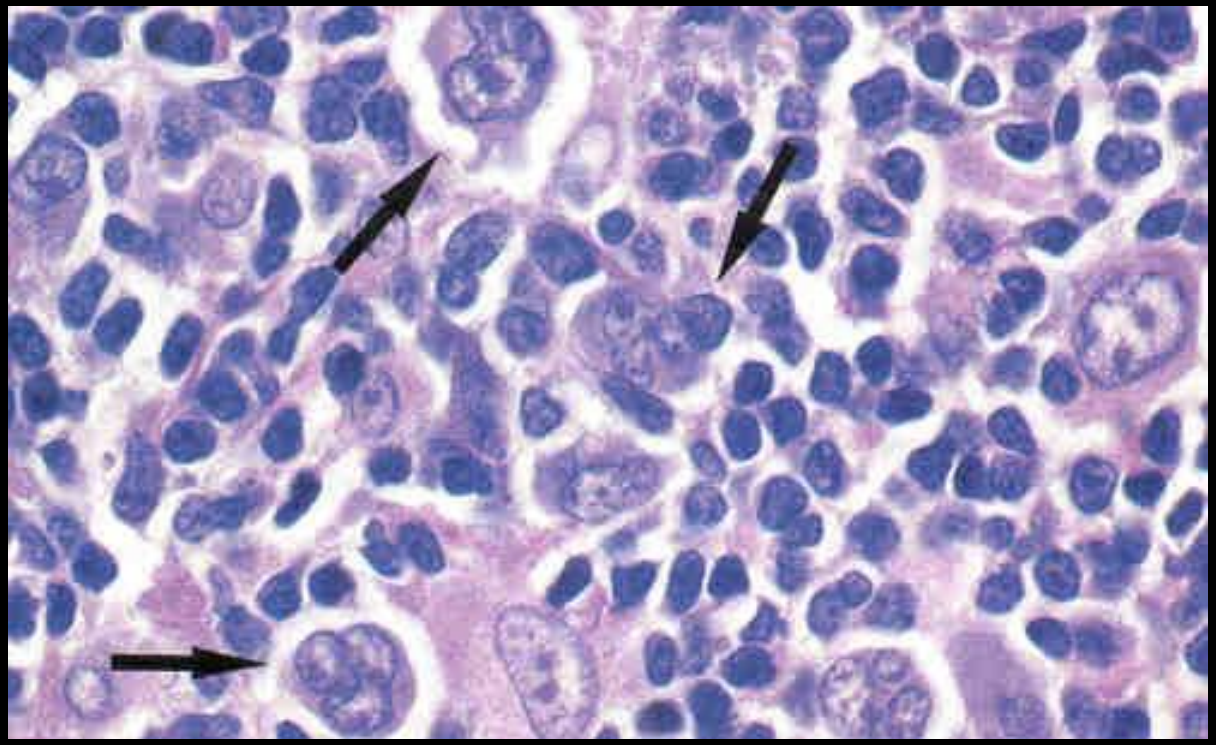
NLPHL

- Architecture:
  - Nodular
  - Nodular and diffuse





LP cells

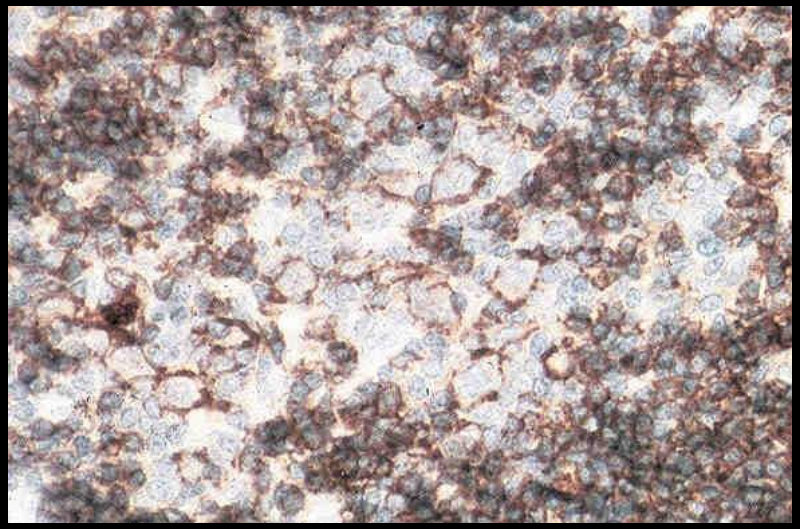


Immunophenotype

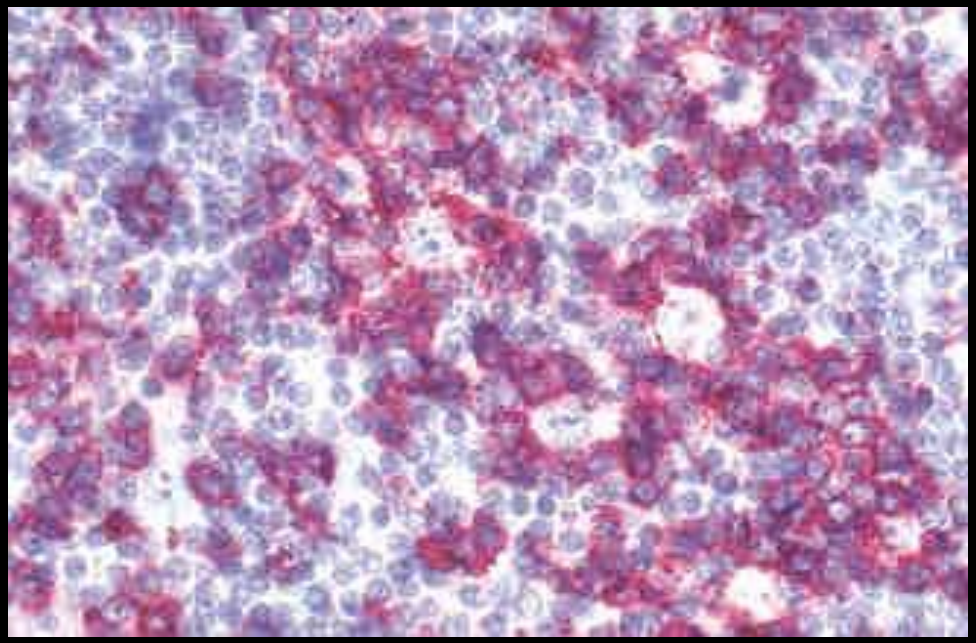
- CD45+
- CD20+
- EMA+ in 50% of cases
- CD 15 and CD30 are negative

CD 20

- Popcorn cells and the back ground cells are CD20 positive; CD20 can be used to highlight the nodularity



CD57



CD57 (+) T cells surround popcorn cells

NLPHL

- Prognosis is good especially for earlier stage
- 2-3% of cases progress to large B-cell lymphoma

Immunoprofile

NLPHL	CHL
CD45+ CD20+ CD15- CD30- EMA+ PAX5+	CD45- CD3- CD20- CD15+ CD30+ PAX5+
ALTCL	**DLBCL**
CD45+ CD20- CD3- CD4+ CD30+ ALK1+ EMA+ PAX5-	CD45+ CD20+ CD3- CD30+/- PAX5+

WHO 2016: NLPHL

- Cases associated with synchronous or subsequent sites that are indistinguishable from T-cell histiocyte-rich large B-cell lymphoma (THRLBCL) without a nodular component (lacking any follicular dendritic cells) should be designated THRLBCL-like transformation of NLPHL.
- Progression to a process with features of THRLBCL is associated with a more aggressive clinical course, and requires different management, such that the term NLPHL in this setting may not be sufficient