Malignant Lymphoid Disorders

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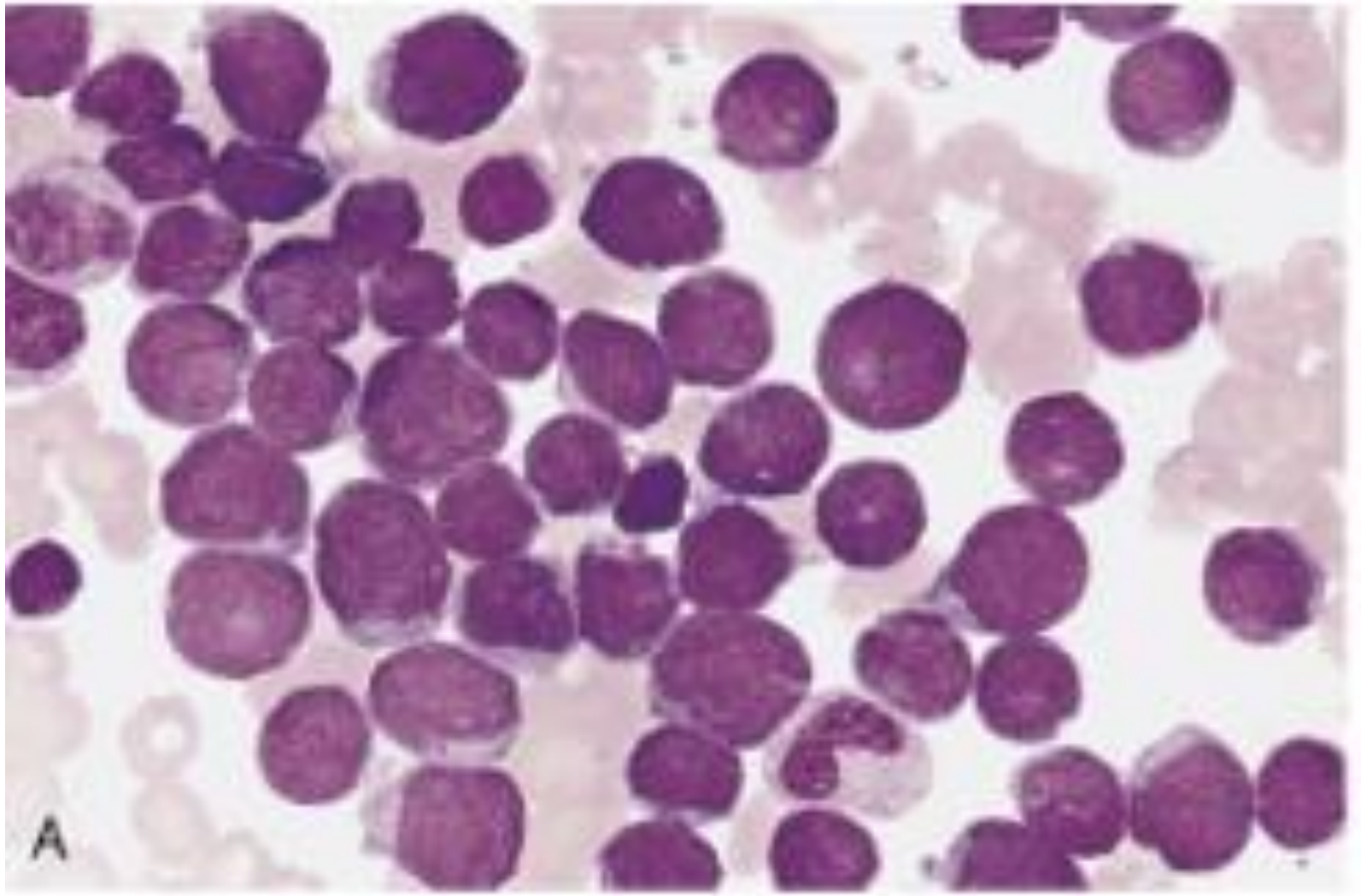
Lymphoid Neoplasms

- Lymphoblastic leukemia/lymphoma(B or T cell)
- Chronic Lymphoproliferative Disorders (B or T cell)
- Lymphoma

Lymphoblastic Leukemia/Lymphoma

- 75% of ALL occur in children < 5 years
- ~25% used as cutoff for leukemia
- B-ALL derived from lymphoblasts and positive for CD19, CD22, CD79a, HLA-DR, and express TdT activity.
- 85% of cases presenting in bone marrow/blood are B-lymphoblastic
- T-ALL derived from immature cells committed to T cell lineage
  - Combination of markers CD2, CD3, CD4, CD5, CD7, and CD8, CD34 may be present
- T-lymphoblastic presents a lymphoma in the mediastinum

Lymphoblasts



B-acute lymphoblastic leukemia (B-ALL)
- B-ALL with recurrent genetic abnormalities
  - B-ALLwith t(9;22)(q34.1;q11.2)/*BCR::ABL1*
    - with lymphoid only involvement
    - with multilineage involvement
  - B-ALLwith t(v;11q23.3)/*KMT2A* rearranged
  - B-ALL with t(12;21)(p13.2;q22.1)/*ETV6::RUNX1*
  - B-ALL, hyperdiploid
  - B-ALL, low hypodiploid
  - B-ALL, near haploid
  - B-ALL with t(5;14)(q31.1;q32.3)/*IL3::IGH*
  - B-ALL with t(1;19)(q23.3;p13.3)/*TCF3::PBX1*
  - B-ALL, *BCR*::*ABL1*–like , ABL-1 class rearranged
  - B-ALL, *BCR*::*ABL1*–like , JAK-STAT activated
  - B-ALL, *BCR*::*ABL1*–like , NOS
  - B-ALL with iAMP21
  - B-ALL with *MYC* rearrangement
  - B-ALL with *DUX4* rearrangement
  - B-ALL with *MEF2D* rearrangement
  - B-ALL with *ZNF384(362)* rearrangement
  - B-ALL with *NUTM1* rearrangement
  - B-ALL with *HLF* rearrangement
  - B-ALL with *UBTF::ATXN7L3/PAN3,CDX2* ("CDX2/UBTF")
  - B-ALL with mutated *IKZF1* N159Y
  - B-ALLwith mutated *PAX5* P80R
    - Provisional entity: B-ALL, *ETV6::RUNX1*-like
    - Provisional entity: B-ALL, with *PAX5* alteration
    - Provisional entity: B-ALL, with mutated *ZEB2* (p.H1038R)/IGH::*CEBPE*
    - Provisional entity: B-ALL, *ZNF384* rearranged-like
    - Provisional entity: B-ALL, *KMT2A* rearranged-like
- B-ALL, NOS

T-ALL
- Early T-cell precursor ALLwith *BCL11B* rearrangement
- Early T-cell precursor ALL, NOS
- T-ALL, NOS
  - Provisional entities (see Supplemental Table 7)

Provisional entity: Natural killer (NK) cell ALL

Subtype	Frequency	Prognosis	Diagnostic approach	Partner genes	Immunophenotype	Comment	References
B-ALL with *MYC* rearrangement	2-5%, higher in adults and AYA)	Poor	FISH *MYC/BCL2/BCL6* ; Ig V(H) mutational status	IGH	TdT+CD34-CD20+/- ; may be SIg+	May have *BCL2/ BCL6* rearrangements	217,218,241
B-ALL with *DUX4* rearrangement	5-10%, highest in AYA and adult	Excellent	WTS[a], IHC for DUX4 overexpression	Enhancers, most commonly IGH	CD371+; CD2+	Common *ERG* and *IKZF1* deletions	221-225
B-ALL with *MEF2D* rearrangement	3-5%	Poor	WTS; FISH *MEF2D*	*BCL9*, *HNRNPUL1*	CD10-/dim; CD38+; cu+		226,227
B-ALL with *ZNF384 or ZNF362* rearrangement	5-10%, higher inAYA	Variable	WTS; FISH possible	*EP300* (most common and good prognosis), *TCF3*, *TAF15*, *CREBBP*	CD10-/dim; myeloid antigen +	~50% of B/My MPAL in children, but not adults; FLT3 overexpression	229-232
B-ALL with *NUTM1* rearrangement	2% or less; rare in adults, mostly in infants lacking *KMT2A* rearrangements	Good	FISH *NUTM1* ; WTS; NUTM1 overexpression (WTS, RT-PCR, IHC)	*ACIN1*, *ZNF618*, *BRD9*, *IKZF1*, *CUX1*	CD10-/dim; expression of myeloid markers (CD13/CD15/CD33)	Common overexpression of HOXA9	234,235
B-ALL/LL with *HLF* rearrangement	<<1% children	Very poor	WTS; FISH HLF	*TCF3*; *TCF4*	Unknown	May respond to anti-CD19 therapy	237
CDX2/UBTF	<1%; higher in AYA and female;	Poor	RT PCR, WTS	*UBTF*::*ATXN7L3* by cryptic deletion of 17q21.31 ; high expression of CDX2 by deletion *FLT3/PAN3* at 13q12.2)	CD10 negative and cytoplasmic IgM positive		238-240
B-ALL/LL with mutated *IKZF1* N159Y	<1% all ages	Intermediate	Exome/ gene panel sequencing	N.A.	Unknown	Distinct gene expression profile; gain of chromosome 21 in 75% of cases	241,244
B-ALL/LL with mutated *PAX5* P80R	2-5% higher in adult	Intermediate, good in adults	Exome/gene panel sequencing	N.A.		Biallelic *PAX5* alterations from deletion or LOF mutation of second allele; *CDKN2A* loss; *JAK* and *RAS* signaling gene mutations	241,242,263

B Lymphoblastic Leukemia/Lymphoma Poor Prognosis

With t(9;22)(q34.1;q11.2): BCR-ABL1	With t(v;11q23.3): KMT2A-rearranged	With hypodiploidy(<46 chromosomes)
• 25% of adult cases, 2-4% pediatric • Traditionally worst outcome of B-ALL	• Most common B-ALL in infants	

B Lymphoblastic Leukemia/Lymphoma favorable prognosis

With t(12;21)(p13.2;q22.1): ETV-RUNX1	With hyper diploidy(>50 chromosomes)
• 25% of pediatric (non-infant) • Excellent prognosis	

Each accounts for 25% of cases in children (non-infants)

Both excellent prognosis with >90% cure

B Lymphoblastic Leukemia/ Lymphoma others

With t(5;14)(q31.1;q32.1); IGH/IL3

- <1% of B-ALL
- Eosinophilia

With t(1;19)(q23;p13.3); TCF3-PBX1

- Traditionally poor prognosis, now better
- High risk of CNS relapse

Lymphoproliferative Disorders

- Clonal, malignant proliferation of B-cells, T-cells, or rarely NK cells
- Usually chronic but some behave more aggressively
- Often are related to stage of development of the lymphocyte

Mature B-cell Lymphoproliferative Disorders

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
*Large B-cell lymphoma with IRF4 rearrangement**
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*
Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV^+ DLBCL, NOS*
*EBV^+ mucocutaneous ulcer**
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK^+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
*$HHV8^+$ DLBCL, NOS**
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration**
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature B-cell Lymphoproliferative Disorders

- CLL/SLL (chronic lymphocytic leukemia/small lymphocytic leukemia
- Hairy cell leukemia
- Marginal zone lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Burkitt lymphoma
- Large cell lymphoma
- Lymphoplasmacytic lymphoma
- Plasma cell neoplasms

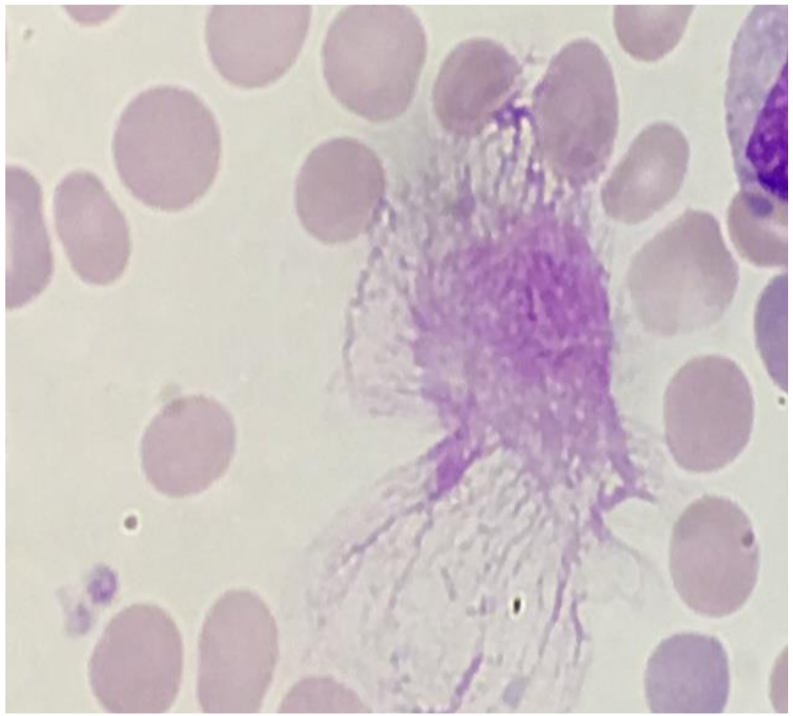
Chronic lymphocytic leukemia (CLL)

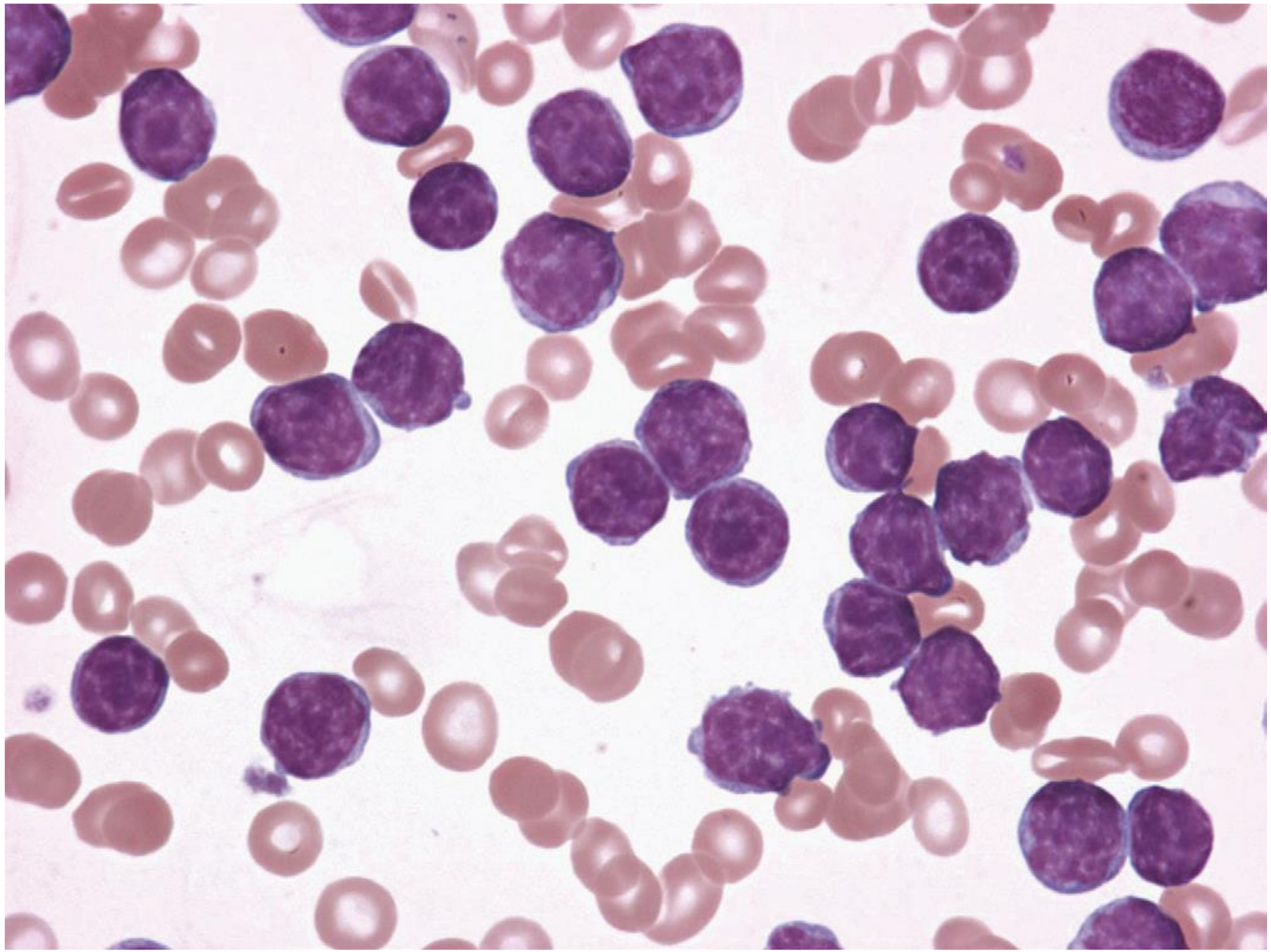
- A disorder of B lymphocytes
- Prevalence: a disease of the older adults, median age at presentation 70 yrs.
- fatigue & lymphadenopathy
- Labs:
  - CBC-HALLMARK: isolated lymphocytosis
  - PB smear-smudged lymphocytes are common findings
  - Prolymphocytes or atypical lymphoid cells may be seen
  - Immunophenotype: CD19, CD20, and CD23 but aberrantly co-express the T cell antigen CD5.

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

- Prognosis is variable. Important factors include cytogenetic abnormalities (del11q and 17p bad, del13q14 good) and whether the LPD arose from a naïve (IGHV non-mutated, good) B-cell or one which underwent somatic hypermutation(bad)
- May have a prolymphocytic transformation
- Transformation into diffuse large B-cell leukemia called Richter transformation

CLL/SLL





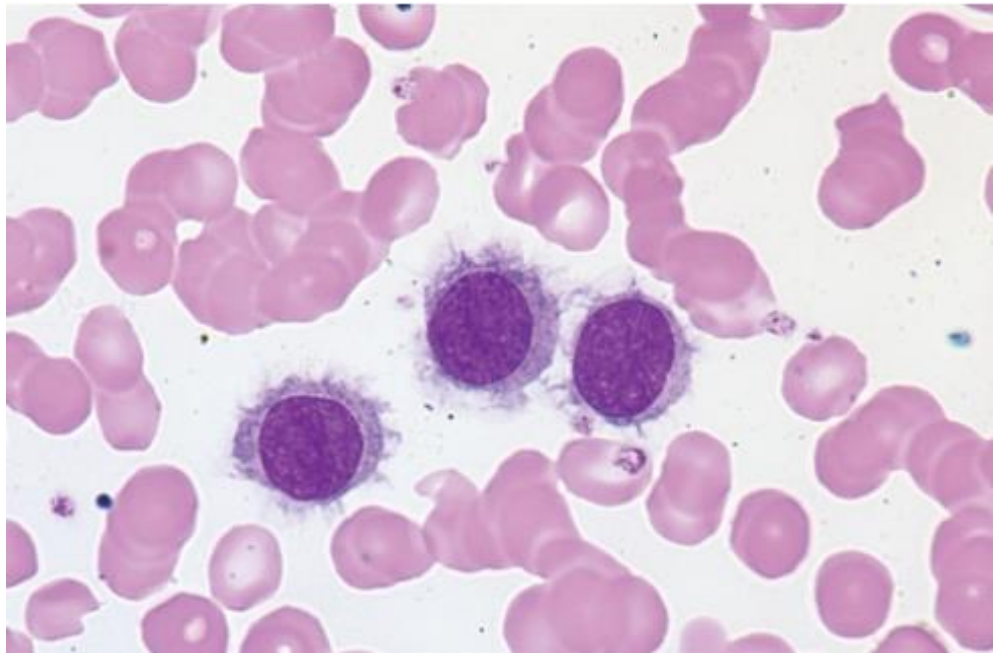
Hairy Cell Leukemia (HCL)

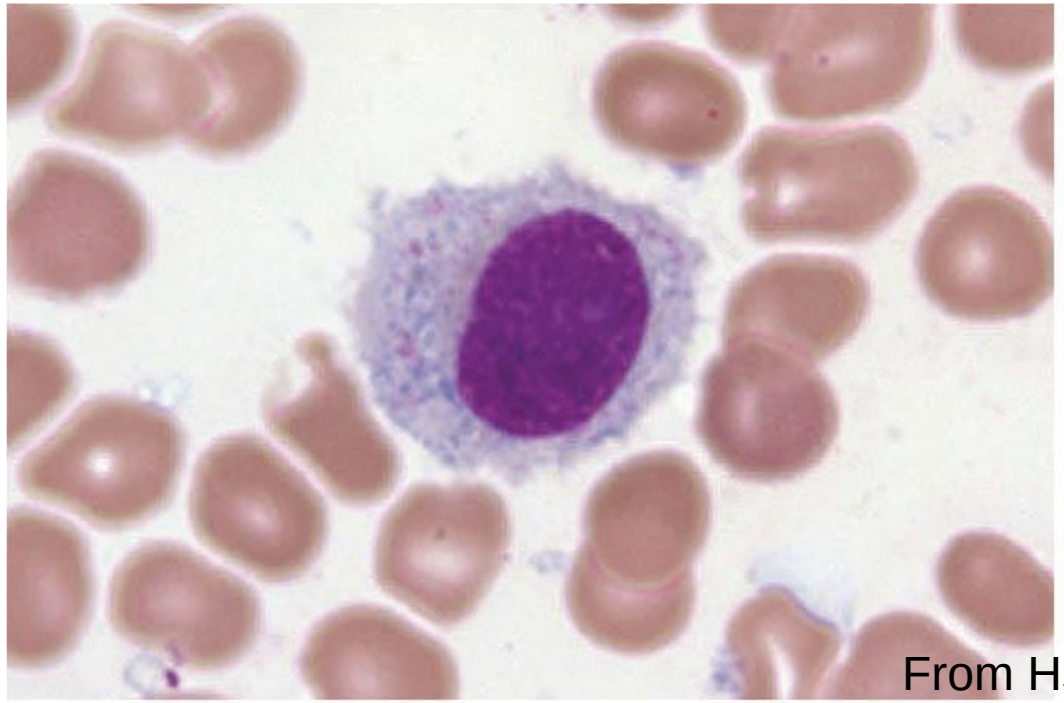
- HCL is an indolent mature B-cell neoplasm most found in middle age group
- Hairy cells
  - Small to intermediate sized cell
  - Round or reniform/indented nucleus
  - Homogenous spongy chromatin, no nucleoli
  - Abundant pale blue cytoplasm with circumferential hair like projections
- Middle aged men presenting with splenomegaly and cytopenias, classically monocytopenia

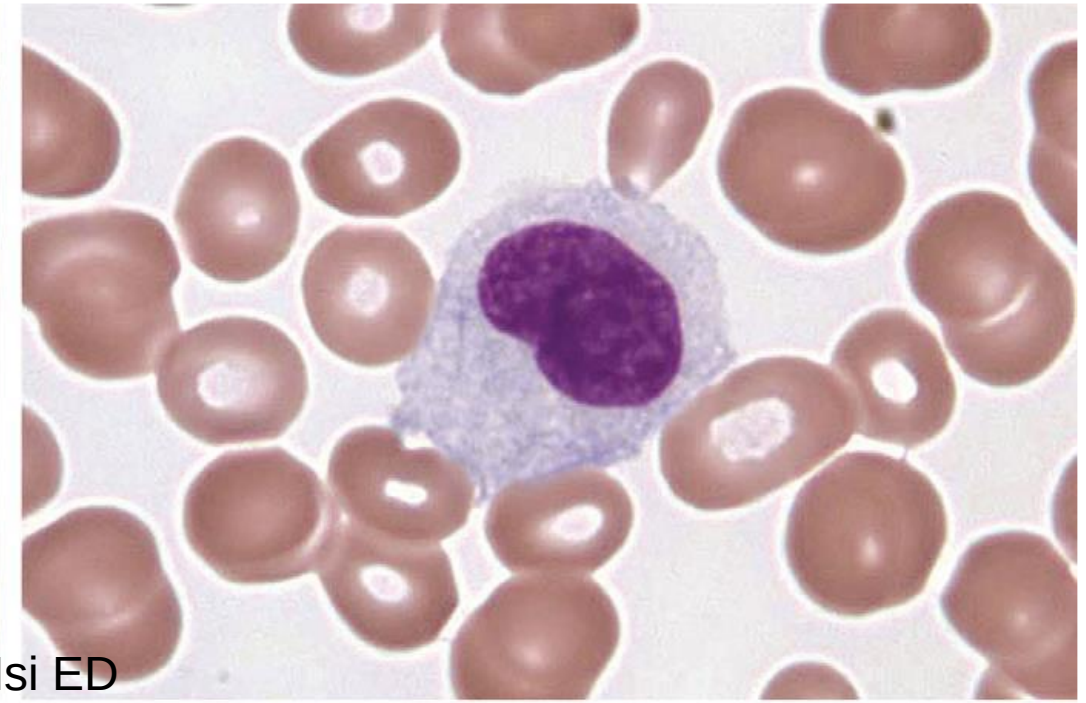
Hairy Cell Leukemia (HCL)

- Tartrate resistant acid phosphatase (TRAP)
  - Hairy cell leukemia will stain positive for acid phosphatase in the presence of tartrate vs normal lymphocytes will not stain in the presence of tartrate
- Replaced largely by flow cytometry(CD22, CD25, CD103, CD123) and IHC (AnnexinA1, BRAF V600E)
- BRAF V600E in nearly all cases

Hairy Cell



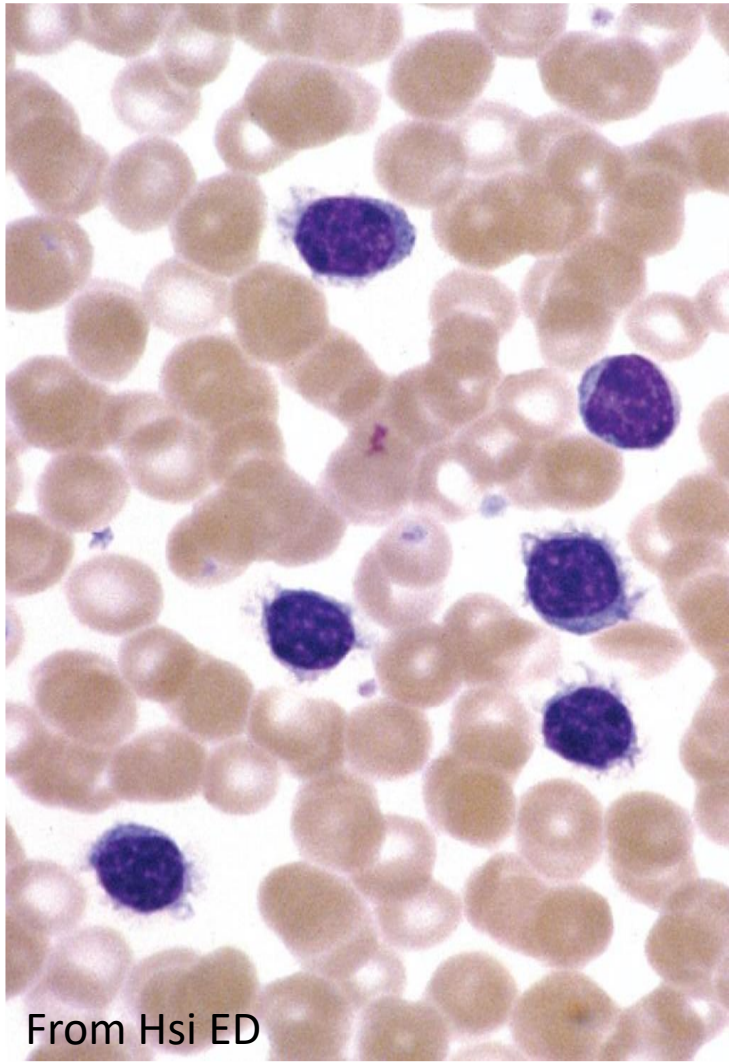




From Hsi ED

Marginal Zone Lymphoma (MZL)

- An indolent B cell lymphoma
- Arises in marginal zone of lymph nodes, spleen, and mucosa-associated lymphoid tissues (MALT) eg. GI tract, eye
- Splenic marginal zone B cell lymphoma usually involve PB and BM
- An absolute lymphocytosis is present
- Can have villous lymphocytes (esp splenic)- short and polar, vs hairy cells



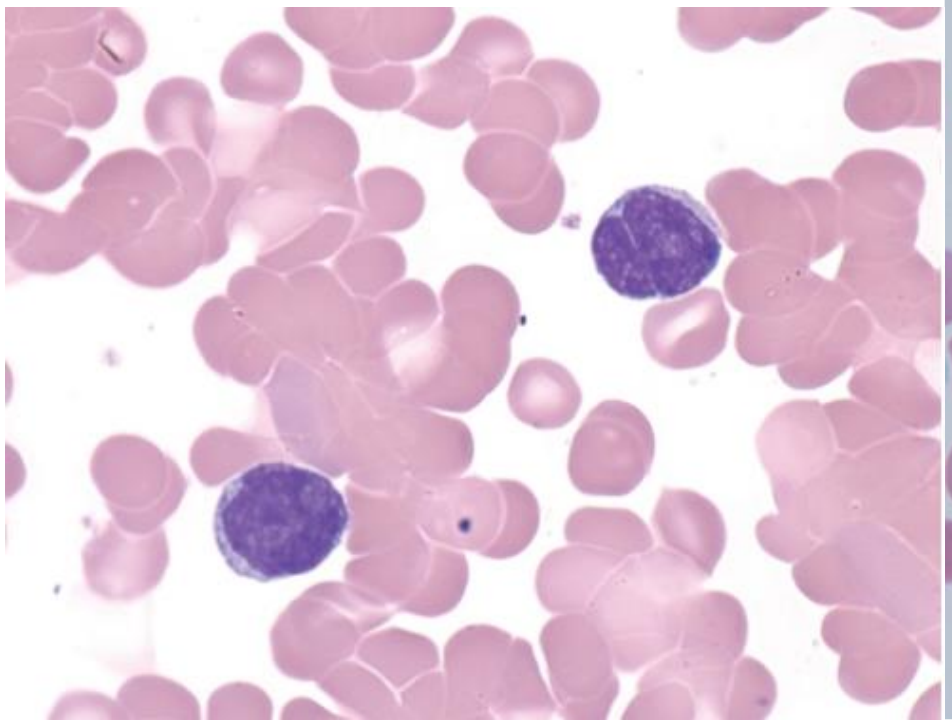
From Hsi ED

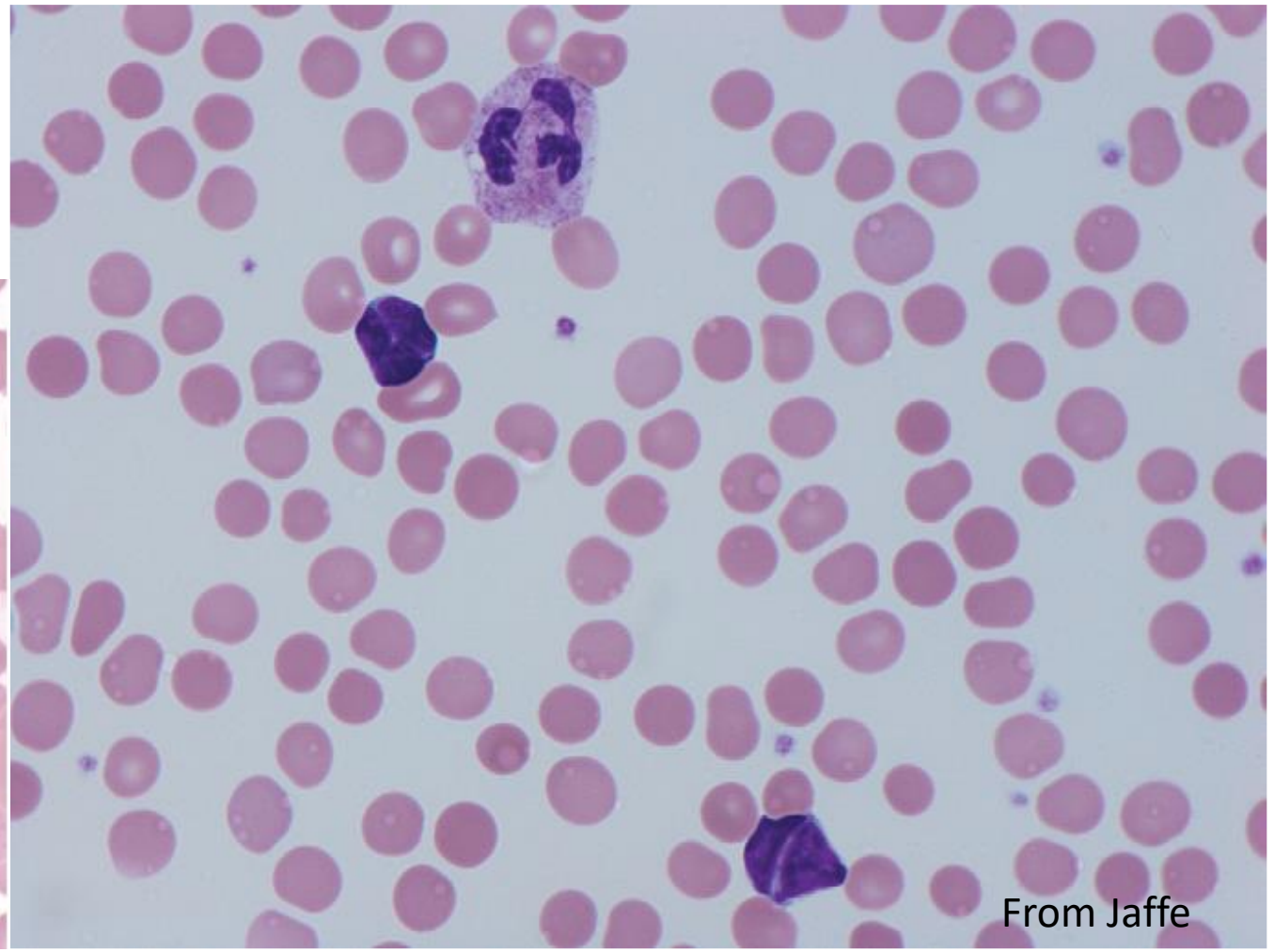
Follicular Lymphoma

- Follicular lymphoma is a B-cell lymphoma and typically affects middle-aged or older adults
- Composed of cells from the germinal center with centrocytic (small cleaved cells) and centroblastic cells, with at least a partially follicular pattern
- Germinal center cells are positive for CD10 and BCL. Aberrant co-expression of BCL-2 due to t(14,18)(q32;q21)
- It is the most common subtype of indolent (slow-growing) NHL
- The most common sign of follicular NHL is painless swelling in the lymph nodes of the neck, armpit or groin.

Follicular lymphoma

- In PB, can see nuclei with cleaves



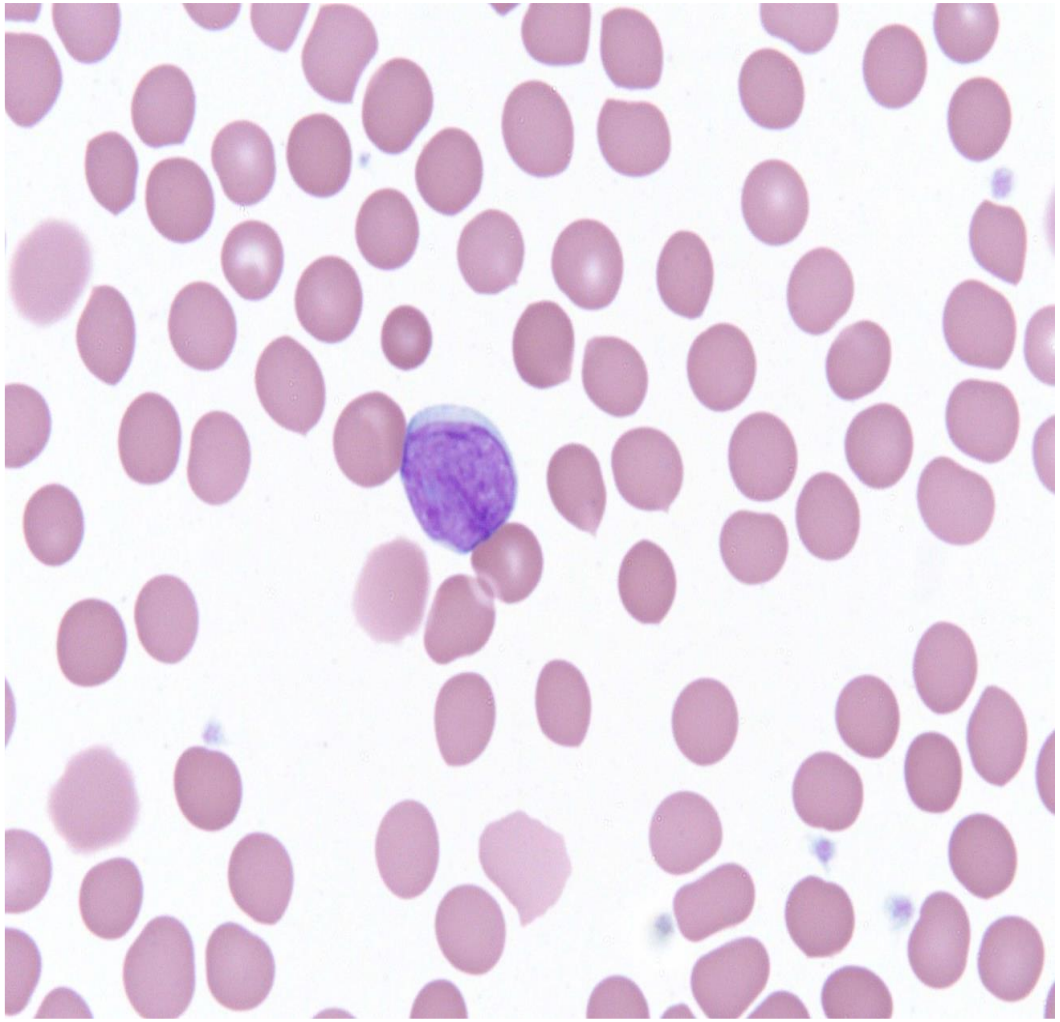


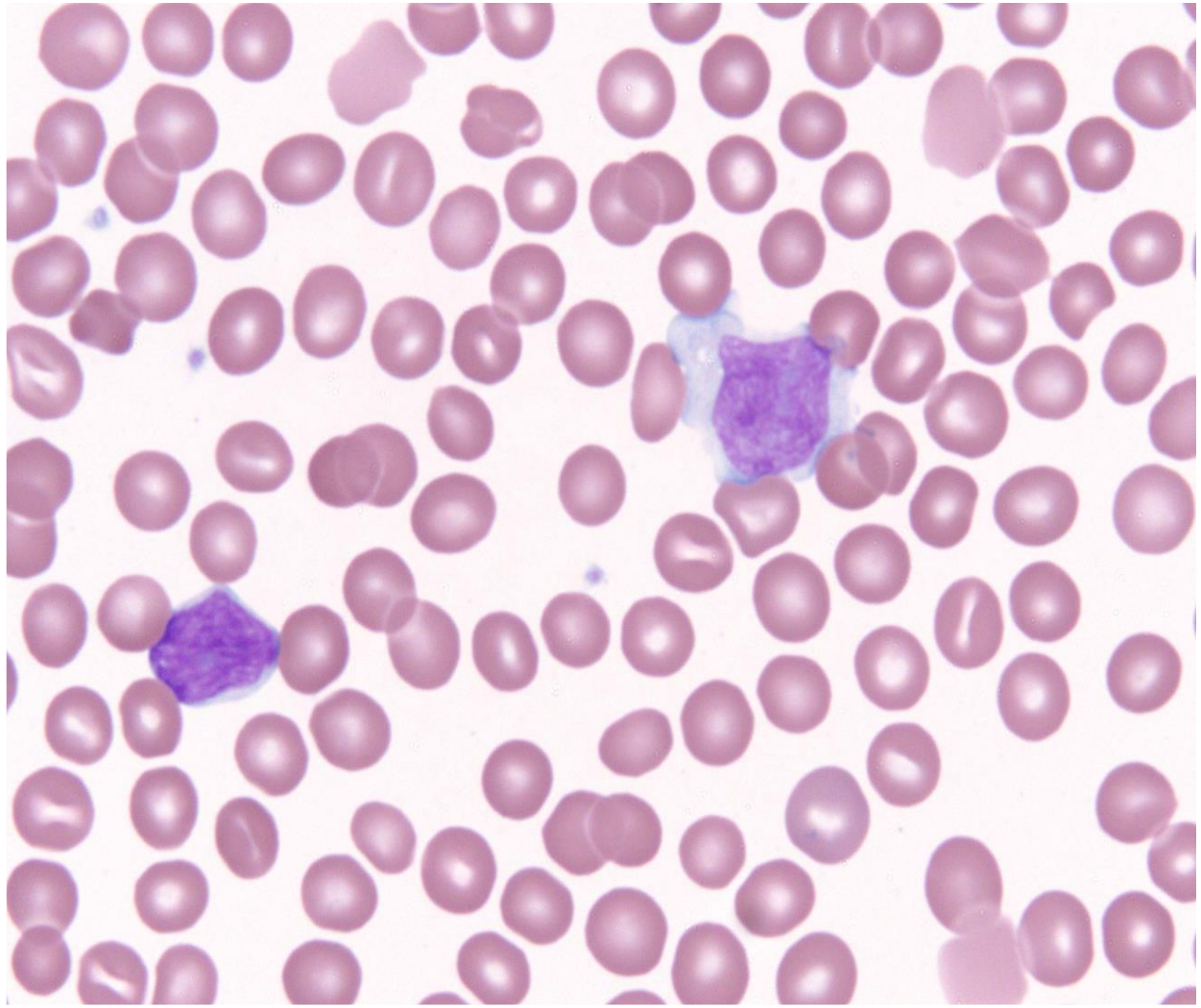
From Jaffe

Mantle Cell Lymphoma

- Mantle cell lymphoma is a type of aggressive B-cell lymphoma
- Most commonly affects men, median age at diagnosis is 68 yrs.
- Accurate diagnosis requires demonstration of t(11;14) or overexpression of cyclin D1 by IHC
- CD5-positive, CD23 and CD200 negative
- Typically nodal, can also be in blood

Mantle cell lymphoma

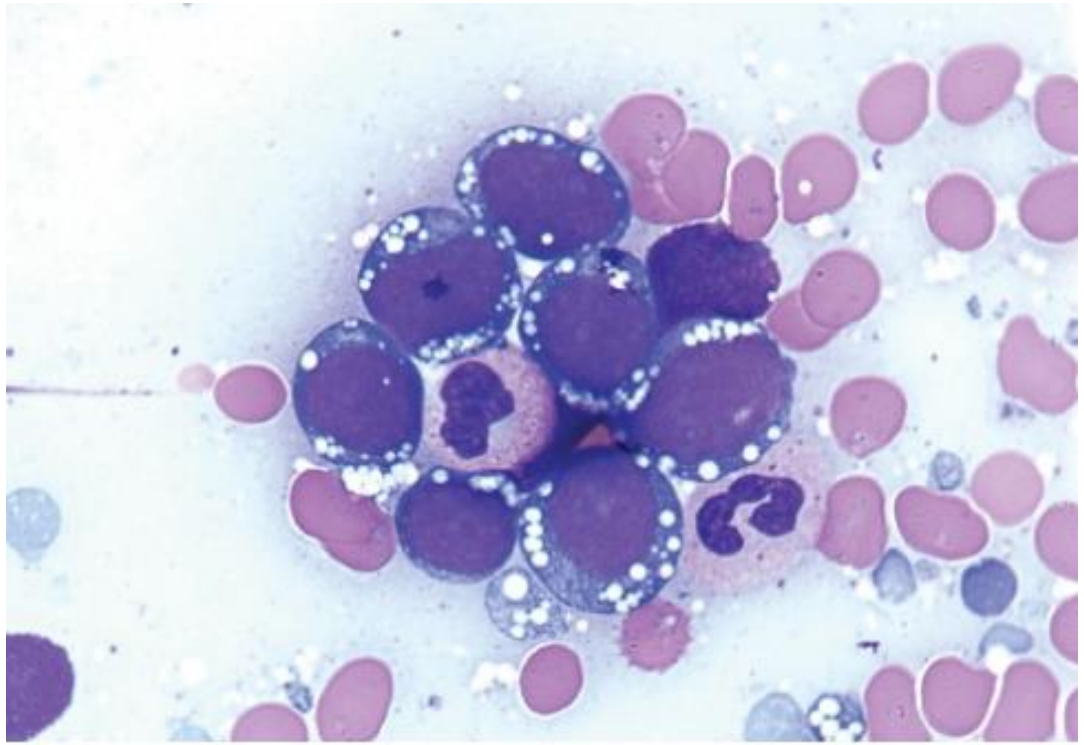




Burkitt Lymphoma

- Highly aggressive but curable lymphoma
- Classically associated w/ t(8;14)(q24;q32)
- Associated with EBV
  - Endemic (age 4-7): >95%
  - Sporadic (kids/young adults): 20-30%
  - Immunodeficiency-associated (HIV): 25-40%
- Monomorphic, medium size w deeply basophilic, vacuolated cytoplasm.

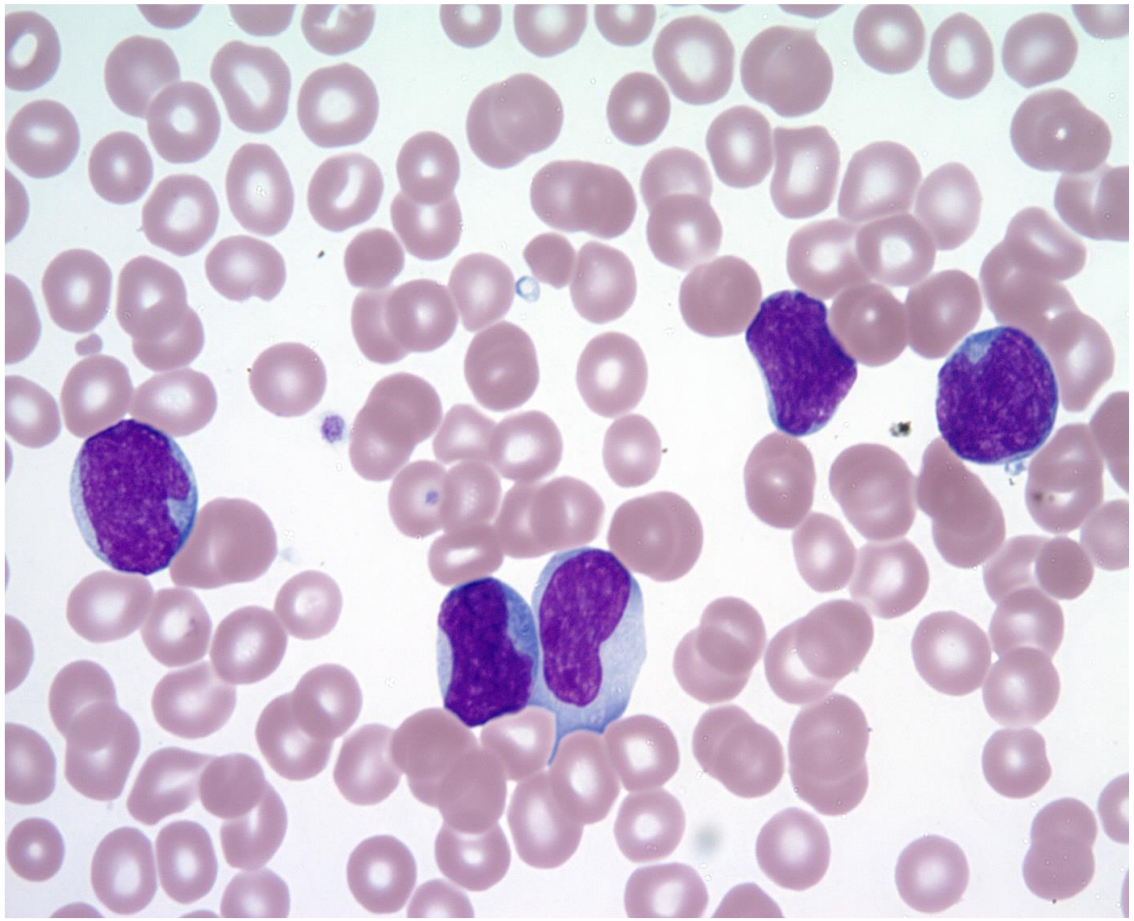
Burkitt Lymphoma

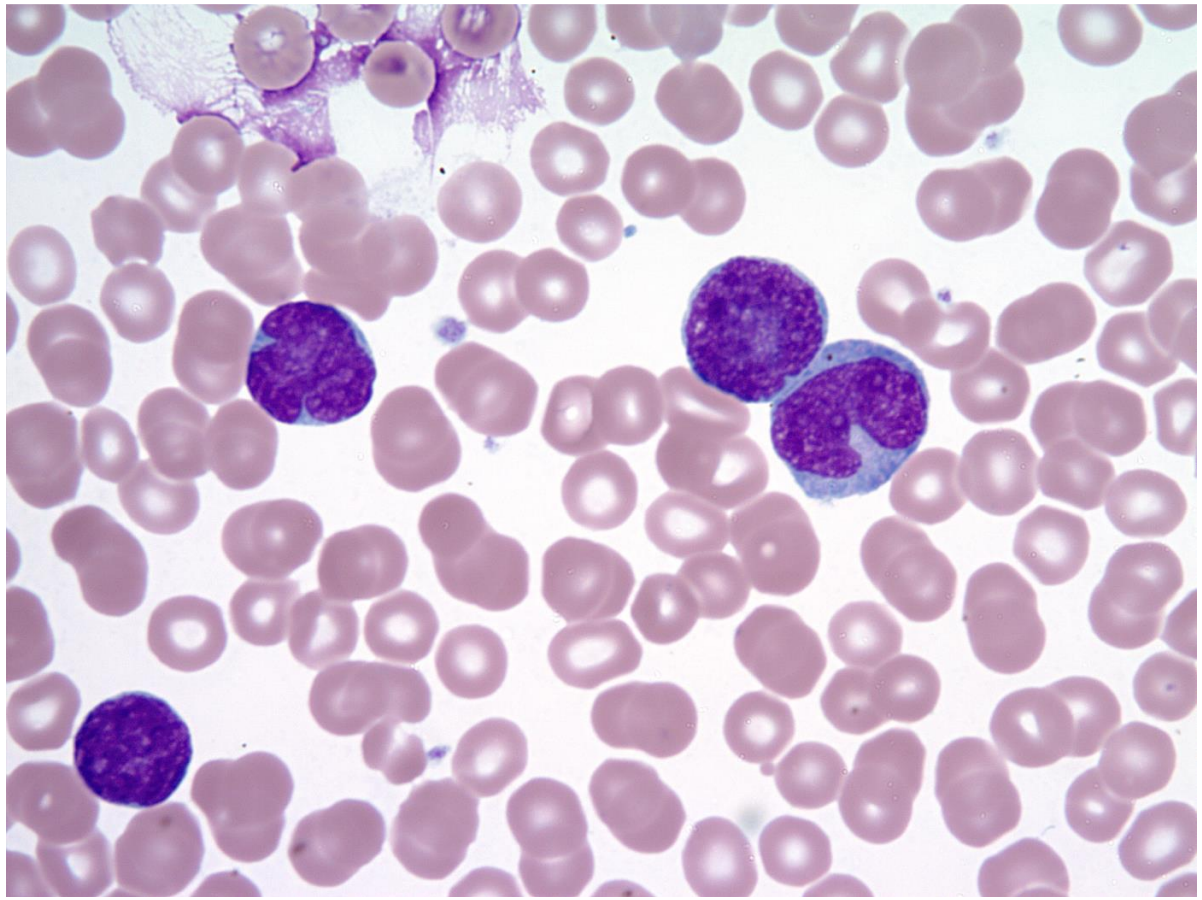


Large Cell Lymphomas

- The most common form of NHL, diverse group subclassified by site of involvement, histologic pattern etc.
- The broadest category, diffuse large B-cell lymphoma (DLBCL) is the most common adult lymphoma
- Typically, aggressive requiring strong chemo
- Some associated with EBV
- Cells may be morphologically difficult to distinguish from blasts. Often need flow!

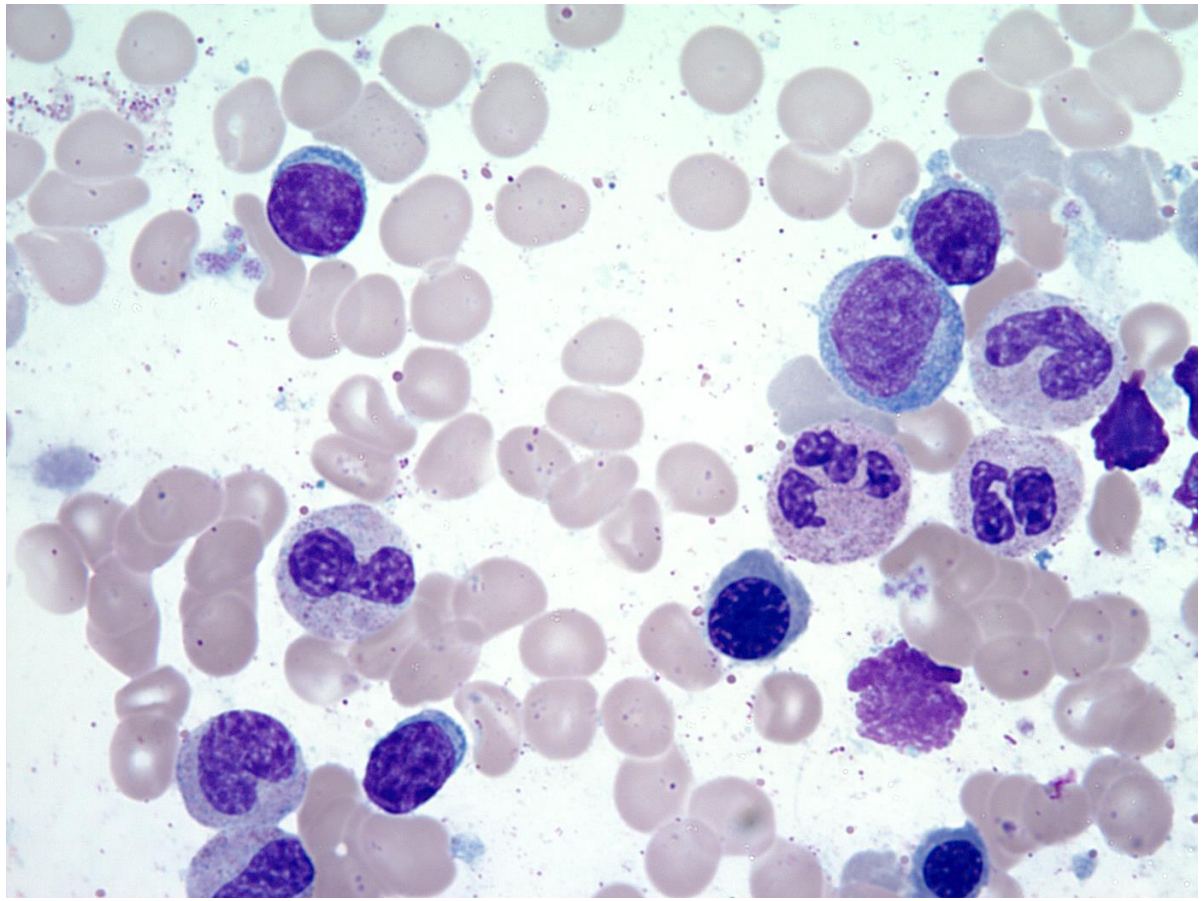
Circulating Large Lymphoma Cell





Lymphoplasmacytic Lymphoma

- Lymphoma with a spectrum of neoplastic cells: small lymphocytes →plasmacytoid lymphocytes →plasma cells
- Associated with IgM paraprotein: Waldenström Macroglobulinemia
- MYD88L265P mutation
  - Also found in IgM MGUS



Plasma cell neoplasms

A malignant disorder of terminally differentiated B cells

Several types:

Monoclonal Gammopathy Undetermined Significance (MGUS)	Plasma Cell/Multiple Myeloma	Plasmacytoma	Immunoglobulin deposition diseases and amyloidosis

MGUS

- Presence of monoclonal protein without evidence of lymphoma, myeloma, or other related disorder
- Clonal, pre-malignant disorder
- Usually an incidental finding
- 3-4% of population >50 years, >5% > 70 years
- Basically <10% of bone marrow is clonal cells

Plasma Cell Myeloma

- >10% clonal plasma cells in marrow, and multiple lesions of bone
- Smoldering cases lack SLM-CRAB criteria for symptomatic myeloma

S	Sixty: Clonal bone marrow PC ≥60%	C	Hypercalcemia: Serum calcium >0.25 mmol/L (1 mg/dL) above normal or >2.75 mmol/L (11 mg/dL)
L	Light chain: Involved/uninvolved free light chain ratio ≥100	R	Renal insufficiency: CrCl <40mL/minute or serum creatinine >177 µmol/L (2 mg/dL)
M	MRI: >1 focal lesion on MRI	A	Anemia: HGB >20g/L below normal or HGB <100g/L
		B	Bone lesions: ≥ 1 lesion by radiograph, (PET/)CT

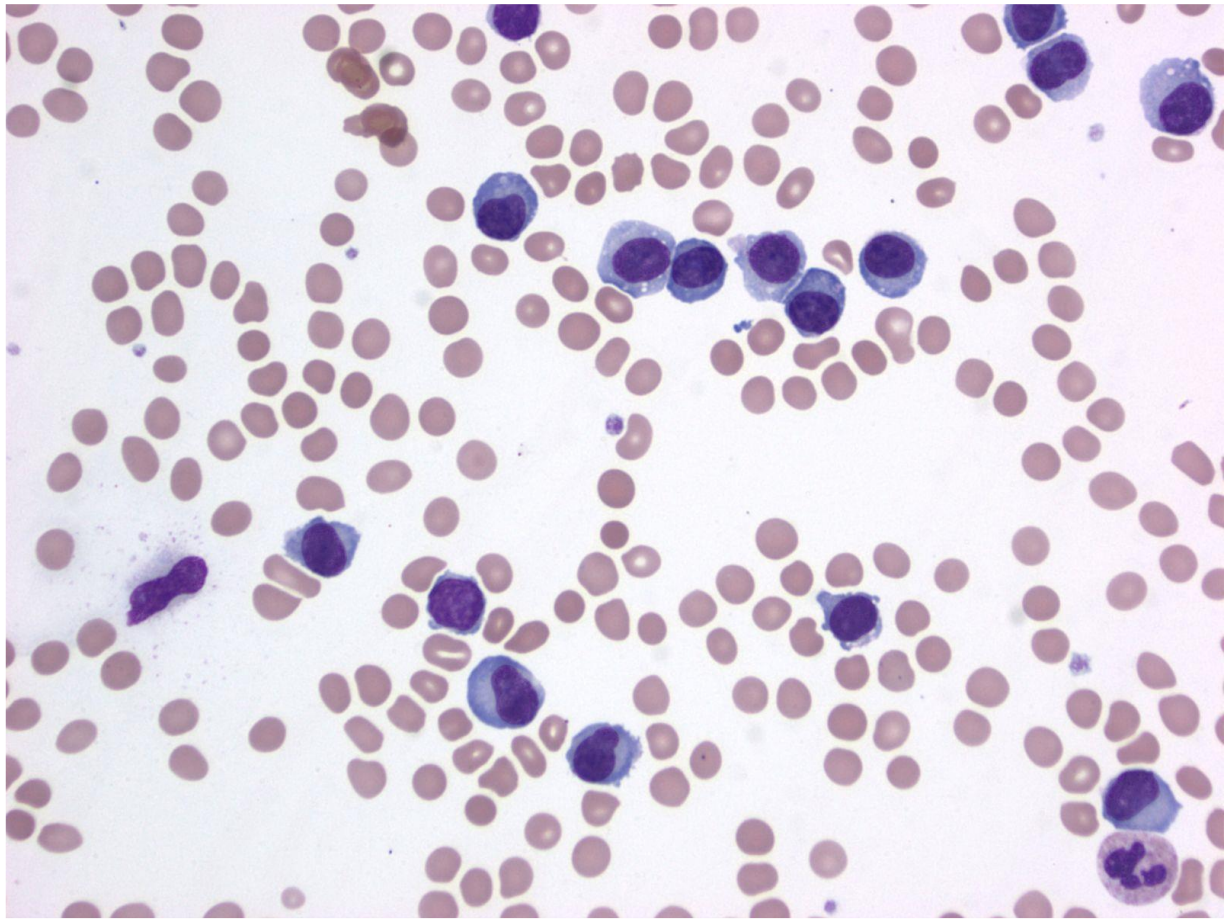
Plasma cell myeloma

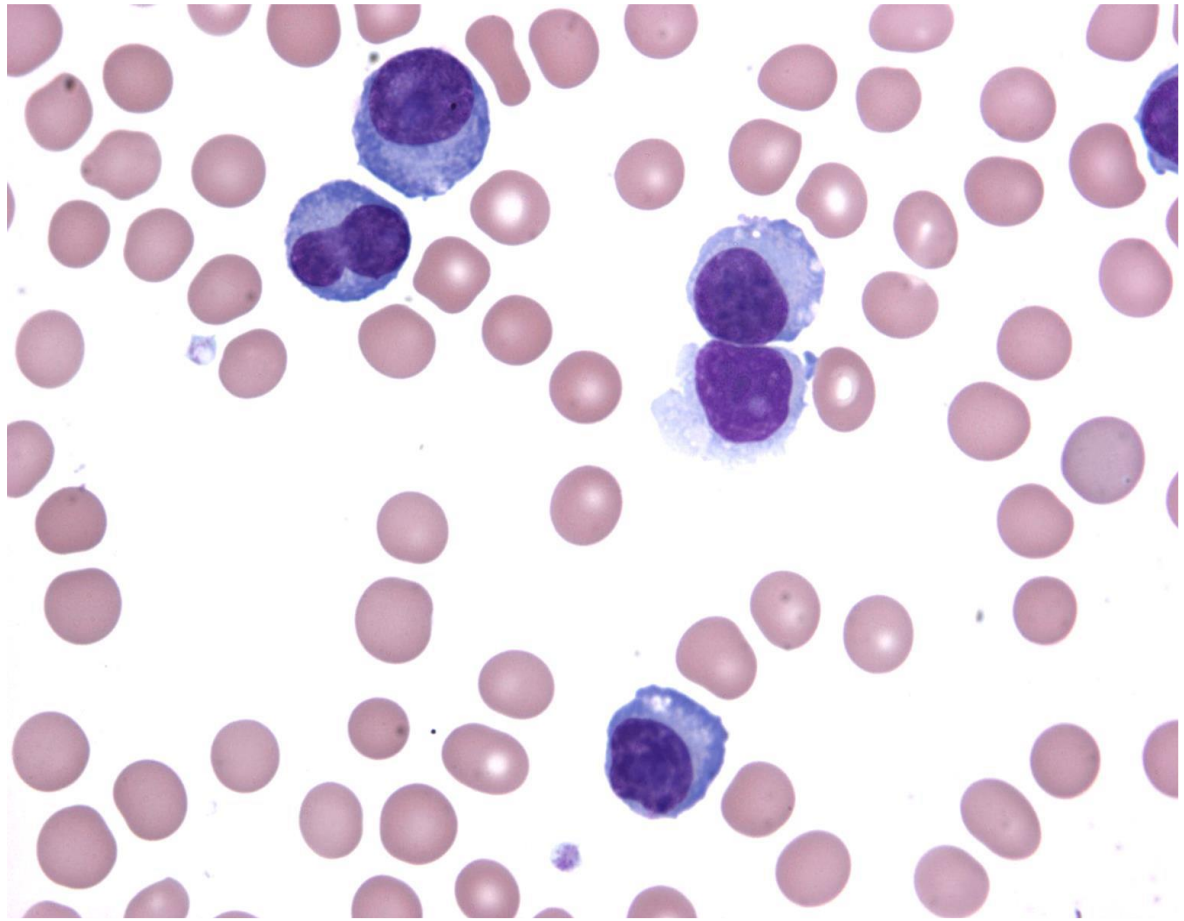
- >90% have abnormal karyotype by FISH
- FISH preferred because PC are difficult to culture
- Major prognostic risk indicator
  - High: t(14;1)(q32;q32), del(17p13)
  - intermediate: t(4;14)(p16;q32), del13
  - Standard: t(11;14)(q13;q32), hyper/hypodiploid
- New therapies have extended median survival from ~3 years to 5.5-6 years

Plasma cell leukemia

- >5% circulating plasma cells
- Very bad prognosis
- Progression of PCM or can arise de novo
- Malignant plasma cells express CD 38, and CD138
- Plasma cells in circulation can look quite atypical and mimic anything from blasts to lymphocytes-when in doubt, please ask!

Plasma cell leukemia





Mature T-and NK cell Lymphoproliferative Disorders

Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral CD8$^+$ T-cell lymphoma**
*Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK$^+$
Anaplastic large-cell lymphoma, ALK$^-$*
*Breast implant–associated anaplastic large-cell lymphoma**

Swerdlow SH et al. *Blood*2016;127(20):2375-2390

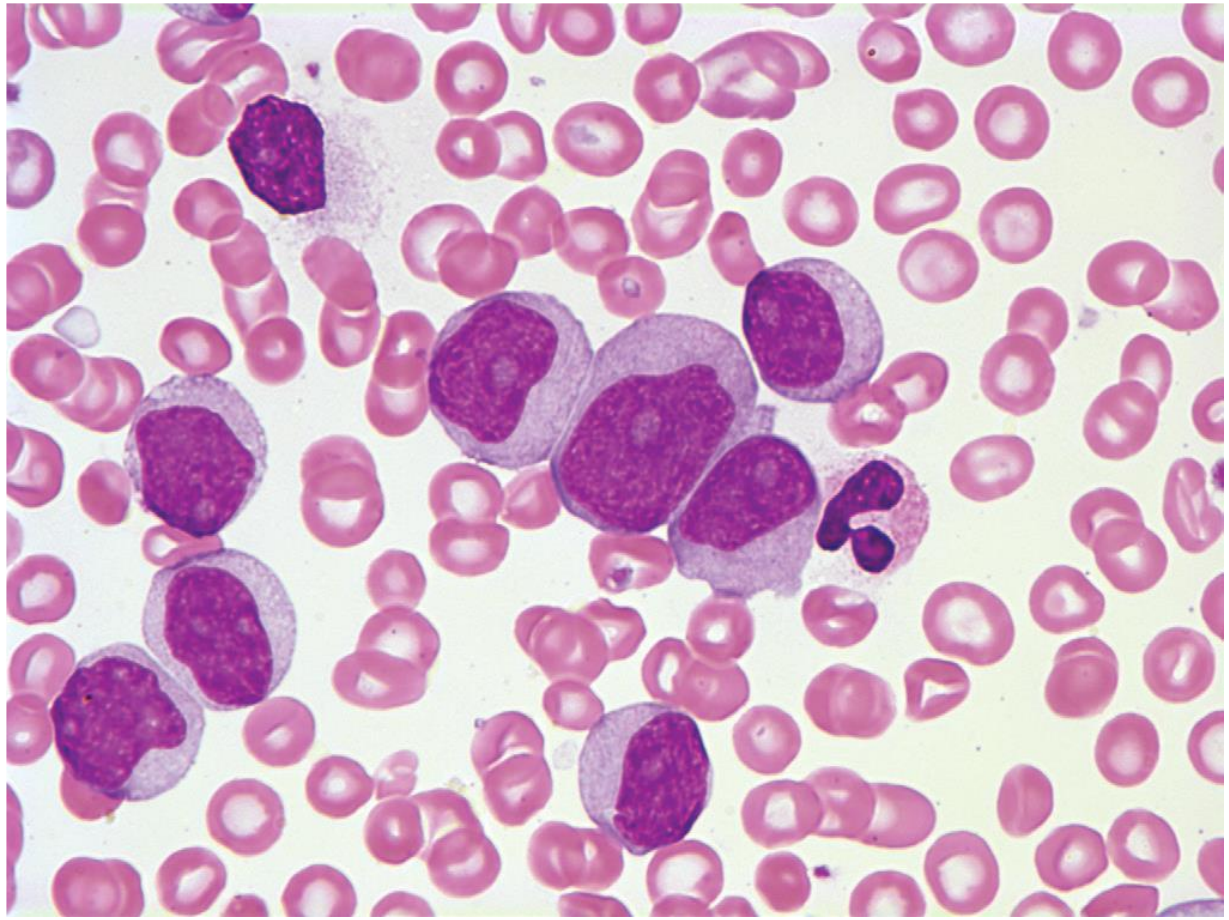
Mature T and NK cell Lymphoproliferative Disorders

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic (LGL) leukemia
- Aggressive NK cell leukemia
- Adult T-cell Leukemia/Lymphoma
- Sezary Syndrome

T-cell Prolymphocytic Leukemia

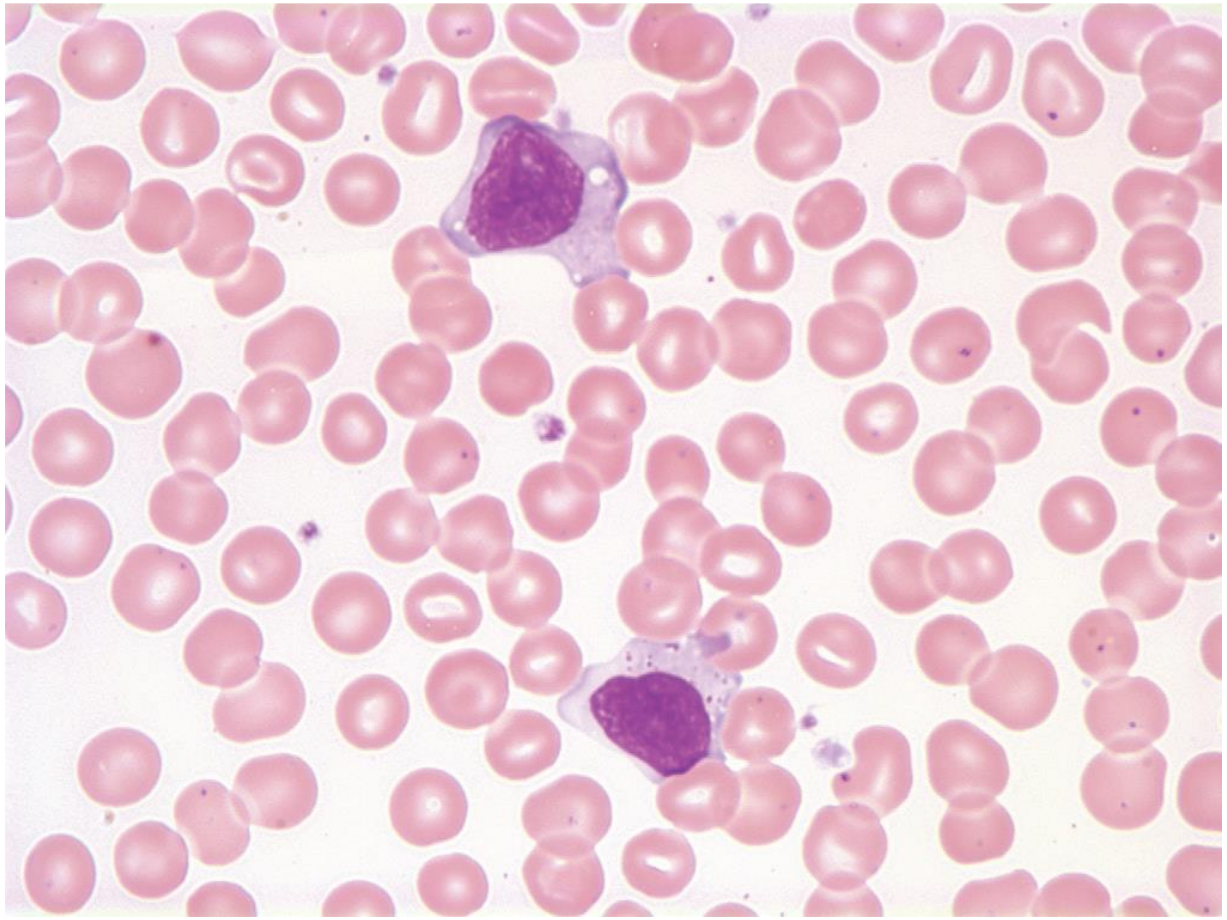
- Rare, aggressive T-cell neoplasm
- Pts have hepatosplenomegaly, lymphadenopathy, 20% with skin involvement, and ALC typically >100
- Small to medium lymphocytes with agranular cytoplasm, round, oval or irregular nuclei, and visible nucleoli. Cytoplasmic blebs
  - Some with smaller cells may not have nucleoli

T-cell Prolymphocytic Leukemia



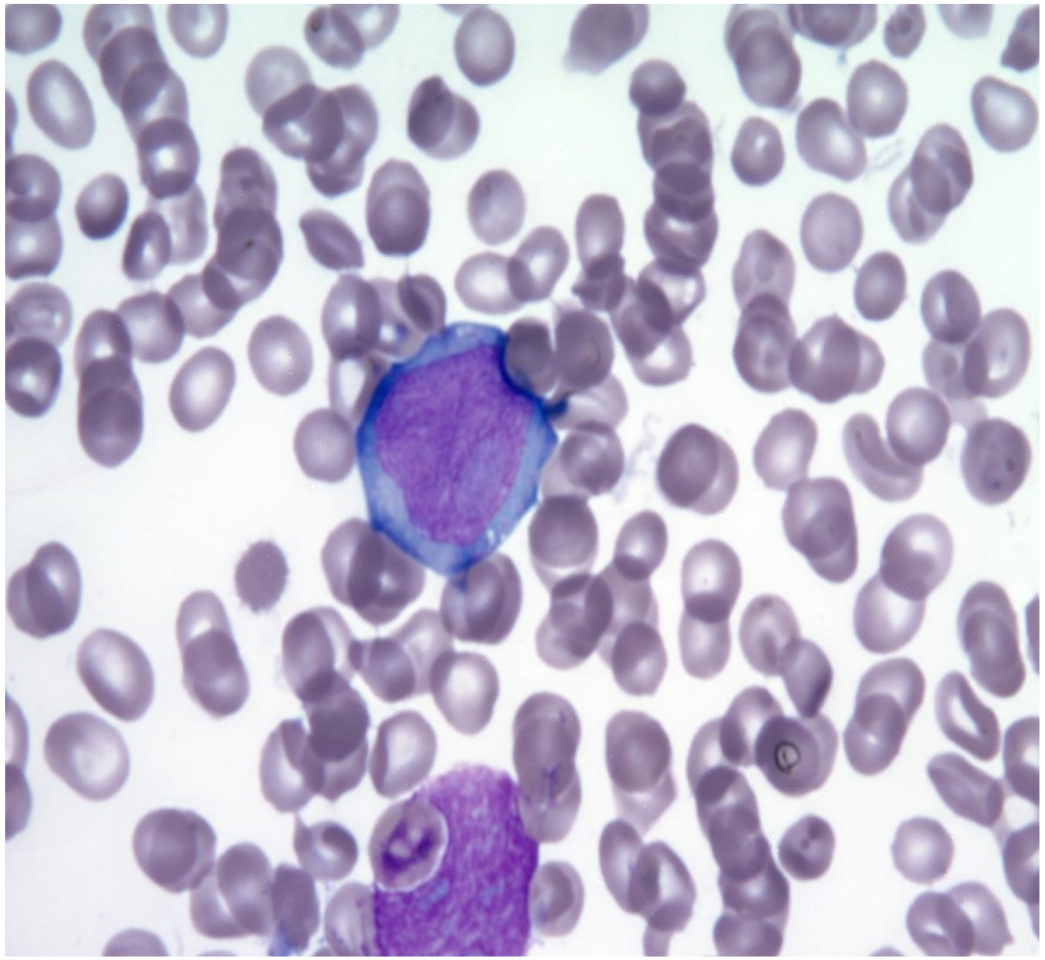
From Hsi ED

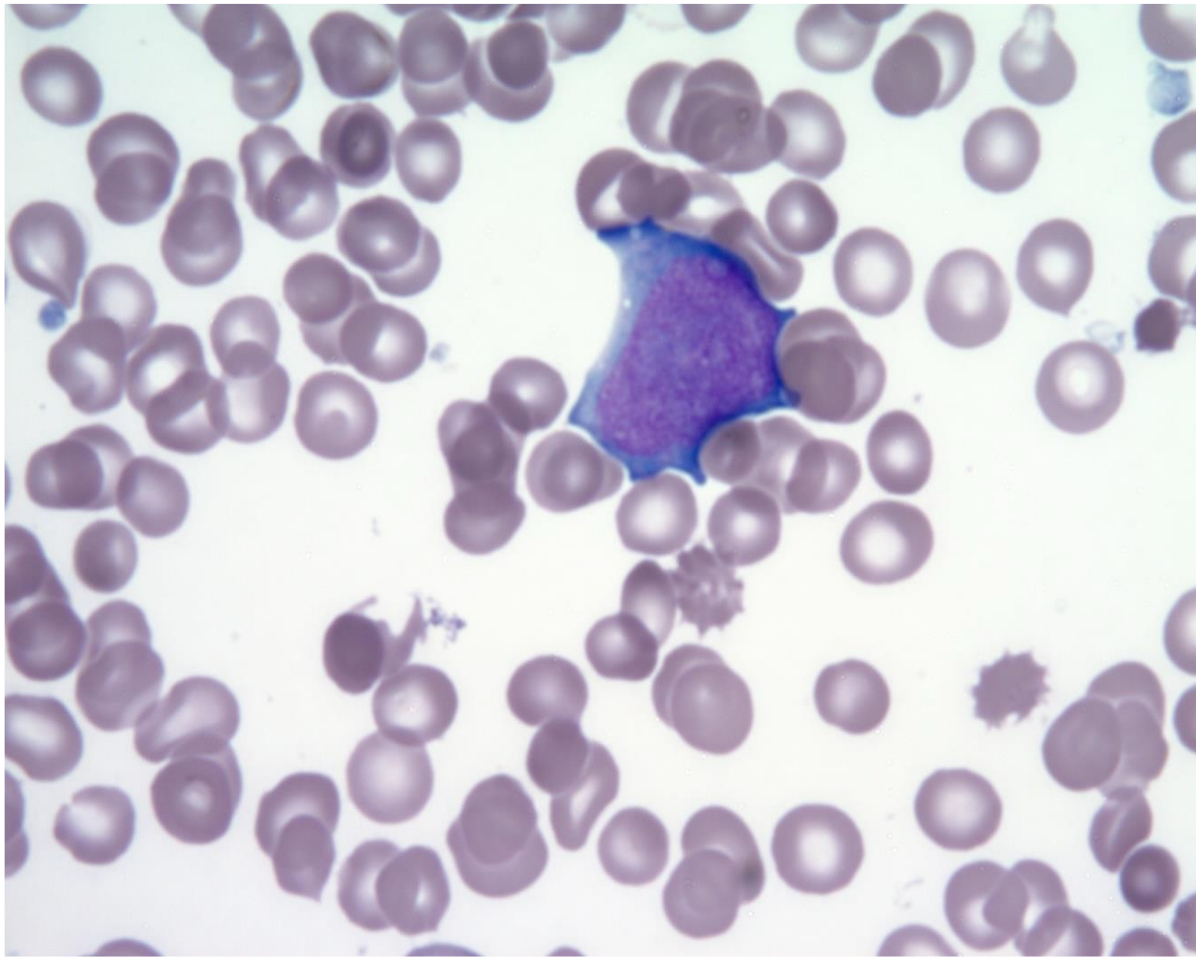
T-cell Large Granulocytic Lymphocytic Leukemia



From Hsi ED

Aggressive NK leukemia

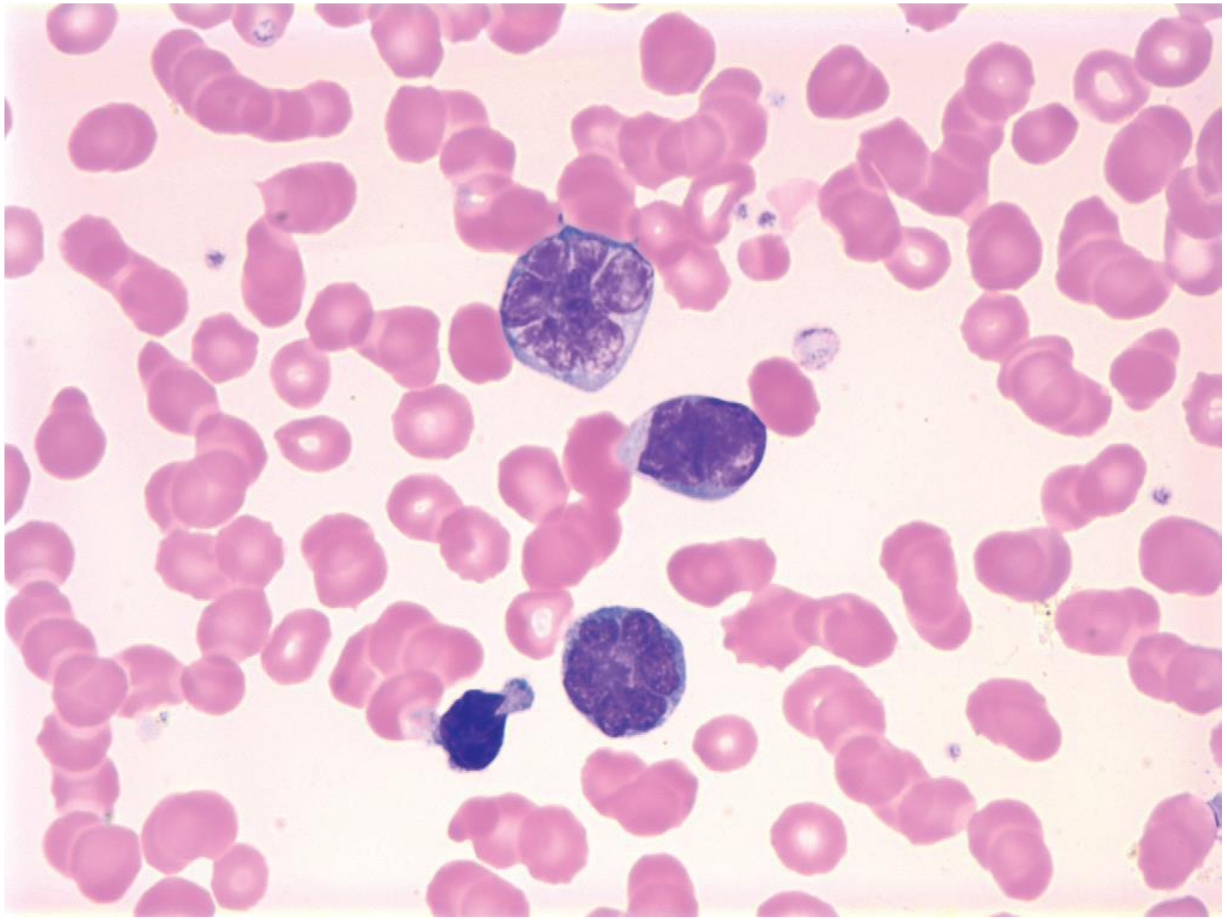




Adult T-cell lymphoma or leukemia

- Mature T-cell lymphoma with pleomorphic cells
  - Multi-lobed nuclei= flower cells
- HTLV1 virus (Japan, Caribbean), ave age 58
- CD3+, CD4+, CD7-, usually CD8-, CD25+
- Widespread involvement of LN, blood, skin (>50%)
- Acute, chronic and smoldering variants
  - Hypercalcemia+/-lytic lesions in acute form

Adult T-cell lymphoma or leukemia

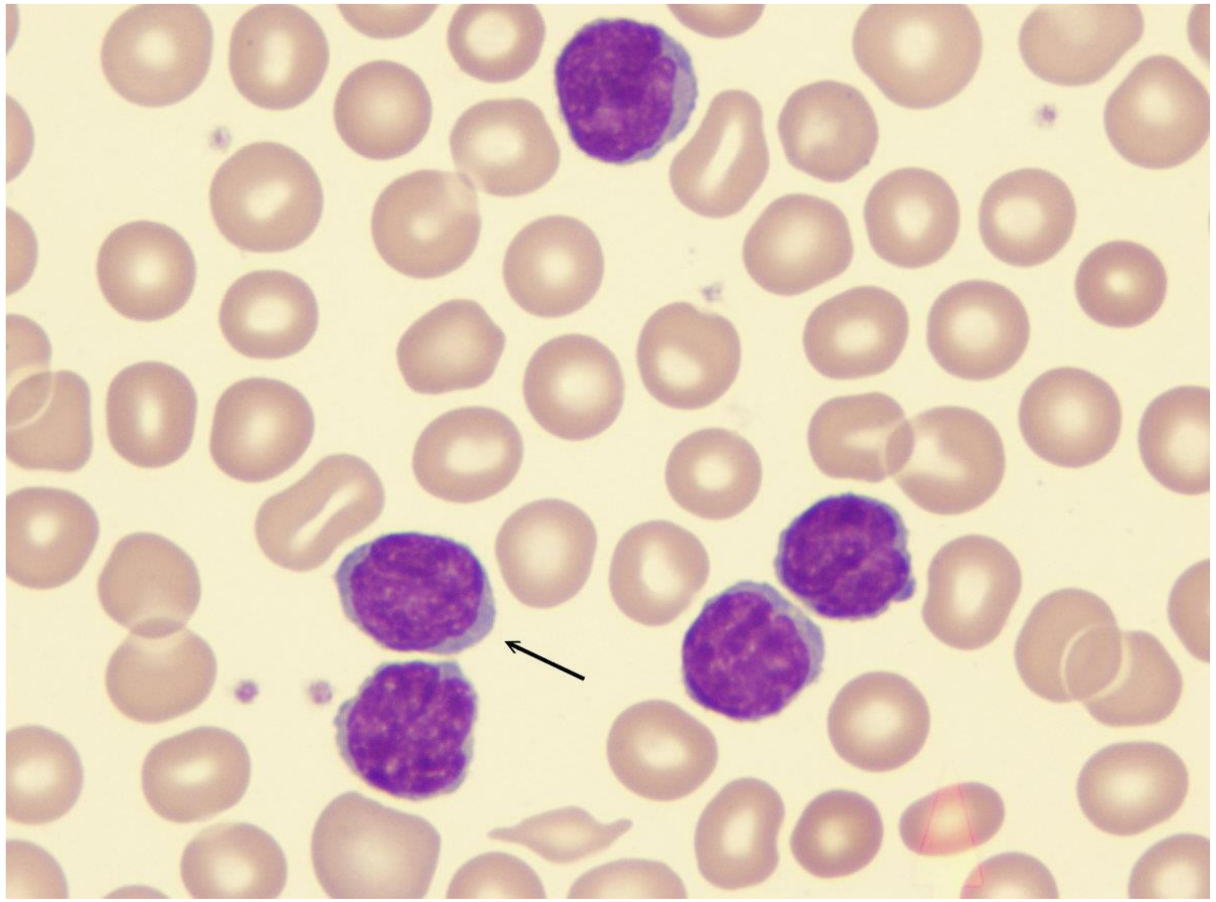


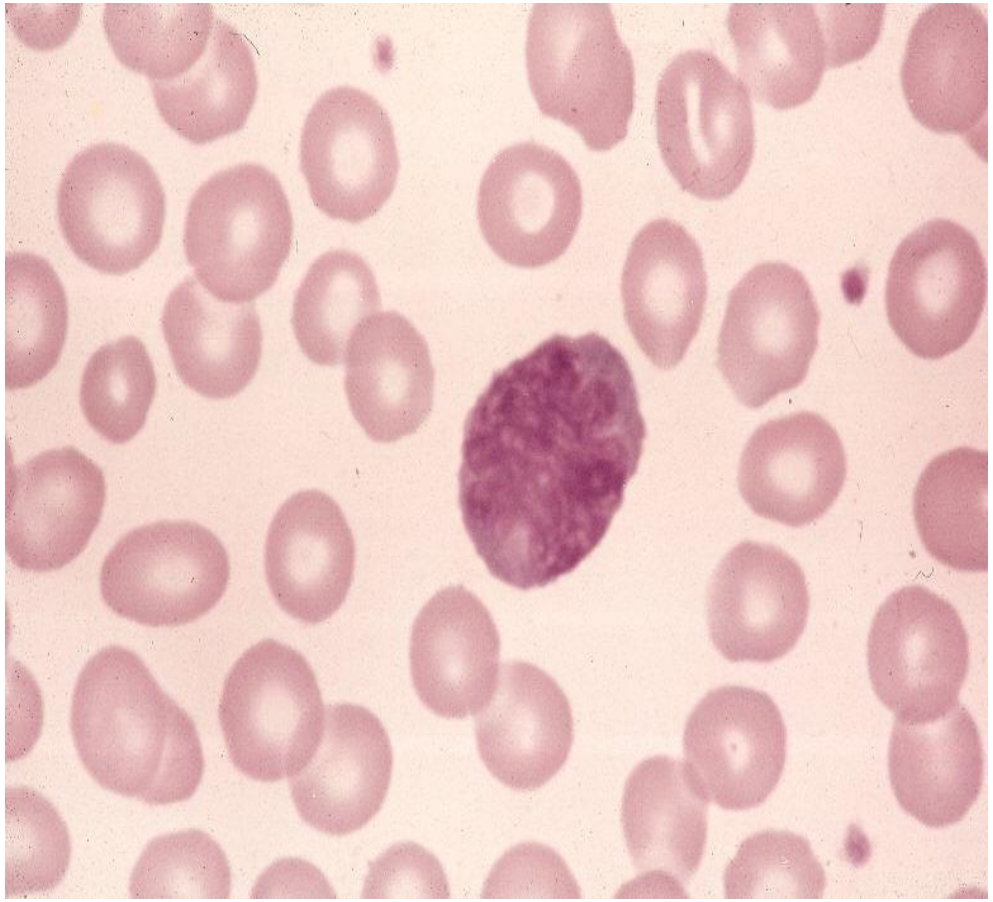
From Hsi ED

Sézary Syndrome

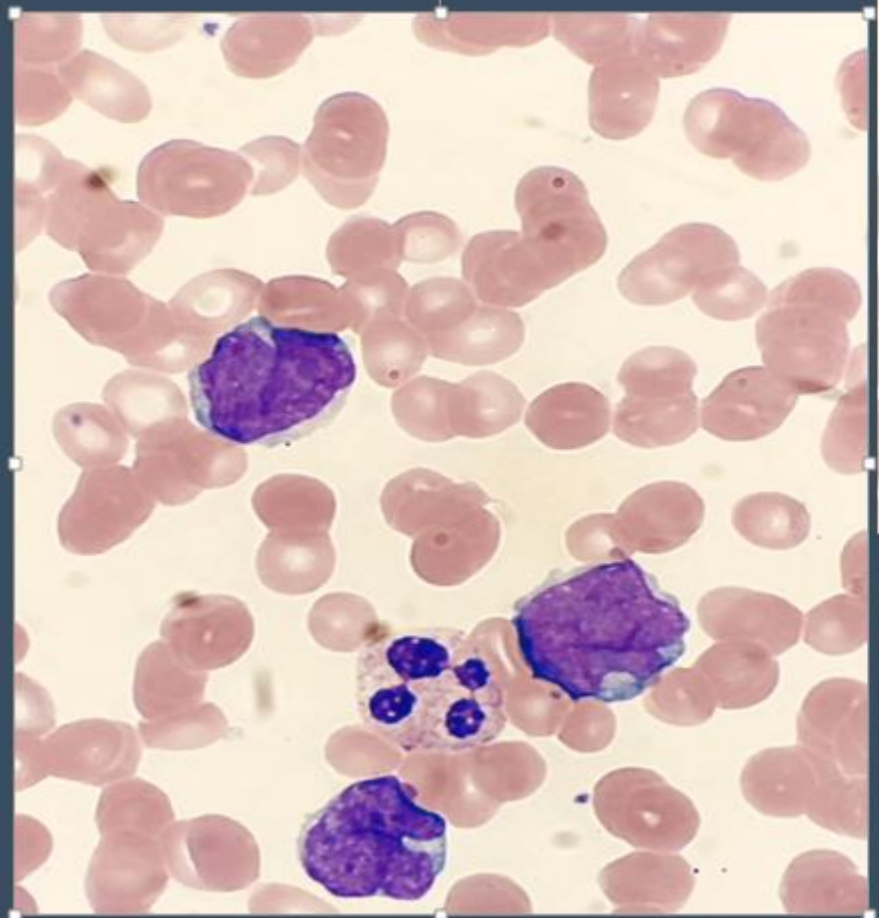
- Leukemic manifestation of mycosis fungoides, a primary cutaneous T-cell lymphoma
- Syndrome = erythroderma, generalized LAD, and presence of Sézary cells in circulation
- Sézary cells: cerebriform nuclei, CD3+, CD4+, CD7-, CD8-, CD26-
- Uncommon manifestation; 5% of cutaneous T-cell lymphomas
  - MF is 50% of primary cutaneous lymphomas

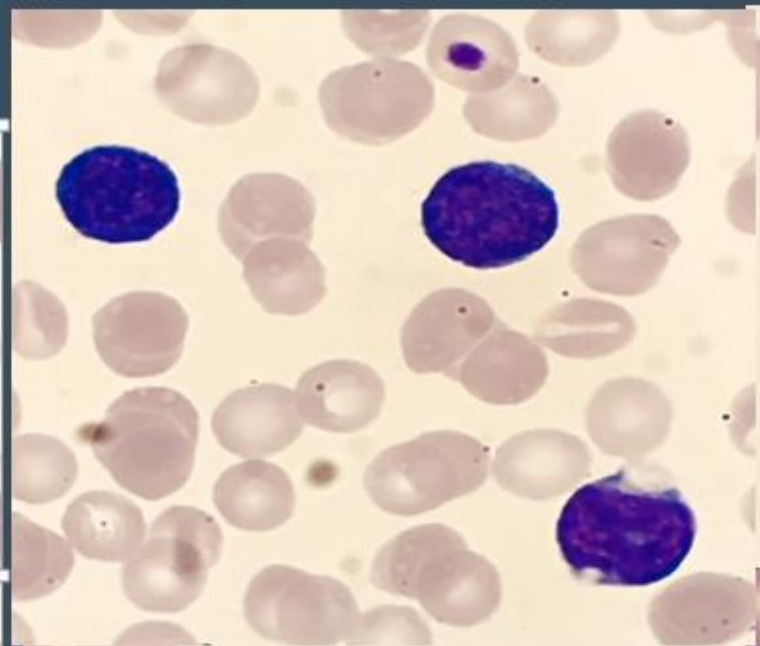
Sezary Cells

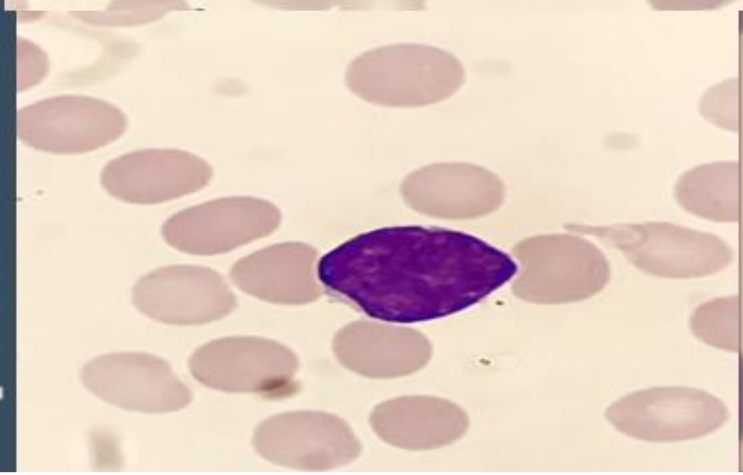


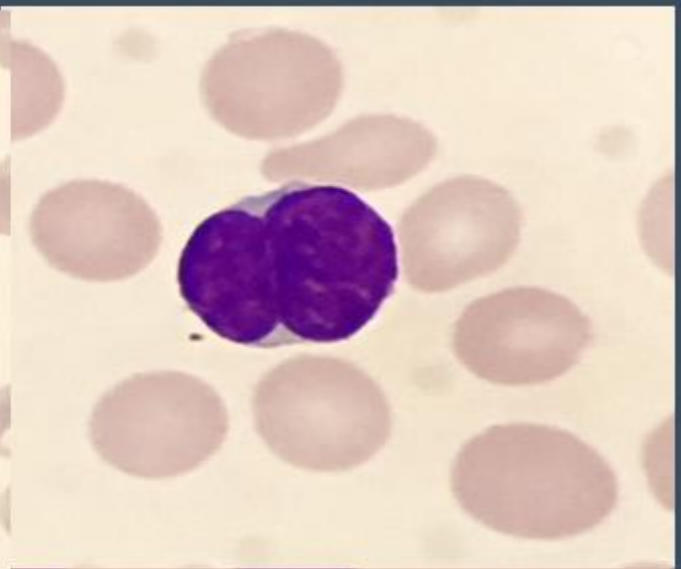


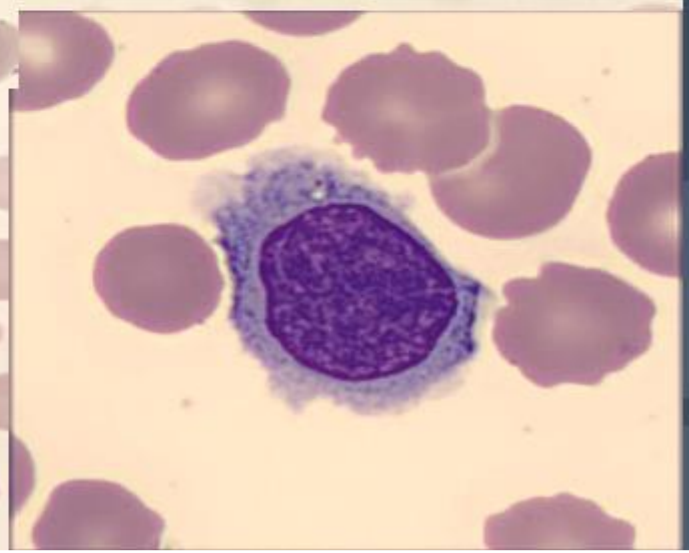
Lymphoma cells in PB











Hodgkin Lymphoma and PTLD

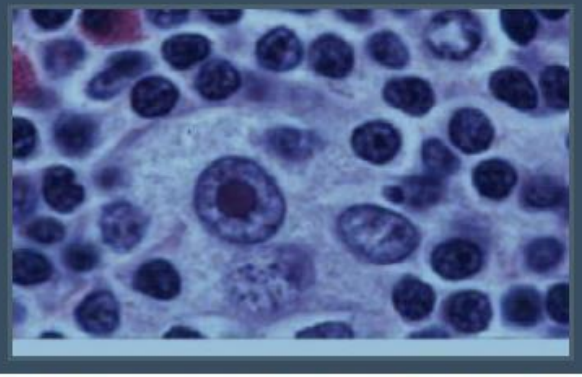
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD

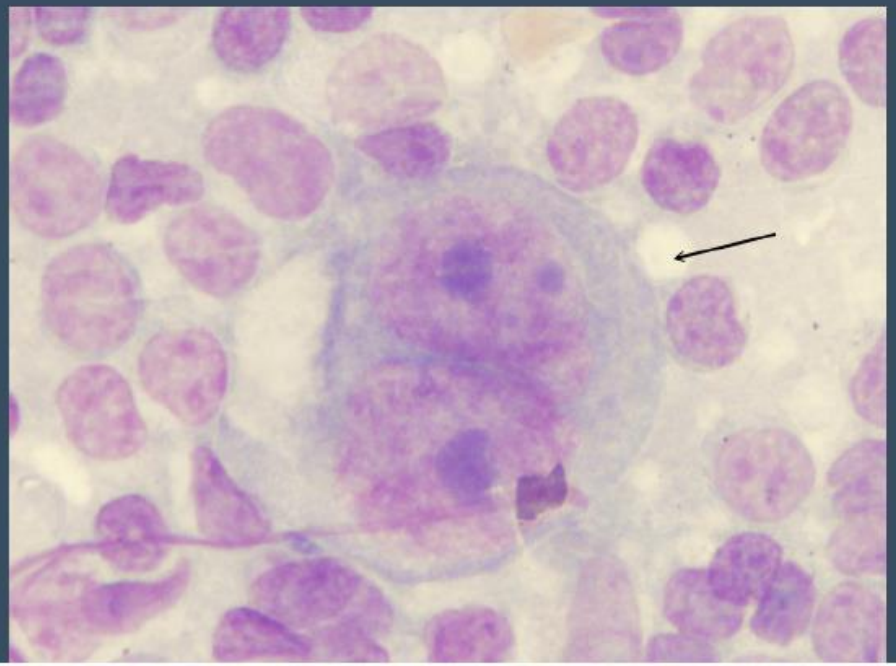
Hodgkin Lymphoma

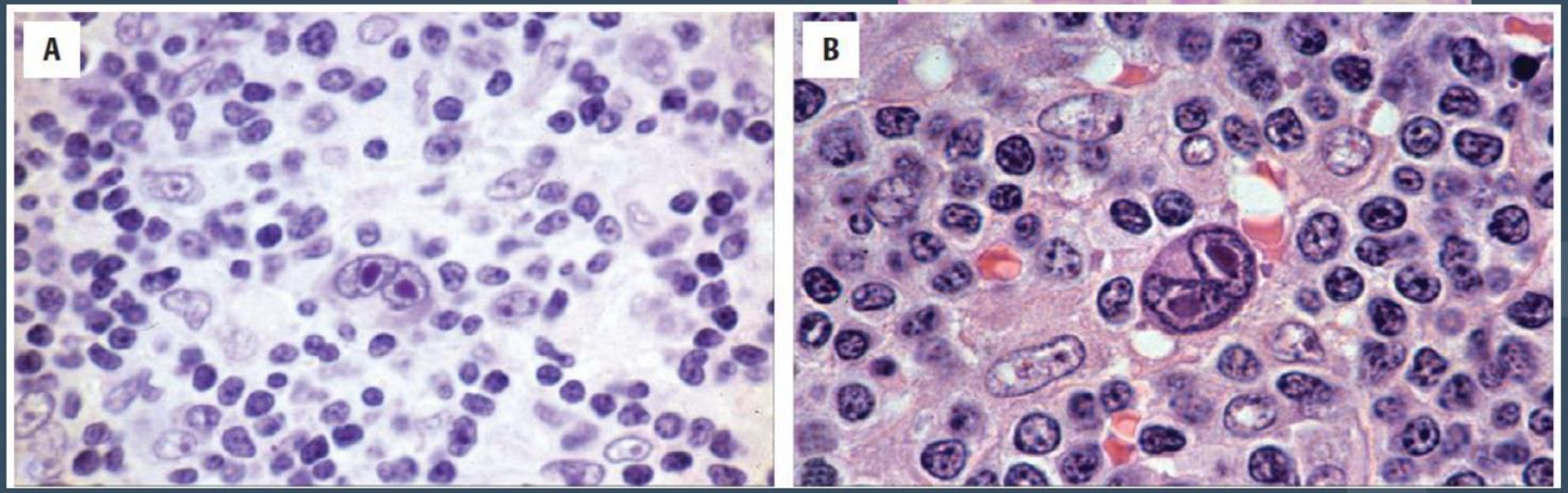
- Classic Hodgkin lymphoma (90% of HL)
  - Nodular sclerosis (70% of cHL in US and Europe); 10-25% EBV+
  - Lymphocyte-rich; between 25-75% EBV+
  - Mixed-cellularity (more common in HIV+ and developing countries); 75% EBV+
  - Lymphocyte-depleted; rarest, assoc w/ HIV, EBV
- Classic morphology is Hodgkin Reed-Sternberg cell (HRS)

HRS cells

From Hsi ED





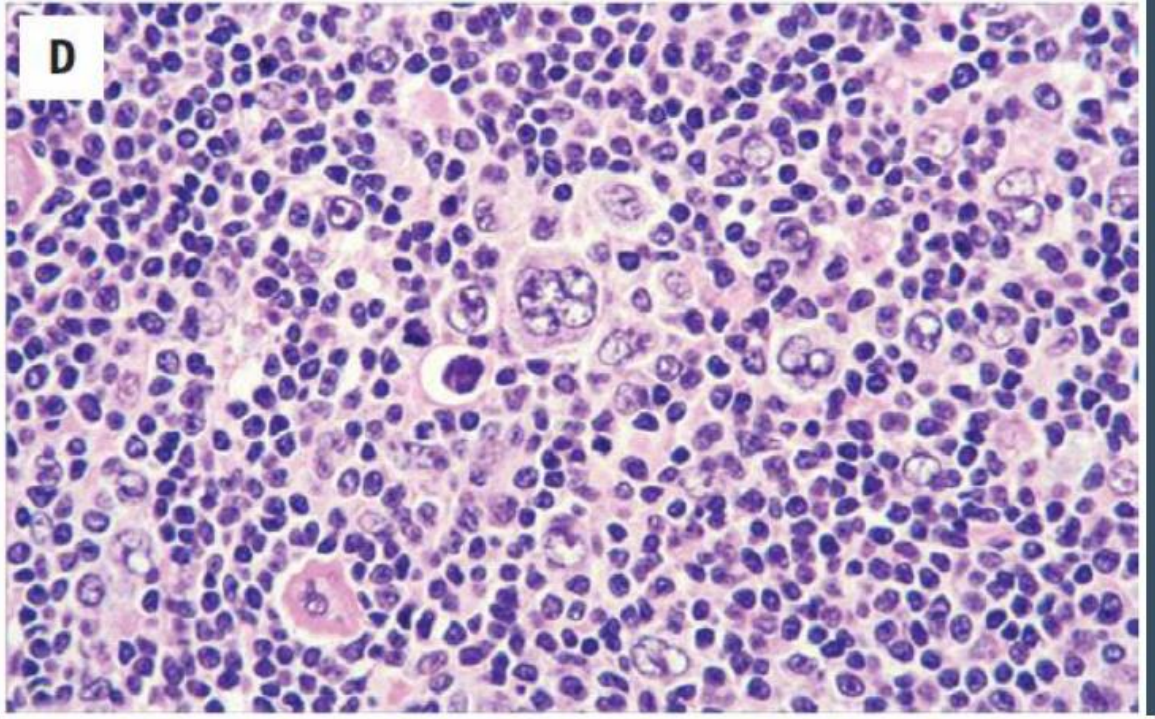


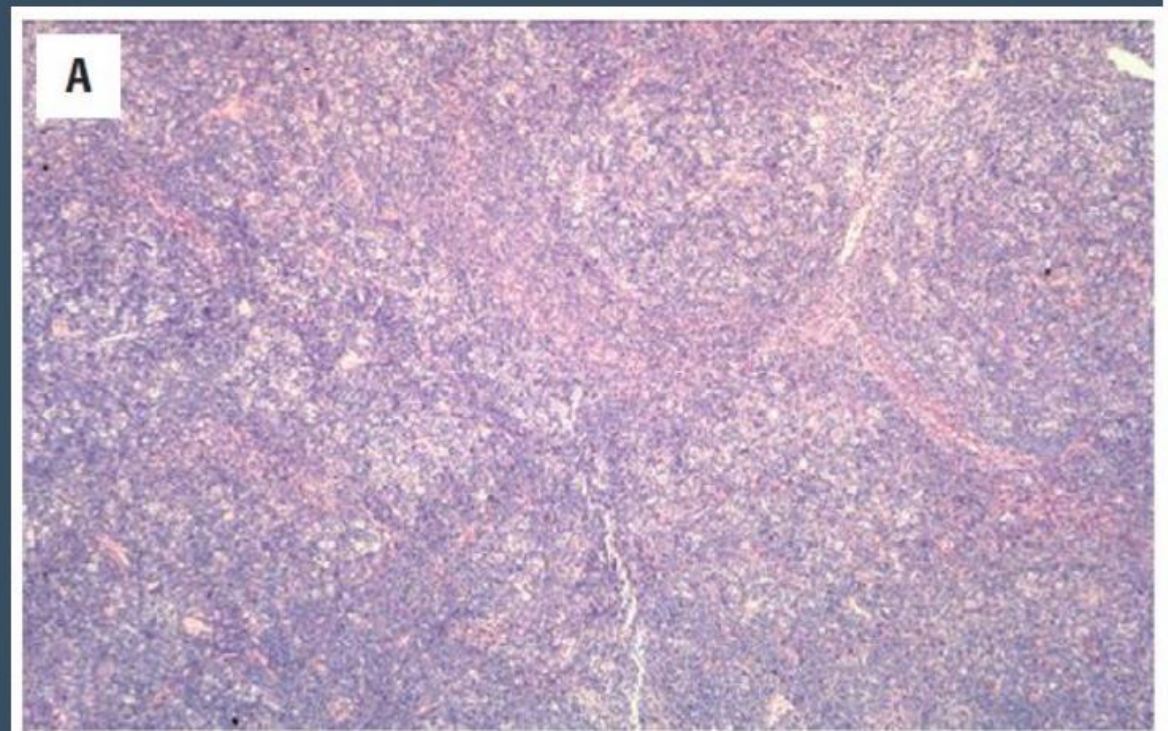
Nodular Lymphocyte Predominant Hodgkin B-cell Lymphoma

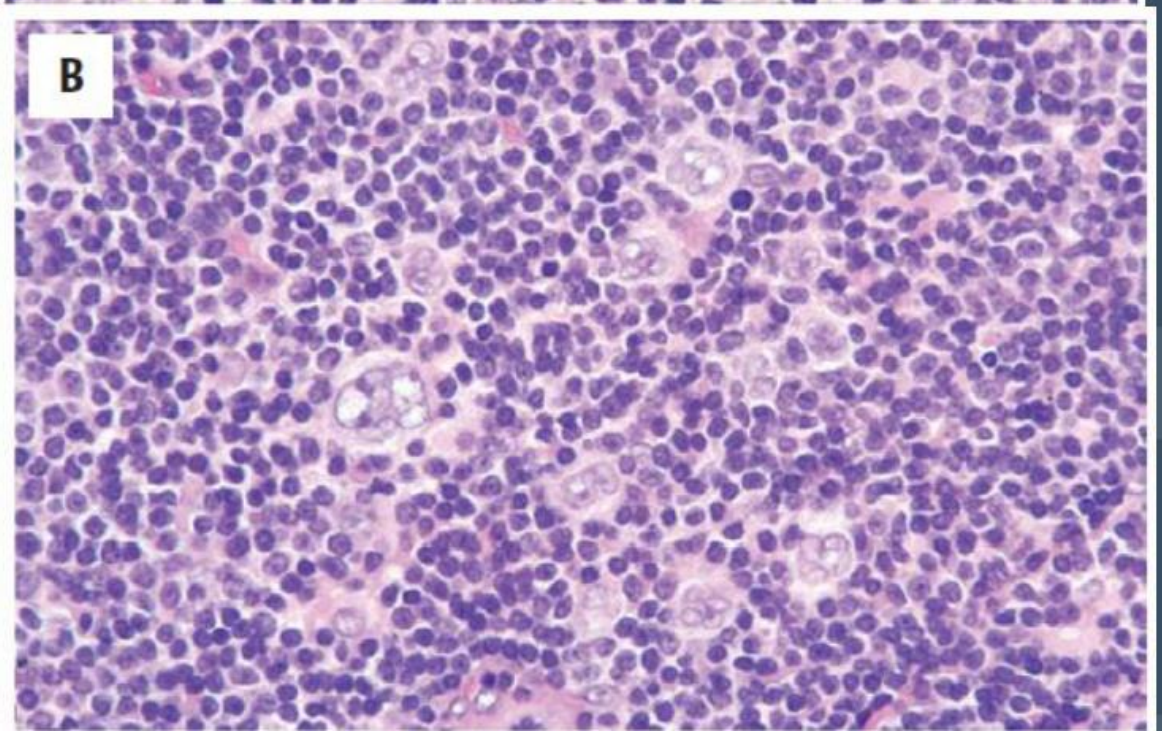
- Scattered large neoplastic cells are lymphocyte predominant or popcorn cells
- 10% of HL, men 30-50 yrs.
- LN: cervical, axillary, inguinal
- 3-5% EBV+
- very good prognosis if limited disease

Lymphocyte predominant “popcorn” cell

From Hsi ED







References:
Rodak’s Hematology, Clinical Principles and Applications 6th Edition
Additional material courtesy of Dr. Megan Nakashima, MD