PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM–

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NEOPLASTIC PROLIFERATION OF WBC

malignant cells circulate in peripheral blood
in constant to solid tumors, if they reach the blood → metastasis

- Mostly considered as malignant, fluid tumors
- Differs in biologic behavior, ranging from indolent (slowly progressive) to very aggressive cancers
- Common cancers
- Current classification system: World Health Organization (WHO) classification system for Hematolymphoid neoplasms
- Classified according to lineage (myeloid vs lymphoid, B vs T, etc…), based on morphology, protein and molecular tests

LYMPHOMA → most common neoplasms of WBCs

- Neoplasm of lymphocyte, malignant
- Called leukemia (lymphoid) if affects bone marrow or peripheral blood (circulating in), lymphoma if affects lymph nodes or solid organs (extranodal lymphoma) (skin, stomach...)
  bc they're immune cells, distributed in various sites through the body + may turn into malignancy
- Classified into Hodgkin and non-Hodgkin lymphoma
- Non-Hodgkin lymphoma is classified into B and T-cell lymphoma
- B-cell lymphomas are more common, involve immunoglobulin gene (accidents during class-switch) T cells are more stable
- All are malignant, but can be of low-grade (indolent) (mild disease) or high-grade (aggressive) behaviour
- Diagnosis is made through morphologic and immunophenotypic (immunohistochemistry or flow cytometry) examination of biopsy
  Biopsy
  antigens, CDs, bc we can't know B from T according to morphology
  tissue
  fluid (peripheral blood or BM)
- Sometimes a test for mutations is performed
- Immunodeficiency is a risk factor for lymphoma, and vice versa
  AIDs
  malignant lymphocytes suppress and interfere with normal lymphocytes

COMMONLY TESTES IMMUNOPHENOTYPES

- CD45: common leukocyte antigen (all WBCs (myeloid + lymphoid))
- B-cells express CD19, CD20, CD22 (normal + malignant, mature and immature)
- T-cells express CD2, CD3, CD5, CD7 (cytotoxic, suppressor and helper)
- Germinal center lymphocytes express CD10 and Bcl6 (follicular lymphoma; TF)
- Plasma cells express CD138
- T-helper lymphocytes express CD4
- Cytotoxic lymphocytes express CD8
- Blasts express CD34 (myeloblasts or lymphoblasts)
- Lymphoblasts express TDT (terminal deoxynucleotidyl transferase) and CD10 (nuclear protein)

HODGKIN LYMPHOMA

from germinal center B cells

- Constitutes 30-40% of all lymphomas
- Most common type of lymphoma in Jordan, in children and young adults
- The neoplastic cells are giant, different morphology and immunophenotype from normal lymphocytes, forms less than 10% of tumor mass, while the rest are normal inflammatory cells

normal lymphocytes are the smallest leukocytes

CD45 -, B+T cell CD5 -

rare phenomena

but they enlarge due to recruitment of

[Always in the lymph nodes, different than other lymphomas]

- Arises primarily in a localized area of lymph nodes (neck, axilla, mediastinum), then spreads to anatomically adjacent LN group

so it's predictable not haphazard

adenoids in the nasal cavity

if not treated, spreads to visceral organs s spleen, BM and liver

- Mesenteric LNs and Waldeyer ring are rarely involved

other cancers are unimodal (single peak)

- Bimodal age distribution (first peak in children, then in old age groups)

rarely in middle aged

more aggressive

- B-symptoms: patients commonly have fever, night sweats and weight loss

PATHOGENESIS AND OUTCOME

- Originate from germinal center B-cells
- Frequent association with EBV
- RS cells secrete IL-5, chemoattractant for eosinophils
- Also secrete IL-13 and transforming growth-B (TGF-ß) which activates other RS cells
- Express programmed death (PD) ligands which antagonize T cell response, escaping immune surveillance
- Prognosis is generally good

very different morphologically and immunologically

the infection precedes

* but not in all *

unlike hypercellularity subtype

causing peripheral eosinophilia

autocrine

causing progression of the tumor

$CD8^+$

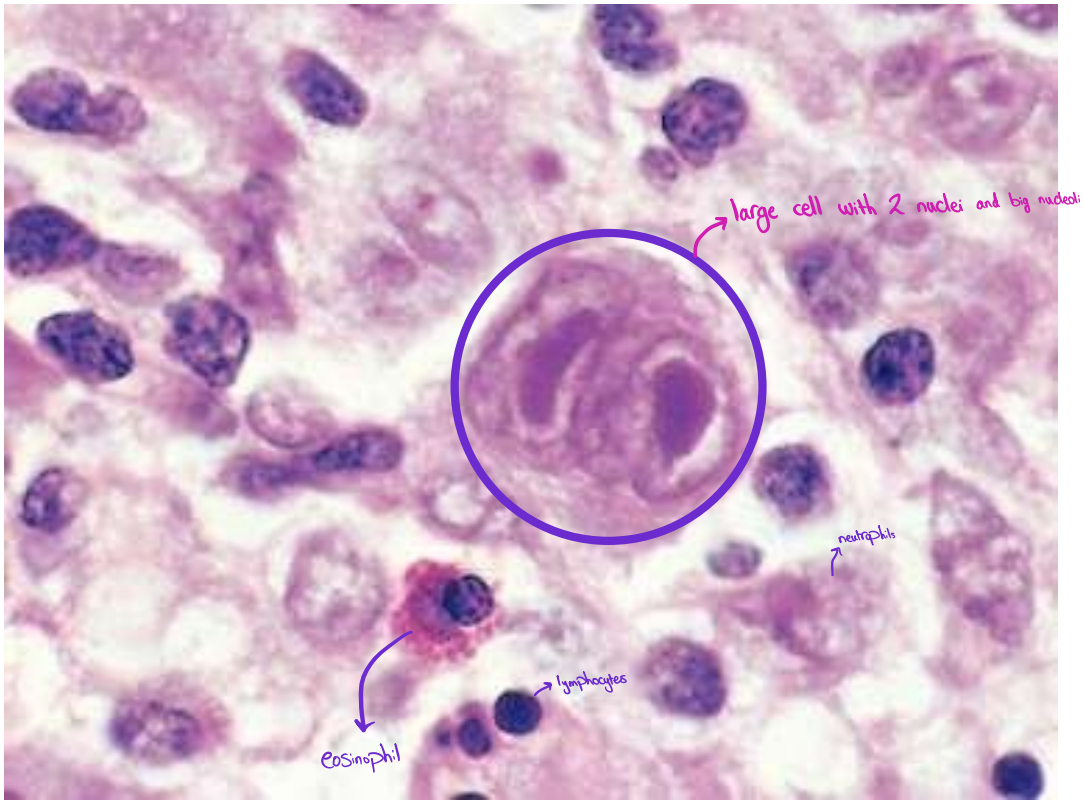
very responsive to therapy

CLASSIFICATION

- Classic Hodgkin lymphoma (95%):
  - 1) nodular sclerosis — most common; large LNs with extensive fibrosis, look like nodules
  - 2) mixed cellularity — common; sheets of normal cells + tumor cells
  - 3) lymphocyte-rich — rare; normal
  - 4) lymphocyte-depleted — only malignant cells are seen

4 Histological types

- Non-Classic Hodgkin (5%):
  - Nodular lymphocyte-predominant — like 1 / like 3



Classic

- Reed-Sternberg cells: bi or multi-nucleated giant cell, prominent nucleoli, abundant cytoplasm → pink

* common in mixed cellularity type *

Both are present + large no. of WBCs attracted by them

- Hodgkin cells: mononuclear giant cell
- Both express CD30 and CD15, and negative for CD20, CD3 and CD45

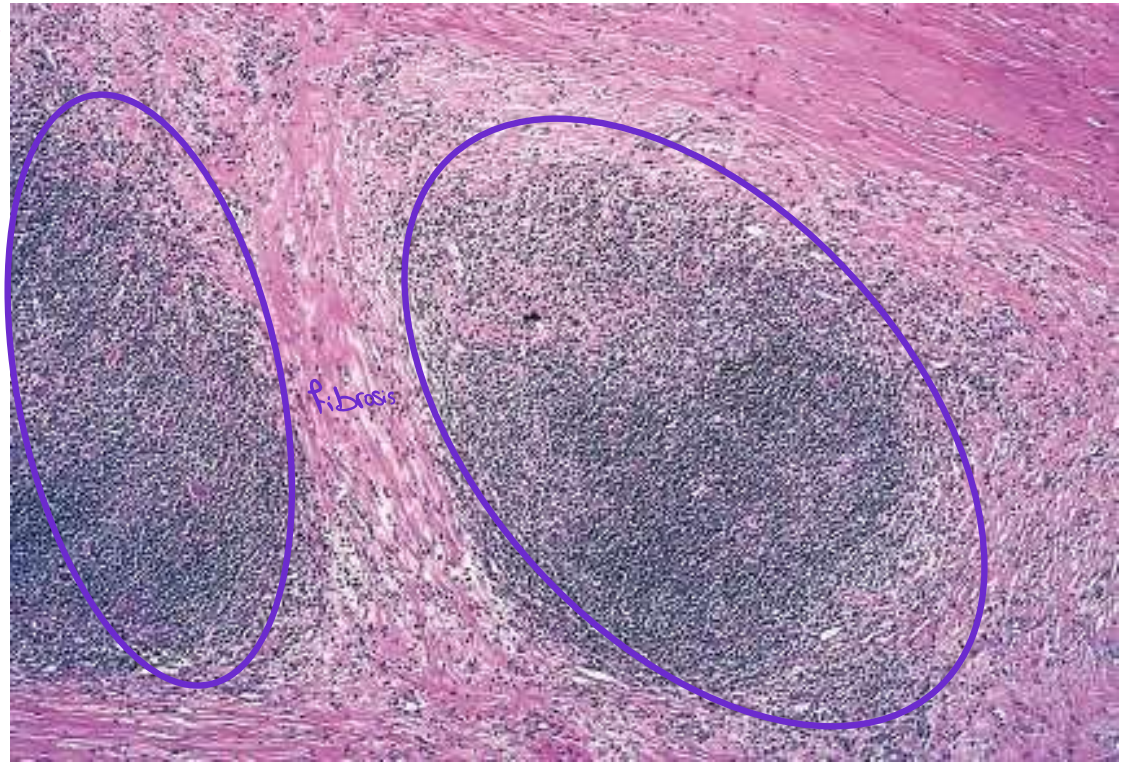
abnormal

all B + T antigens

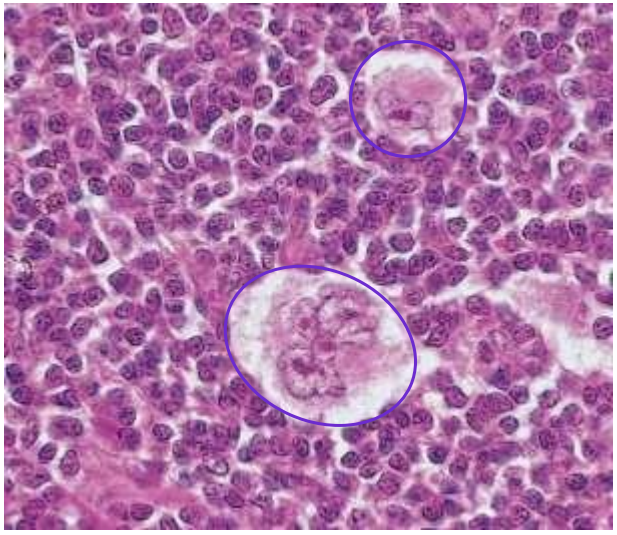
a classic HL

NODULAR SCLEROSIS HL

low power view



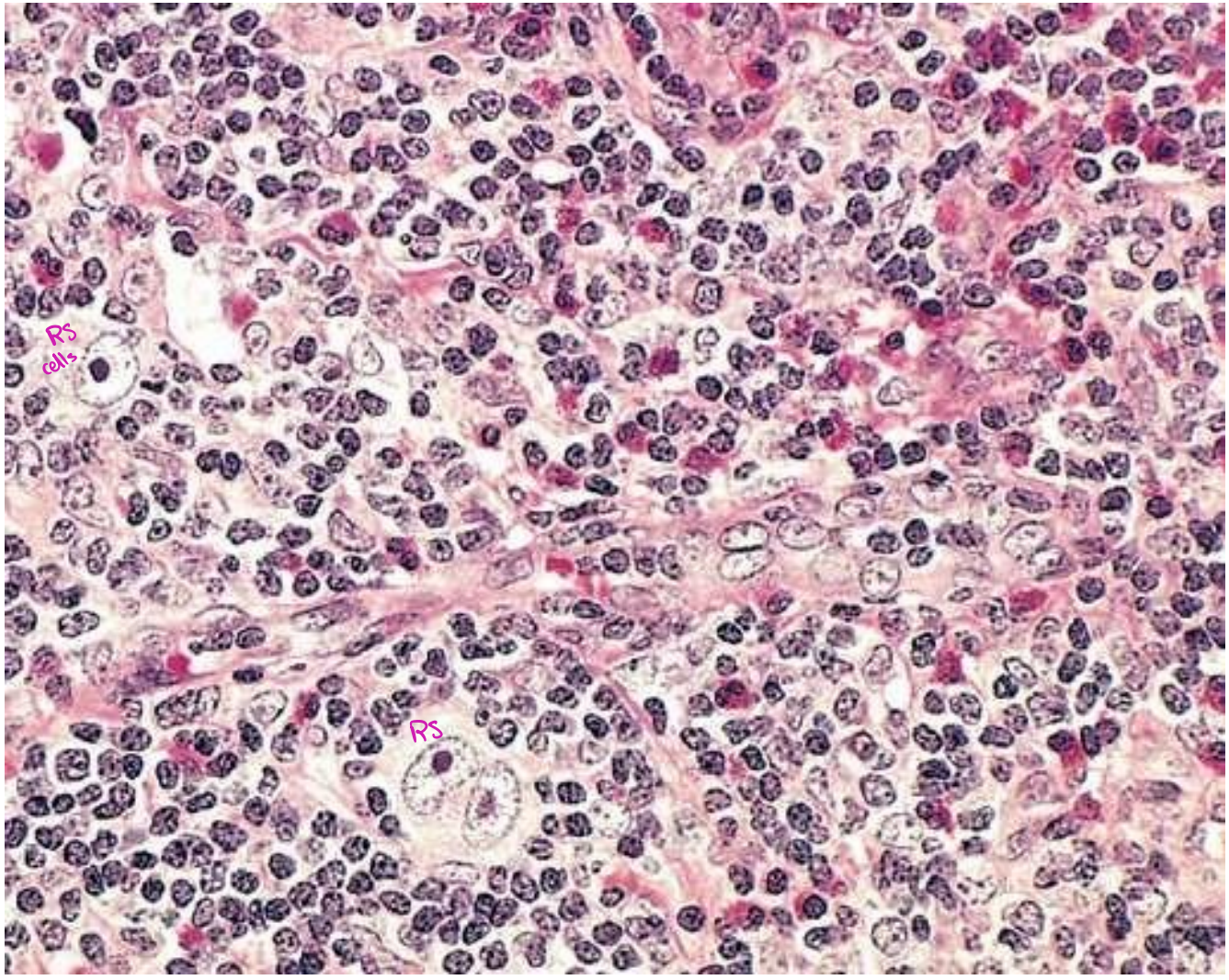
2 giant cells with multi nucleation + prominent nucleoli



- Common in children and young adults
- Thick fibrous bands separating nodules of lymphocytes
- RS cells show clear cytoplasm (pale staining), as a retraction artifact from formalin, called Lacunar cells

MIXED CELLULARITY HL

- Common in old people
- Numerous RS cells (classic) + cellular background
- Lacks fibrous bands (in nodular sclerosis)
- Associated with EBV (positive in RS cells)
- Background: mixed neutrophils, eosinophils, lymphocytes, plasma cells and histiocytes



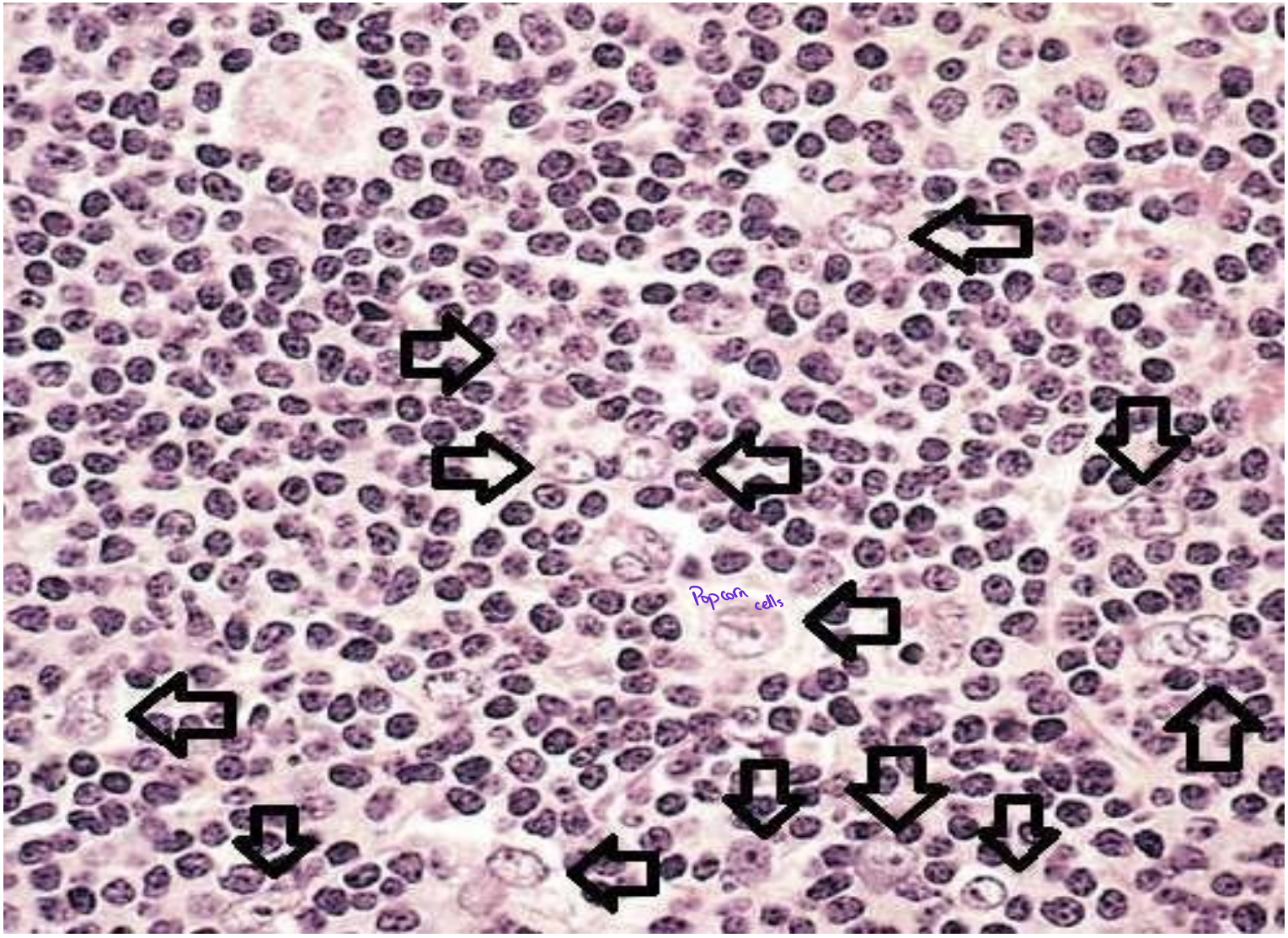
* no fibrous bands *

- Mixed cellularity HL

LYMPHOCYTE-PREDOMINANT HL

- Malignant cells are called lymphohistiocyte (L&H) variant RS cell, or simply LP cells
- Resemble popcorn (popcorn cells)
- Giant cell with multilobated vesicular nuclear lobes and small blue nucleoli
- Express normal B-cell markers (CD45, CD20), negative for CD30 and CD15
- Background of lymphocytes, arranged in nodules
- Excellent prognosis

Background has lymphocytes



- Popcorn cells

* NHL *

DIFFUSE LARGE B-CELL LYMPHOMA

- Most common NHL
- Predominantly in adults
- High-grade (rapidly growing mass)
- Most common non-cutaneous extranodal lymphoma (GI most common)
- 2/3 have activating mutation of Bcl6 promotor gene, which is an important regulator of gene expression in germinal center B-cells
- 30% have t(14;18) (Bcl2 → IgH) which results in overexpression of Bcl2 protein (anti-apoptotic)
- Few has mutation in MYC gene

in LNs and extranodal sites

visceral

Types of mutations 8

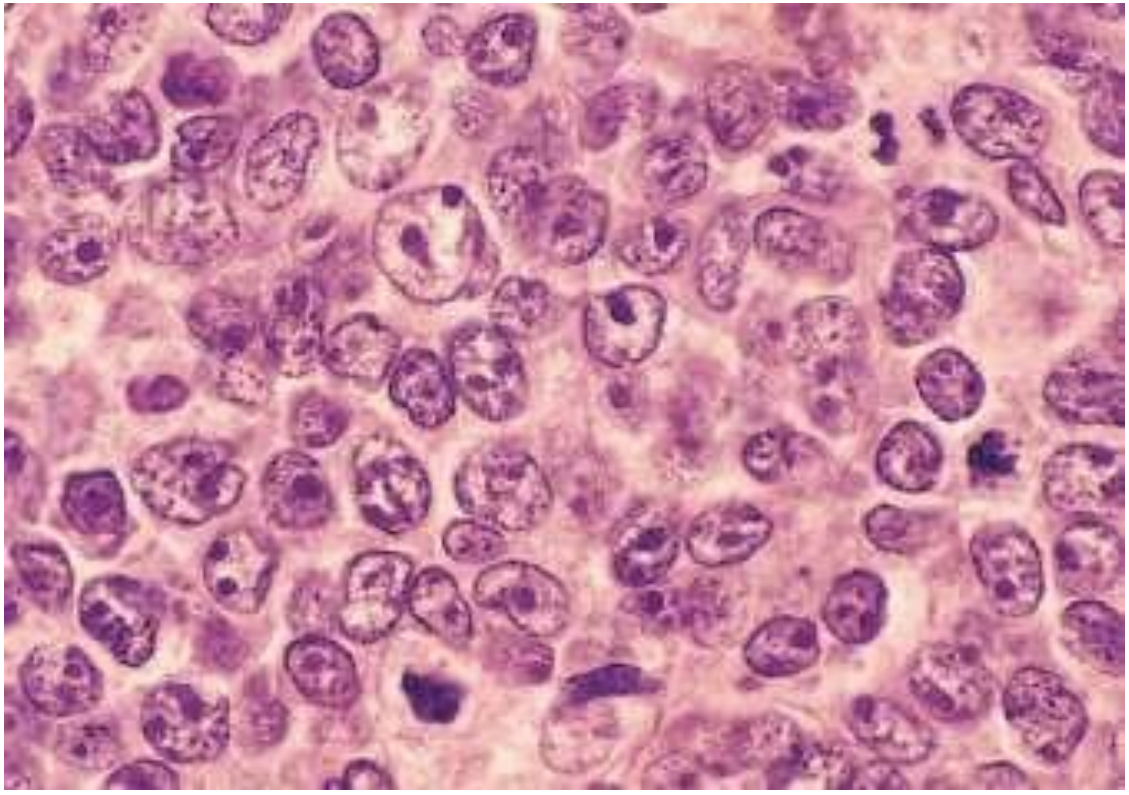
survive for a long time

very active, synthesizes Ig

potent activator of cell cycle

MORPHOLOGY

Diffuse, no nodules or follicles



LNs have lost their architecture and very large

- DLBCL: cells are large (3x normal lymphocytes), irregular nuclei, small nucleoli, frequent mitosis. Positive for CD20, CD45, CD19, CD22

DLBCL-SUBTYPES

- Most cases arise de novo (Primary), few complicate a previous low-grade B-cell lymphoma (Secondary DLBCL) → turning into the high grade DLBCL
- Primary mediastinal large B-cell lymphoma (in the thymus): arises from thymic B-cells, most patients are middle age women, spread to CNS (unusual mode of dissemination) and visceral organs
- EBV-associated DLBCL: arise in immune suppressed patients and in elderly, begin as polyclonal B-cell proliferation (EBV → Proliferation of B cells (polyclonal) → monoclonal (malignancy)) → may regress if immune function is restored
- Human Herpes Virus-8 (HHV-8, doesn't cause a disease in immunocompetent pts): causes DLBCL in pleural cavity, encodes cyclin D1 mimicker protein (in the HHV-8 infected lymphocytes), seen in immune suppressed patients

FOLLICULAR LYMPHOMA

- Second most common NHL
- Common in the West (less in Asian countries)
- Mainly in > 50 years
- M>F
- Patients present with generalized lymphadenopathy
- Commonly disseminates to BM, liver and spleen (80%)

low grade lymphoma (slow) → so it has time to affect multiple LNs, unlike DLBCL

PATHOGENESIS

- t(14;18) (Bcl2 IgH)
- Overexpression of Bcl2 (anti-apoptotic) results in prolonged survival of lymphoma cells
- 1/3 of patients have mutations in genes encoding histone-modifying proteins (epigenetic change)
  - more active DNA without a mutation

MORPHOLOGY

not diffuse as in DLBCL

LNs are larger than the normal & contain numerous follicles

- The normal architecture of lymph node is effaced by nodular proliferation (follicles)

looks like reactive follicular hyperplasia

2 populations of cells &

- The follicles are composed of small irregular "cleaved" lymphocytes "centrocytes" and large lymphocytes with vesicular nuclei and small nucleoli (centroblasts)

like in DLBCL

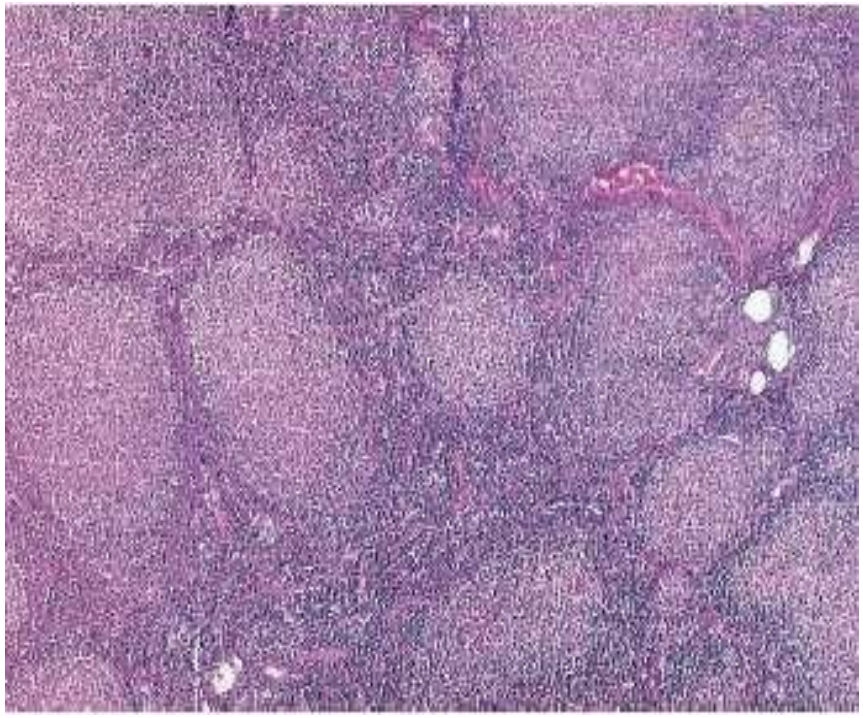
- In most cases, the centrocytes predominate (low-grade). With time, centroblasts increase and the disease becomes high-grade

aggressive

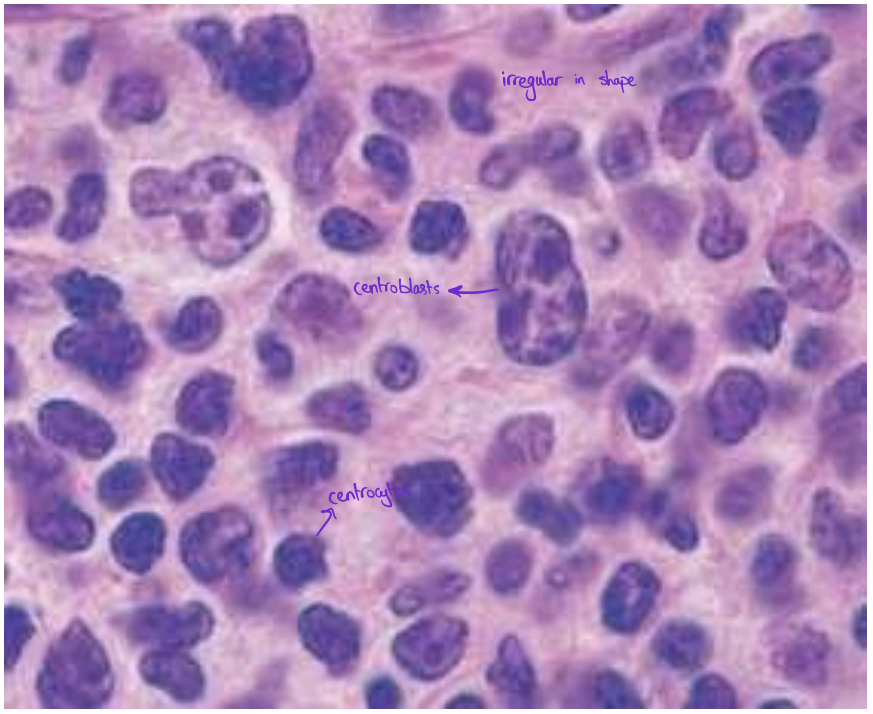
- Cells express CD20, Bcl2, Bcl6, CD10, CD19, CD22

that's how we differentiate it from reactive follicular hyperplasia

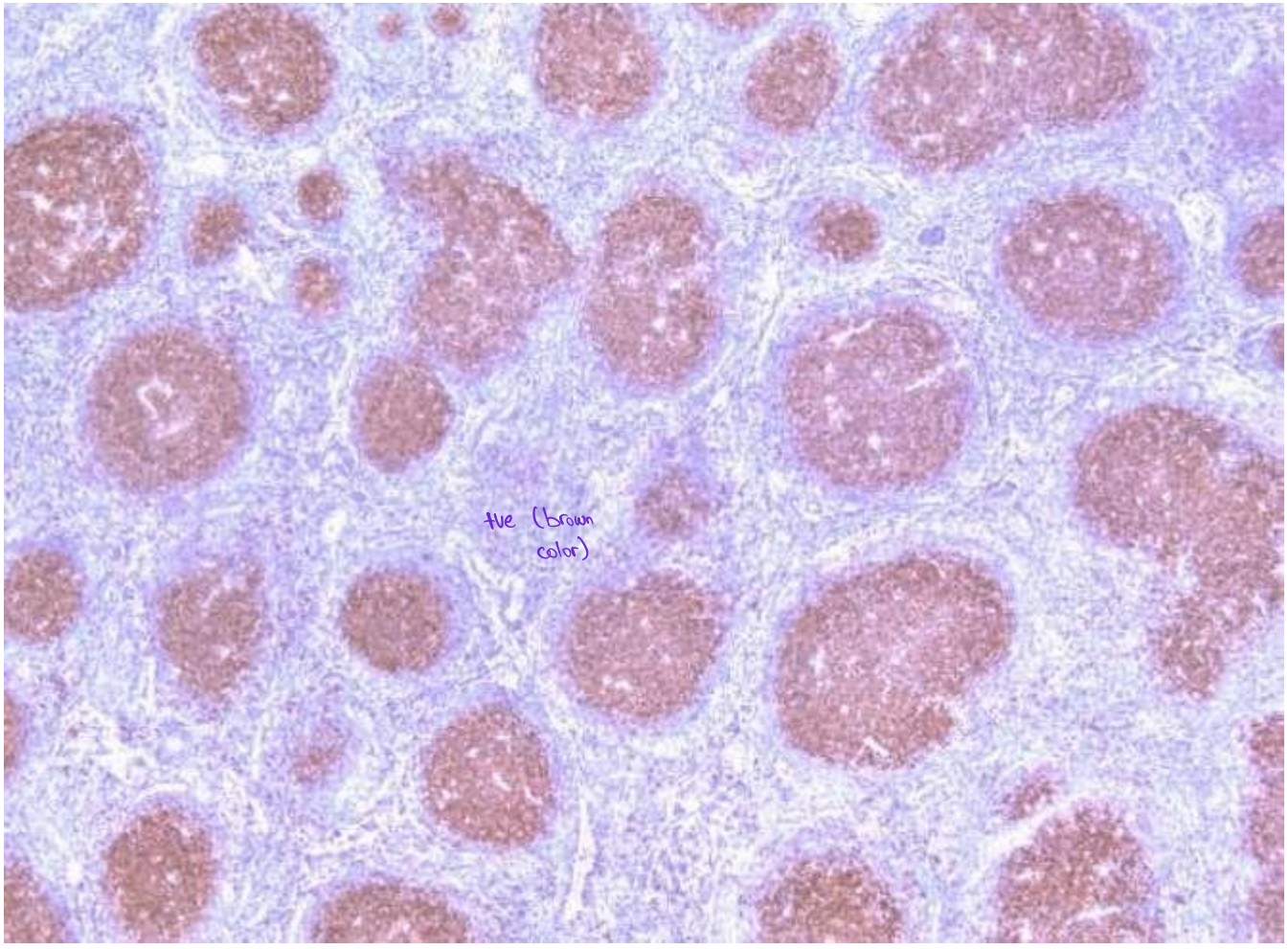
In benign + malignant



Only in the malignant



- Morphology of FL, left: nodular (follicular growth of neoplastic cells effacing the entire lymph node architecture. Right: most cells in this field are centrocytes, appear as small fark cells with cleaved nuclei. There are few large cells with multiple nucleoli, corresponding to centroblasts



searching for an antigen in a tissue

- Bcl2 immunohistochemical stain is positive in follicles in follicular lymphoma

-ve in hyperplasia

PROGNOSIS

low grade

- Indolent course

targets rapidly dividing cells, but cells here have prolonged survival, rather than rapid proliferation

- Conventional chemotherapy is ineffective
- Overall median survival is 10 years

not fatal

no longer follicles

- 40% develop transformation to DLBCL (worse than de novo DLBCL)

no small centrocytes, only large centroblasts

- Therapy is reserved to symptomatic patients, bulky tumors and transformation (cytotoxic chemotherapy, anti-CD20, anti-Bcl2)

Burkitt lymphoma

- Most common NHL in children
- Three types:

1) Endemic in parts of Africa (100% EBV +)
2) Sporadic in the rest of the world (20% EBV +), latent infection
3) Immunodeficiency associated BL

- Extranodal disease: jaw (endemic), terminal ileum, retroperitoneum, ovary, CNS (sporadic), sometimes leukemic

not primary, previous

EBV is kissing disease

most common site (sporadic)

in BM, looks like leukemia

Pathogenesis

- t(8;14) MYC→IgH
  - normal site of
- Overexpression of MYC transcription factor, potent regulator of Warburg metabolism (aerobic glycolysis)
- Neoplastic lymphocytes are B-cells of germinal center origin (CD20, Bcl6)
  - all B cell antigens
  - + CD10
- Aggressive, but responsive to chemotherapy
  - bc of rapid proliferation
  - fastest growing tumor ever, due to MYC

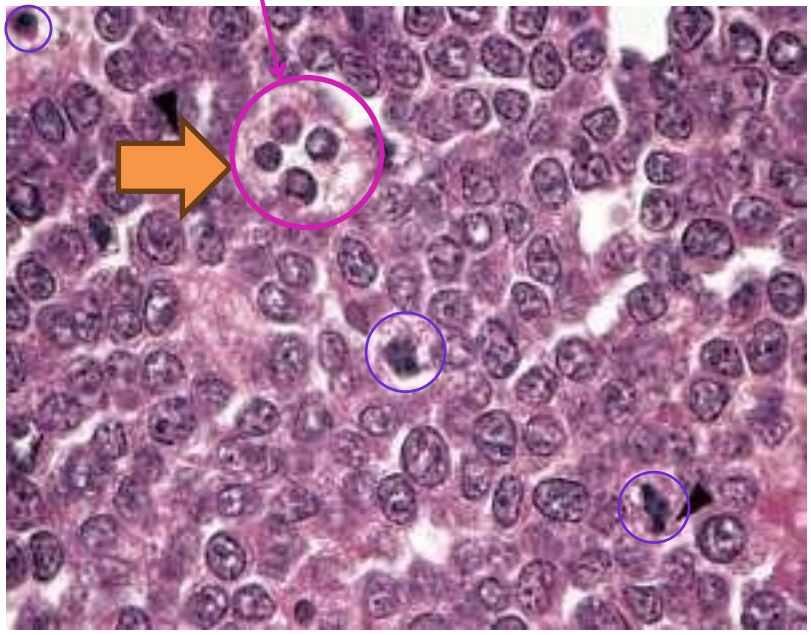
Morphology

Diffuse growth like DLBCL, but size of cells is different

- Intermediate size cells
- Monomorphic (identical shape)
- Round or oval, multiple small nucleoli
- Lipid vacuoles in cytoplasm (Difficult to see)
- Very high mitosis, tingible body macrophages engulfing nuclear debris

rapid proliferation → ↑↑ Death

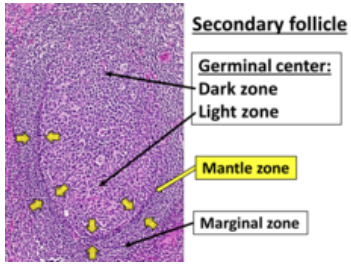
mitotic figures inside circles



Extranodal marginal zone lymphoma

develop in marginal zone's B cells

and resemble normal marginal zone's cells



- Indolent B-cell lymphoma

First & DLBCL

- Second most common lymphoma in extranodal sites in adults

Children → Burkitt lymphoma

follows

- Arises in the setting of chronic inflammation
- Can complicate autoimmune disease in localized areas (Hashimoto thyroiditis, Sjogren syndrome)
- Can complicate Helicobacter pylori-chronic gastritis
- Infiltrate the epithelium and causes destruction

Mantle cell lymphoma

- Arises from naïve B-cells in mantle zone (haven't entered follicular germinal center)
- Most commonly in older men
- t(11;14) that fuses cyclin D1 gene to IgH locus (shared by most mutations; on Chromome 11)
- Overexpression of cyclinD1, promote progression of cell cycle
- Affects LNs, Waldeyer ring (tonsils, adenoids ...)
- Commonly involve BM, blood in 20%, sometimes in GIT, appears as submucosal nodules (lymphomatoid polyposis) (resembles a lymphoid leukemia; like polyps in colon or stomach)
- Morphology: small centrocytes, but in diffuse pattern (like in follicular lymphoma, but diffuse)

Small lymphocytic lymphoma / chronic lymphocytic leukemia

- Low-grade B-cell neoplasm
- Affects elderly
- Can arise in LNs and solid tissue (SLL), or in BM and peripheral blood (CLL)
  same malignant lymphocytes, but different sites
- Most common leukemia in adults, while SLL represents only 4% of NHL
  CLL
- Not common in Asia

PATHOGENESIS

- Increased Bcl2 protein, secondary to deletion mutation in genes encoding micro-RNAs that are negative regulators of Bcl2
- A surface immunoglobulin called B-cell receptor (BCR), is autonomously active, activating a intermediary called Bruton tyrosine kinase (BTK) that activates genes promoting cell survival
- Chromosomal translocation is rare
- Lymphoma cells express CD20, Bcl2 and CD5

mutant

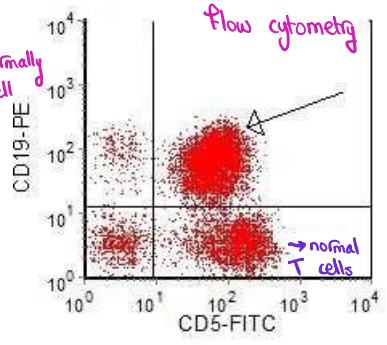
small lymphocyte with a long life

characteristic

it's normally a T cell marker

+ CD19

+ CD22

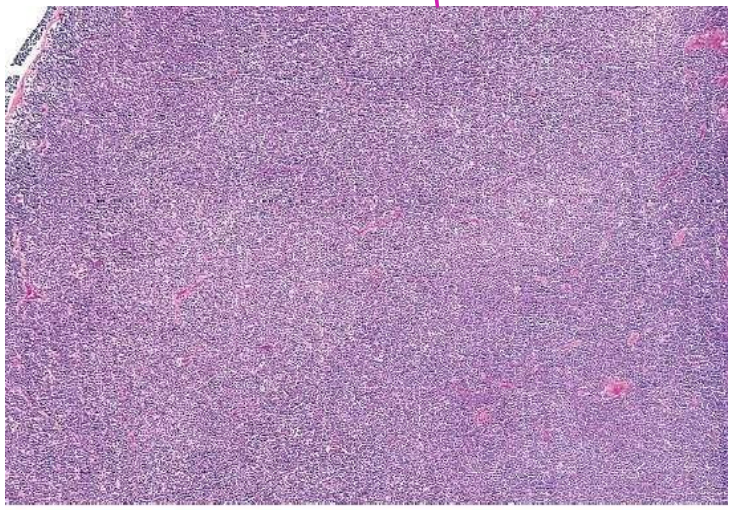


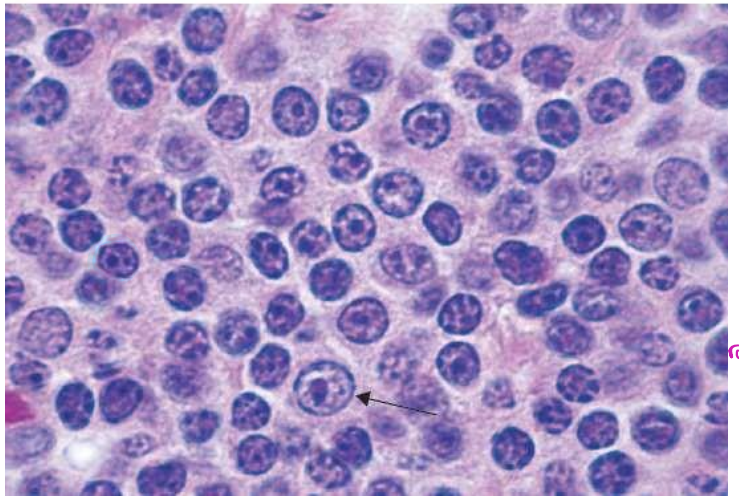
MORPHOLOGY OF SLL

- LN shows effacement of architecture
- Most of neoplastic cells are small in size, round, dark chromatin, along with few large cells with central prominent nucleolus (prolymphocyte)
- Proliferation centers: focal areas containing large number of prolymphocytes and increased mitosis

large LNs

effacement of nodules



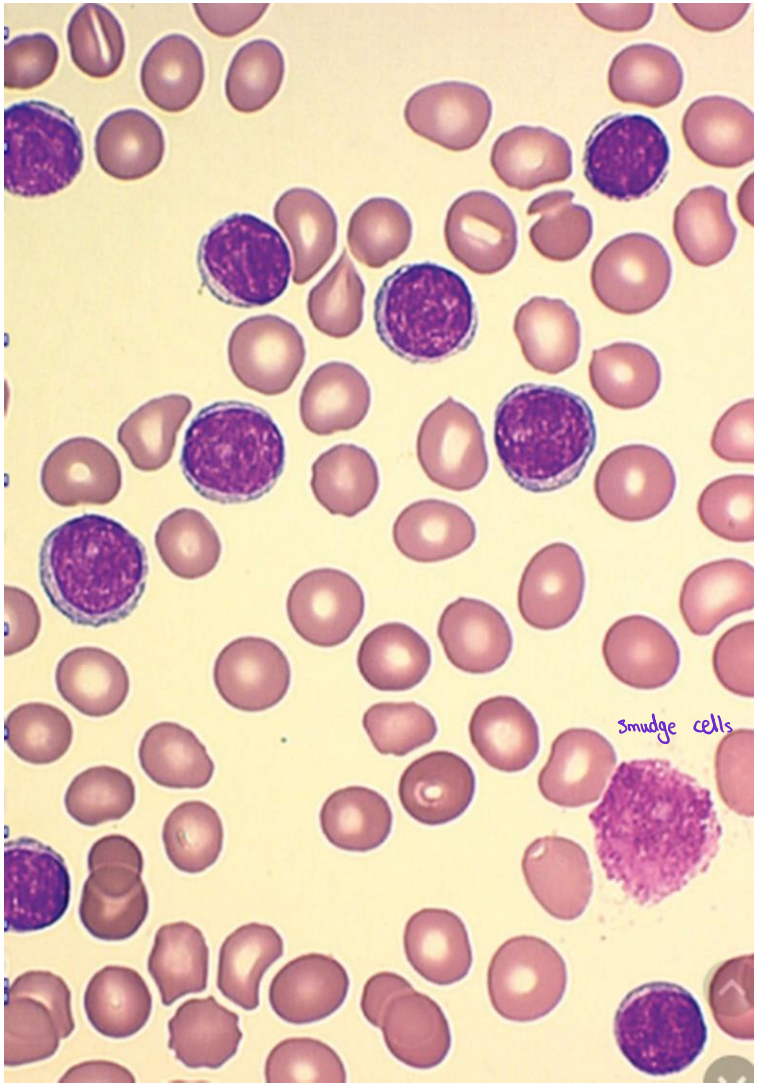


small dark (lymphocyte) + large light (pro-lymphocyte)

round, in follicular lymphoma, they're irregular in shape with angle

MORPHOLOGY OF CLL

- Leukemic cells appear similar to lymphocytes
- Occasional prolymphocytes
- Smudge cells very fragile



CLINICAL FEATURES

- Many patients are asymptomatic
- Leukocytosis (by lymphocytes) can reach very high levels (>200,000)
- 50% have generalized lymphadenopathy and hepatosplenomegaly
- Immune dysfunction is common, by suppressing normal B-cells, resulting in hypogammaglobulinemia (50% of patients) (normal Abs in serum ↓, ↑ infections)
- Anemia: 15% of patients develop auto antibodies against RBCs and platelets (cold type), secreted by normal B-cells
- Thrombocytopenia: similar to ITP
- Variable outcome: many patients have similar survival to general population. In contrast, P53 mutation makes prognosis worse
- Richter transformation: predominance of large cells, patients survive <1 year (bad prognosis)

CLL → then
- lymphoma in LNs
- leukemia in BM and blood

PLASMA CELL MYELOMA

- AKA multiple myeloma
- Common neoplasm
- Commonly in elderly, more common in men, African origin
- Malignant plasma cells secrete monoclonal protein (M protein), most commonly IgG (60%), then IgA (20-25%), followed by other types.
  same for all
- Sometimes only light chain (kappa or lambda), can be detected in urine (Bence Jones proteins)

PATHOGENESIS

like in mantle cell lymphoma

- t(11;14) IgH-cyclinD1 and cyclinD3
- MYC gene mutation occurs late in disease

Part of therapy is interrupting this rxn

- IL-6 is important is plasma cell survival, secreted from BM macrophages and fibroblasts
- Malignant plasma cells activate expression of receptor activator of NF-kB ligand (RANKL), that activates osteoclasts, causing bone resorption. Other products inhibit osteoblast function (hypercalcemia and pathologic fracture)

from osteoid

cause weakning in multiple bone through the body

+ Plasma cells

- Suppression of normal B-cell function

at the early stages of myeloma, when the count of plasma cells is still low

- Directly inhibits erythropoiesis (early onset anemia)

excaberates anemia

- Renal failure: obstruction to distal collecting tubules by proteinaceous cast (Bence Jones protein, immunoglobulin, albumin). Hypercalcemia produces kidney stones, causing further obstruction and renal infection

MORPHOLOGY

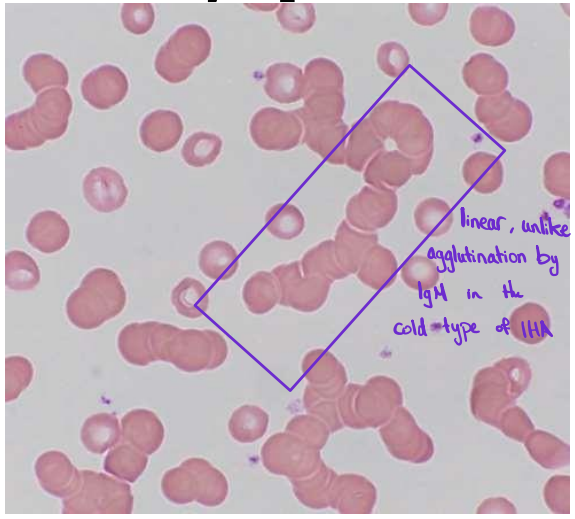
malignant cells stay in the BM

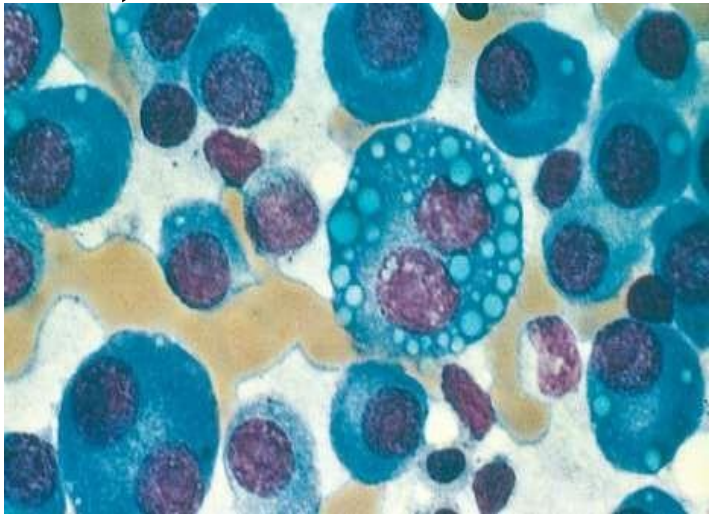
Igs bind RBCs together

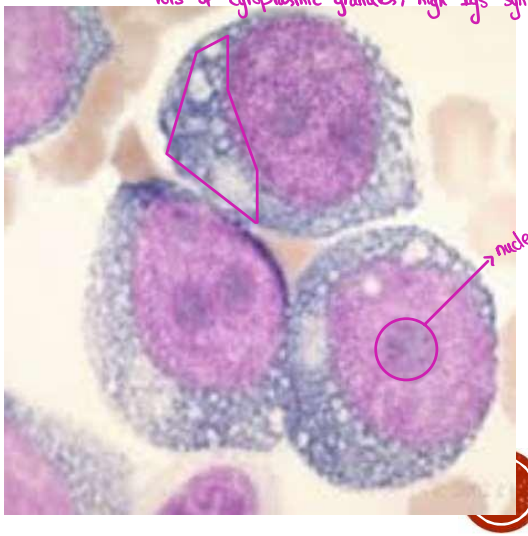
- Peripheral blood: RBCs show rouleaux formation → high ESR
- BM: increased number of plasma cells (>10% of bone marrow cells)

normally less than 2%

- Morphologically might resemble normal plasma cells, or become abnormal (prominent nucleoli, multinucleation, cytoplasmic vacuoles)





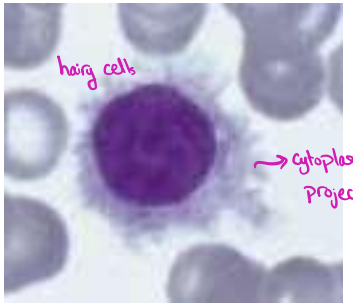


CLINICAL AND LABORATORY FINDINGS

- Very high ESR (Anemia)
- CRAB (hypercalcemia, renal failure, anemia, bone fracture)
- Amyloidosis: occurs in few patients, secondary to deposition of light chain (AL-amyloid) (Infiltrative) (in heart, endocrine glands)
- In advanced disease: pancytopenia (myelophtisic anemia), plasma cell leukemia (spread to blood), visceral damage
- Slowly growing, not curable with conventional chemotherapy
- Lenalidomide: inhibits oncogenic proteins (changes the environment around plasma cells)
- Proteasome inhibitors: inhibit degradation of misfolded proteins. When accumulate, cause apoptosis in plasma cells (very effective)

HAIRY CELL LEUKEMIA

- Uncommon low-grade B-cell leukemia (BM, liver and spleen / doesn't affect LNs; all have large spleen)
- Affects older patients, more common in men, smokers
- Leukemic cells are few in number (bc they circulate in blood; opposite to all leukemias), have prominent cytoplasmic projections
- Splenomegaly, pancytopenia (Leukemic cells heavily infiltrate BM and spleen)
- Leukemic cells are biologically active, inhibit hematopoiesis and cause bone marrow fibrosis (not only inhibition)
- LN involvement is very rare
- Mutation in serine/threonine kinase BRAF gene (BRAF mutation)
- Very sensitive to chemotherapy



PERIPHERAL T-CELL LYMPHOMA

not blasts

- Most common mature T-cell lymphoma
- Aggressive, poor prognosis

HHL

- Neoplastic cells secrete inflammatory cytokines, causing severe inflammation

T cell markers

- Positive for CD2, CD3, CD5, CD7

* arises in any tissue *

Skin → Viscera

Skin & Viscera & blood

MYCOSIS FUNGOIDES AND SEZARY SYNDROME

- Neoplastic CD4+ T-cells, that home to skin
- Patients present with erythema, progressive to plaque then tumor
- Neoplastic lymphocytes have irregular nuclear membrane (cerebriform), affecting epidermis and dermis.

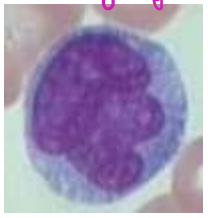
involuted

looks like the brain

then they move into adjacent LNs, circulate into blood and into viscera

- With disease progression, lymphoma disseminates to LNs and viscera
- Sezary syndrome: a variant of MF, patients present initially with widespread erythema and blood leukemia of neoplastic cells (Sezary cells)

Present from the beginning



ADULT T-CELL LEUKEMIA/LYMPHOMA

- Neoplastic CD4+ T-lymphocyte
- Caused by a retrovirus; human T-cell leukemia virus 1 (HTLV-1)
- Endemic in Japan, Caribbean basin, West Africa and some parts of South America
- Sporadic everywhere
- Virus is transmitted through body fluids (blood, breastfeeding, sexual intercourse)
- 5% of carrier develop neoplasm, after a latent period of 40-60 years
- Tax protein is essential for viral mRNA transcription, also interacts with PI3 kinase and cyclin D, represses expression of CDK inhibitors, and activates NF-kB, all promote cell survival. Tax also causes genomic instability, inhibiting DNA-repair
- Patients present with skin lesions, lymphadenopathy, lymphocytosis, hepatosplenomegaly and hypercalcemia
- Neoplastic cells express CD25 (IL-2 receptor)
- Poor prognosis