Doctor.021

no.8

HLS
PATHOLOGY

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NEOPLASTIC PROLIFERATION OF WBC

- **Mostly considered as malignant** (very few considered benign).
- They are **fluid tumors,** in contrast to most cancers in the body which is called (solid tumors).
- Many of them circulate in the blood (they don't form a mass)
- **Differs in biologic behavior, ranging from indolent** (low grade slowly growing) **to very aggressive cancers**
- They are **Common cancers.**

They are the third or forth most common cancer in adults, and they are the most common in children.

- **Current classification system: World Health Organization (WHO) classification system for Hematolymphoid neoplasms**

Classified according to lineage (myeloid vs lymphoid vs histiocytic, lymphoid has B vs T cell types, etc…), based on morphology, protein, and molecular tests.

LYMPHOMA

Most common neoplasm of WBCs.

- **Neoplasm of lymphocyte, malignant** (no benign lymphoma)
- **It can be Called:**

- leukemia: if it affects bone marrow or peripheral blood.

- lymphoma: if it affects lymph nodes or solid organs (extra-nodal lymphoma), most cases are in lymph nodes and 1/3 of cases are extra-nodal (in solid organs: skin, stomach, CNS….), We already know that lymphoid cells don't only reside in the lymph nodes.

- **Lymphomas are 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), since the immune System is dynamic and involves continuous immunoglobulin synthesis, so, accidents during class-switching can happen in the Immunoglobulin gene which cause mutations to be more probable in

B cells than in T-cells), T cell have more stable genome.

- **All are malignant but can be of low-grade (indolent)** which persists for a long time, **or high-grade (aggressive)** which causes death faster.
- **Diagnosis is made through morphologic and immunophenotypic** (examination of protein expression) **(immunohistochemistry** (solid) **or flow cytometry**(blood-BM)**) examination of biopsy.**
- **Sometimes a test for mutations is performed for confirmation.**
- **Immunodeficiency is a risk factor for lymphoma, and vice versa** (the most common cancer that the patients with HIV(AIDs) can develop is lymphomas, also in inherited/congenital immune deficiency they have higher tendency to develop lymphomas).

COMMONLY TESTES IMMUNOPHENOTYPE

- **CD45: common leukocyte antigen,** (if it's positive so it's a hematolymphoid neoplasm, if it's negative so it's a solid tumor of another organ)
- **B-cells (mature) express: CD19, CD20, CD22**

- Germinal center (inside follicles) **lymphocytes express: CD10 and Bcl6**(it's a transcription factor)**.** If they are positive= follicular lymphoma.

- Plasma cells express: CD138.

- **T-cells (mature) express: CD2, CD3, CD5, CD7** (small numbers).

- T-helper lymphocytes express: CD4.

- Cytotoxic lymphocytes express: CD8.

- **Blasts** (immature) **express: CD34.**

-Lymphoblasts (immature) express: TDT (terminal deoxynucleotidyl transferase) and CD10.

*Clarification example: T helper cell has CD45 AND CD2,3,5,7 AND CD4.

HODGKIN LYMPHOMA

- **Constitutes 30-40% of all lymphomas.**

- **Most common type of lymphoma in Jordan, in children and young adults,** but in adults non-Hodgkin is more common.

❖ Unique characteristeics:

- **The neoplastic cells are giant** [originally, lymphocytes are the smallest nucleated cells in the body].
- They have **different morphology and immunophenotype** (antigen expression) **from normal lymphocytes** (they are CD45 negative + negative to all B or T cell antigens).
- **The number of neoplastic cells form less than 10% of tumor mass, while the rest are normal inflammatory cells** (who got requited by malignant cells).
- **Arises primarily in a localized area of lymph nodes** (only in lymph nodes) **(neck, axilla, mediastinum), then spreads to anatomically adjacent LN group,** (predictable spread, neck → axilla → mediastinal LN → visceral LN in the abdomen then spleen and BM) unlike cancers in general.
- **Mesenteric LNs and Waldeyer ring** (oral and nasal cavity) **are rarely involved,** so if there is lymphoma here it's probably non-Hodgkin lymphoma.
- **Bimodal age distribution** there is 2 peaks **(first peak in children** and young adults**, second peak in old age groups)**
- **B-symptoms: patients commonly have fever, night sweats and weight loss,** which are systemic symptoms of inflammation.

-in the past, Hodgkin lymphoma was believed to be a disease rather than a tumor, due to its previously mentioned symptoms)

CLASSIFICATION

- **Classic Hodgkin lymphoma (95%):**

4 subtypes depending on histological appearance:

-nodular sclerosis (most common type all over)

Characterized by large lymph node, and extensive fibrosis.

-mixed cellularity

No sclerosis or nodules, here we have sheaths of tumor cells + normal cells (eosinophils, neutrophils, plasma cells, and macrophages, all have been recruited by tumor cells)

-lymphocyte-rich (rare)

We see lymphocyte with giant cells.

-lymphocyte-depleted (rare)

We see histiocytes in large number, we don't see lymphocyte only malignant cells.

In the first two, normal inflammatory cells make the bulk of the tumor [WBCs]

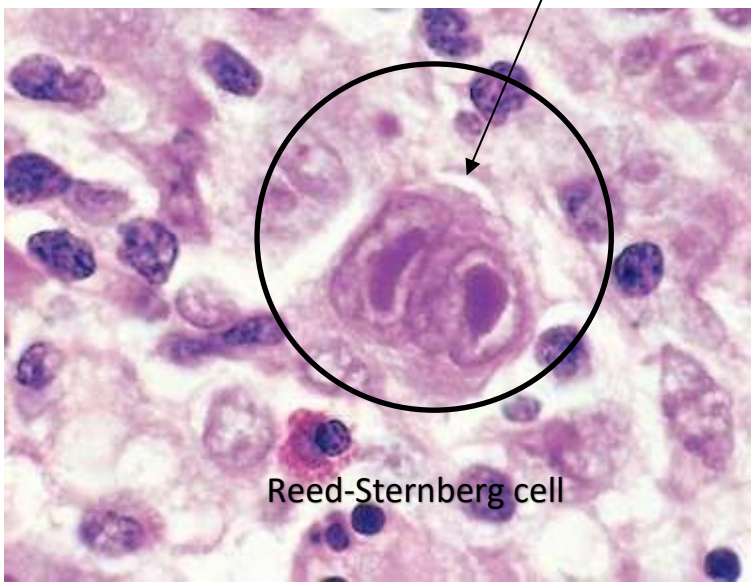
- **Non-Classic Hodgkin lymphoma (5%):**

Single type in morphology:

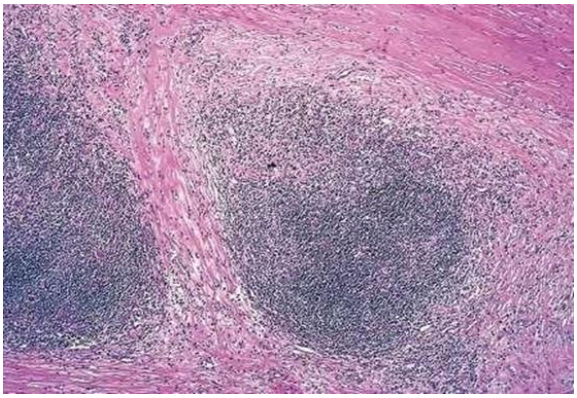
-Nodular lymphocyte-predominant

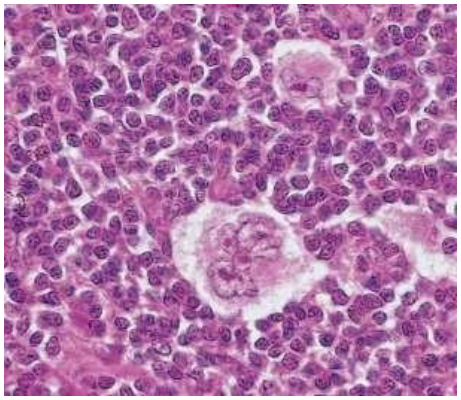
- **Reed-Sternberg cells** (neoplastic cell in HL)**: bi or multi-nucleated giant cell, prominent nucleoli** (pink in color/eosinophilic)**, abundant cytoplasm**
- **Hodgkin cells: mononuclear giant cell** (single nucleus).

Both express CD30 and CD15 which are normally absent but get expressed through the pathogenesis, **and negative for CD20, CD3 and CD45,** and this is why it took a very long time until it was recognized as a neoplastic B-cell (it was thought as an inflammatory cell).



NODULAR SCLEROSIS HL





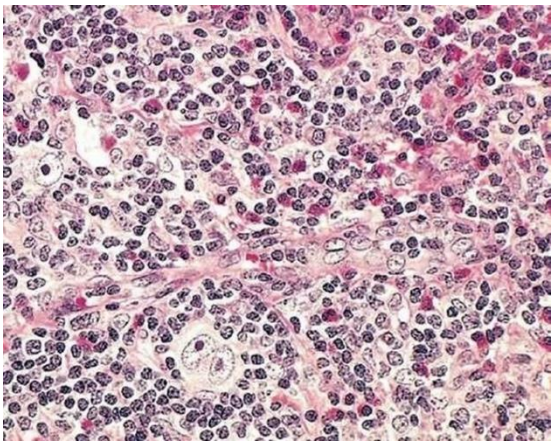
- Lymph node has nodules with dense sclerosis (fibrous band).
- **Common in children and young adults**

- **Thick fibrous bands separating nodules of lymphocytes.**
- **RS cells show clear cytoplasm, as a retraction artifact from formalin, called Lacunar cells.**

MIXED CELLULARITY HL

- **Common in old people**
- **Numerous RS cells**
- **Lacks fibrous bands.** diffuse area with numerous RS (Reed-Sternberg cells) with a background of inflammatory cells [mixed neutrophils,

  eosinophils, lymphocytes, plasma cells and histiocytes]



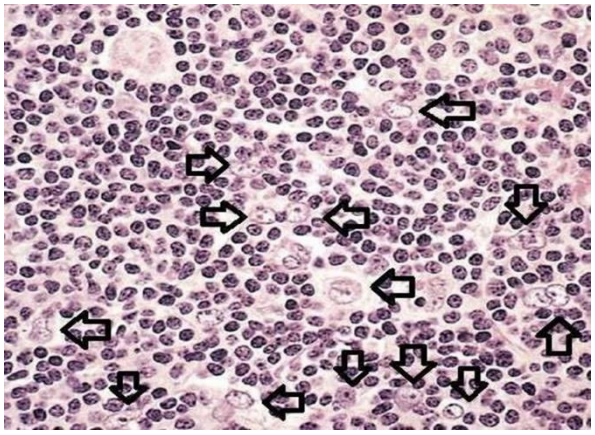
- **Associated with EBV**
- **Background: mixed neutrophils, eosinophils, lymphocytes, plasma cells and histiocytes**

LYMPHOCYTE-PREDOMINANT HL

- **Malignant cells** (few in number) **are called lymphohistiocyte (L&H) variant RS cell, or simply LP** (lymphocyte predominant) **cells.**
- **Resemble popcorn (so now we call them popcorn cells)**
- **Giant cell with multi-lobulated** (not multi-nucleated as RS cells) **vesicular** (which means white nucleus and small blue nucleoli**).**
- **Express normal B-cell markers (CD45, CD20), negative for**

  CD30 and CD15 which are markers of classic HL.
- **Background of lymphocytes, arranged in nodules** but no fibrous septa.

- **Excellent prognosis** better than the classic HL :D



Popcorn cells

PATHOGENESIS AND OUTCOME **of Hodgkin lymphoma:**

- **Neoplastic cells Originate from germinal center B-cells,** but they are different from them (in genetics)
- **Frequent association with EBV,** (mixed cellularity type is the most common one).
- **RS cells secrete IL-5, chemoattractant for eosinophils** → causing eosinophilia in
- the blood in severe cases, **Also secrete IL-13 and transforming growth-B (TGF-ß) which activates other RS cells** (autocrine effect), which support their survival and lead to more progression of the tumor.
- **Express programmed death (PD) ligands** on the surface of RS cells **which antagonize T-cell response** by binding to them causing their apoptosis, **escaping immune surveillance.**

In therapy now we use an antibody that binds these PD ligands so the lymphocytes can act as natural fighters of the cancer.

- **Prognosis is generally good.**

NON-HODGKIN LYMPHOMAS:

Divided into B and T lymphomas (B is more common)

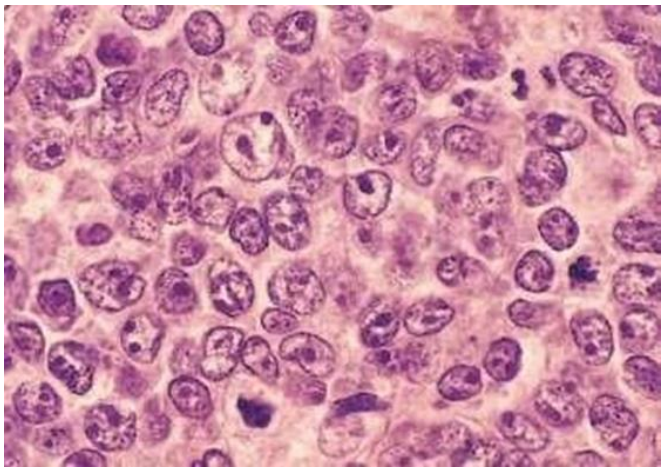
DIFFUSE LARGE B-CELL LYMPHOMA

- **Most common NHL**
- **Predominantly in adults**
- **High-grade (rapidly growing mass) and** doesn't get treated usually → fatal.
- Can be in lymph nodes or extra-nodal, and it's the **Most common non-cutaneous extra-nodal 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** (so it would be present in B-cells in the germinal center phase)
- **30% have t (14;18) (Bcl2 →IgH) which results in overexpression of Bcl2 protein (anti-apoptotic),** [translocation of Bcl2 gene from ch.18 to ch.14, which affects its expression rate]

  [Note: IgH is very active because it produces the heavy chain of Igs]

  - Bcl2 gene fuses with the IgH on chromosome 14, so with every transcript of IgH, we have Bcl2 being expressed which results in overexpression of Bcl2 protein (an anti-apoptotic protein) so it prolongs the cell survival.
- **› Few has mutation in MYC gene [the MYC product activates the cell cycle]**

MORPHOLOGY



DLBCL:

-Diffuse cells and disrupted architecture.

- cells are large (3x normal lymphocytes).

- irregular nuclei, small prominent nucleoli (nucleus is very active)**.**

-frequent mitosis, and apoptosis.

- Positive for CD20 (a B-cell marker).

DLBCL-SUBTYPES

- **1-Most cases arise de novo, few complicate a previous low-grade.**
- **2-**Secondary DLBCL: it arises from low grade **B-cell lymphoma** gaining additional mutations.
- **3-Primary mediastinal large B-cell lymphoma:**

  -arises from thymic B-cells (in the thymus, we have few B-cells, if they get mutated this lymphoma will develop)**.**

  - most patients are middle-aged women (THE only one that's more common in women).

  -spread to CNS and visceral organs. [characteristic of this subtype]
- **4- EBV-associated DLBCL:**

  -arise in immune suppressed patients.

  -and in elderly, Infection with EBV will lead to **normal polyclonal B-cell proliferation,** then if multiple mutations are added this lymphoma will develop

  - Prognosis is BAD.
- **5- Human Herpes Virus-8:**

  -causes DLBCL in pleural cavity, other name for this subtype is primary effusion lymphoma [causes pleural effusion] it appears in pleural cavity by accumulating a fluid that is filled with malignant B-lymphocytes which test +ve for HHV-8 [characteristic for this subtype].

  - HHV-8 encodes cyclin D1 mimicker protein, which in turn keeps the cell cycle ON by alternating the cell phase from G1 phase to S phase.

  -seen in immune suppressed patients.

❖ **Lymphomas are more common in males than females, Primary Exception: mediastinal large B-cell lymphoma.**

FOLLICULAR LYMPHOMA

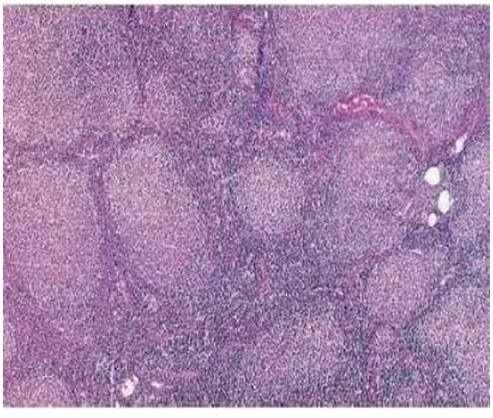
- **Second most common NHL.**
- **Common in the West (less in Asian countries).**
- **Mainly in > 50 years** (old people).
- **M>F** (male>female)
- **Patients present with generalized lymphadenopathy,** (lymph node enlargement in most of the body).
- **Commonly disseminates to BM, liver and spleen (80%),** but it's still a low-grade lymphoma.

Paradoxically, low grade lymphoma easily disseminates but doesn't kill the patient, (they have a longer time so you can see them in different areas of the body it can affect multiple lymph nodes), on the other hand, DLBCL starts at a certain area and destroys very fast.

PATHOGENESIS

- **t (14;18) (Bcl2→IgH),** described earlier, which will lead to Overexpression of Bcl2 resulting in prolonged survival of lymphoma cells → this mutation is found in all follicular lymphomas.
- **Overexpression of Bcl2 results in prolonged survival of lymphoma cells.**
- **1/3 of patients have mutations in genes encoding histone-modifying proteins (epigenetic change,** not in nucleotides**)**

MORPHOLOGY



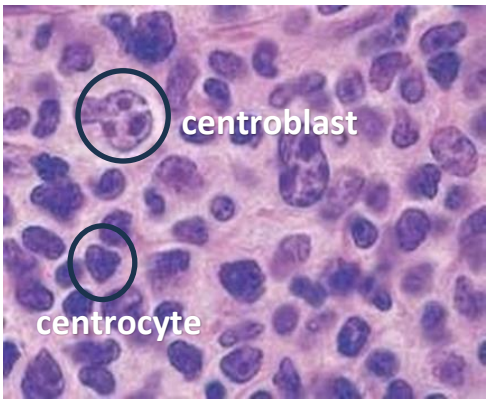
Remember the name: Follicular lymphoma.

- **The normal architecture of lymph node is effaced by nodular proliferation** that forms **(follicles).**

Note: remember! Reactive follicular hyperplasia is a benign case in which B cells proliferate in association with rheumatological diseases, HIV, toxoplasmosis, in this hyperplasia we DON'T have disrupted or effaced architecture like we have here in follicular lymphoma.

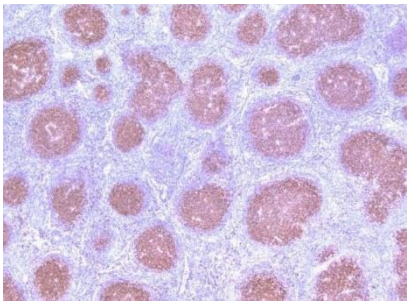
Zooming into the follicles we see 2 population of cells:

- **1- Centrocytes: small irregular** (normal lymphocyte are rounded), **"cleaved" lymphocytes.** (cyte→mature)
- **2- Centroblast: large lymphocytes with vesicular nuclei and small nucleoli.** (blast→immature), more proliferating than cytes.



- Centro → because they are in the germinal center.
  - **In most cases, the centrocytes predominate (**so it's a **low-grade), With time, centroblasts increase and the disease becomes high-grade resembling DLBCL,** and becomes more aggressive in behaviour.
  - **Cells express CD45, CD20, CD10, Bcl2, and Bcl6** (because they are Germinal center cells).

- **Bcl2 immunohistochemical stain is positive in follicles in follicular lymphoma.**



We can differentiate between malignant follicular lymphoma (Bcl2 +ve) and benign reactive follicular hyperplasia (Bcl2 –ve) by Bcl2 immunohistochemical stain.
If the follicle is Bcl2 stain +ve it means malignancy and FL.

PROGNOSIS

- **Indolent course** (low grade).
- **Conventional chemotherapy is ineffective,** (chemotherapy is ineffective in all low-grade lymphoma in general, because chemo drugs target proliferating cells).
- **Overall median survival is 10 years.**
- **40% develop transformation to DLBCL** (secondary DLBCL) → **(worse than de novo DLBCL)**
- If the disease turned to the high state -in which proliferation is accelerated, **Therapy is reserved to these symptomatic patients, with bulky tumors or transformation into DLBCL → we use cytotoxic chemotherapy, anti-CD20** (monoclonal antibody)**, anti-Bcl2.**

BURKITT LYMPHOMA:

- **Most common NHL in children,** (HODGKIN LYMPHOMA is THE MOST common lymphoma in children).
- **Three types:**

  -Endemic in parts of Africa (100% associated with **EBV +)**

  -Sporadic in the rest of the world (20% EBV +), results from **latent infection**

  -Immunodeficiency (+HIV) **associated BL.**

- It's an **Extranodal disease:**

jaw (endemic)→ it causes jaw enlargement and disfigurement of the face (where EBV is usually transmitted).

terminal ileum (most common site of BL)**.**

retroperitoneum, ovary, CNS (sporadic or immunodeficiency**).**

- **Sometimes manifests as a leukemic disease** (in the blood and bone marrow)**.**

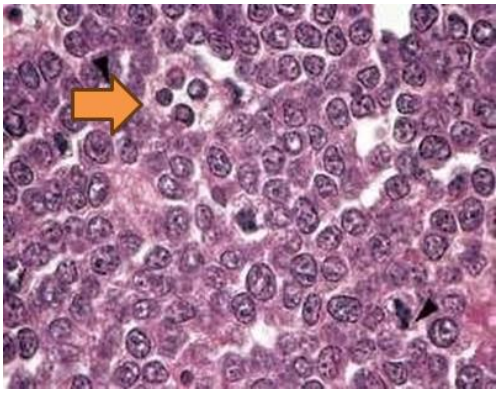
Pathogenesis:

- **t (8;14) MYC→IgH,** MYC gene is translocated to chromosome 14 next to IgH gene, which as we said previously that is very active.
- This will lead to **Overexpression of MYC transcription factor,** which is a **potent regulator of** DNA replication and **Warburg metabolism [**which is an alternative to **normal aerobic glycolysis,** Instead, cancerous cells depend on other pathways that result in more anabolic activity (building/ energy consuming)]

  [Remember: in cancer, cells want to mainly grow and divide, not to do normal functions, and that is why they need this form of modified cellular metabolism].

- **Neoplastic lymphocytes are B-cells of germinal center origin,** so they express **(CD20** [B-cell marker]**, Bcl6** + CD10 [germinal center markers]**)**
- **Aggressive, but responsive to chemotherapy** (high proliferative activity)

Morphology:



- **Intermediate size cells**
- **Monomorphic,** [all have the same appearance] *look at the picture on the side.
- **Round or oval nuclei** [unlike DLBCL and FL]**, multiple small nucleoli**
- **Lipid vacuoles in cytoplasm**

- **Very high mitosis, tangible body macrophages engulfing nuclear debris.**

EXTRANODAL MARGINAL ZONE LYMPHOMA:

Name breakdown:
Extra nodal: Predominantly arises outside the lymph nodes.
Marginal zone: comes after the germinal center, cells in it are more mature and they precede the plasma cell formation [The tumour has a B-cell origin].

- **Indolent B-cell lymphoma.**
- **Second most common lymphoma in extranodal sites in adults,** after DLBCL.
- **Arises in the setting of chronic inflammation:**

-Can complicate autoimmune disease in localized areas (Hashimoto thyroiditis, Sjogren syndrome).

-Can complicate Helicobacter pylori-chronic gastritis, (remember: H. pylori is considered an oncogenic organism).

- **Infiltrate the epithelium and causes destruction.**

MANTLE CELL LYMPHOMA:

- **Arises from naïve B-cells in mantle zone,** [which precedes the B-cell maturation, it's like a reception area before the germinal center].
- **Most commonly in older men**
- **t (11;14) that fuses cyclin D1 gene to IgH locus,** [The same mechanism we talked about before where the genes fusing with IgH gene are highly expressed].
- **Overexpression of cyclinD1, promote progression of cell cycle.**
- **Affects LNs, Waldeyer ring** (oral and nasal cavity).
- **Commonly involve BM, blood in 20%, sometimes in GIT, appears as submucosal nodules (**called→**lymphomatoid polyposis)**
- **Morphology: small centrocytes,** it looks like follicular lymphoma but in **diffuse pattern** (no follicles)

SMALL LYMPHOCYTIC LYMPHOMA / CHRONIC LYMPHOCYTIC LEUKEMIA:

Called (chronic lymphocytic leukemia) when it arises in and circulates the blood.

- **Low-grade B-cell neoplasm.**
- **Affects elderly.**
- **Can arise in LNs and solid tissue (SLL) and SLL represents only 4% of NHL, or in BM and peripheral blood (CLL) and CLL is the Most common leukemia in adults.**
- **Not common in Asia**

PATHOGENESIS

❖ **2 Pathways:**

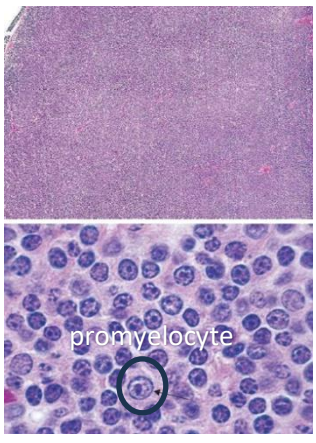
- **1-Increased Bcl2 protein, secondary to deletion mutation** (not through translocation) **in genes encoding micro-RNAs that are negative regulators of Bcl2.**
- **2-A surface immunoglobulin called B-cell receptor (BCR), is autonomously active, activating an intermediary called Bruton tyrosine kinase (BTK) that activates genes promoting cell survival.**
- **Chromosomal translocation is rare.**
- **Lymphoma cells express CD20** (B-cell origin)**, Bcl2 and CD5** (which are a clear sign of malignancy since Bcl2 is positively stained in malignant cells and CD5 is a T-cell marker!).

MORPHOLOGY OF SLL

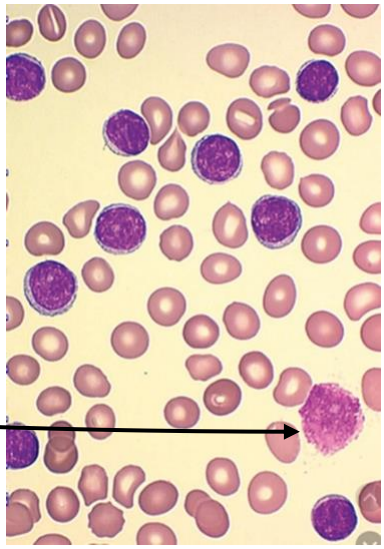
- **LN shows effacement of architecture** (diffuse).
- **We have 2 population of cells:**

  1-Most of them are neoplastic cells that are small in size, round in shape, and have dark chromatin. (lymphocytes)

  2- and other with few large cells with central prominent nucleolus (**prolymphocyte)**
- **Proliferation centers: focal areas containing large number of prolymphocytes and increased mitosis.**



MORPHOLOGY OF CLL



- **Leukemic cells appear similar to lymphocytes,** but they are high in number and very fragile.
- **Occasional prolymphocytes.**
- **Smudge cells, which are Broken, dead lymphocytes.**

CLINICAL FEATURES

- **Many patients are asymptomatic,** (indolent luekemia).
- **Leukocytosis can reach very high levels (>200,000)**
- **50% have generalized lymphadenopathy** (large lymph nodes) **and hepatosplenomegaly.**
- **50% Immune dysfunction is common, by suppressing normal B-cells, resulting in hypogammaglobulinemia** (decreased immunoglobulins).
- **Anemia: 15% of patients develop auto antibodies against RBCs and platelets (cold type immune hemolytic anemia), secreted by normal B-cells.**
- **Thrombocytopenia: similar to ITP** (immune thrombocytopenic purpura).
- **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.**

PLASMA CELL MYELOMA

- **AKA multiple myeloma.**
- **Common neoplasm** arises from malignant plasma cells (terminally differentiated B-cells).

- **Commonly in elderly, more common in men, African origin.**
- **Malignant plasma cells secrete monoclonal protein (M protein**) (Ig of the same type), **most commonly IgG (60%), then IgA (20-25%), followed by other types.**
- **Sometimes only secrete light chain (kappa or lambda), can be detected.**

  in urine (it's called **Bence Jones proteins)**

❖ Bence jones proteins +ve → Plasma Cell myeloma

PATHOGENESIS

- **t (11;14) IgH-cyclinD1 and cyclinD3.**
- **MYC gene mutation occurs late in disease.**
- **IL-6 is important for plasma cell survival, secreted from BM macrophages and fibroblasts,** so part of the therapy is by interrupt this interaction by giving IL-6 blocker.
- **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)→** Patients have fractures, bone pain and symptoms related to hypercalcemia especially in the heart and the brain, also kidney stones.
- Malignant plasma cells **→ Suppression of normal B-cell function.**
- **Directly inhibits erythropoiesis (early onset anemia) → very common.**
- **Renal failure (**multifactorial**):**

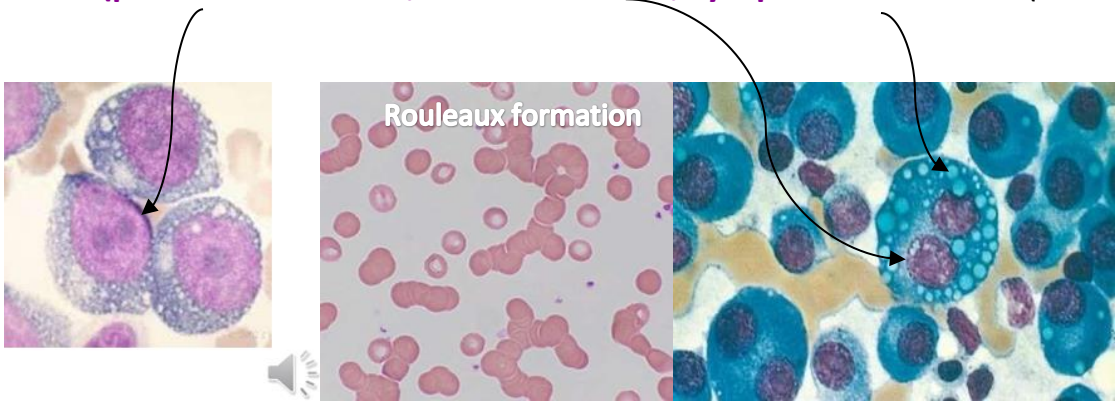
  1-obstruction to distal collecting tubules by proteinaceous cast (Bence Jones protein, immunoglobulin, albumin).

  2- Hypercalcemia produces kidney stones, causing further obstruction and renal infection, which is bad because the patient is immunosuppressed, and it could worsen the anaemia, because there'll be decreased production of erythropoietin, this can be fatal.

MORPHOLOGY

- **Peripheral blood: RBCs show rouleaux formation** (linear + very high ESR) → Immunoglobulins bind multiple RBCs together.
- **BM: increased number of plasma cells (>10% of bone marrow** cells need to be plasma cells for diagnosis to be made, normally they don't exceed 2% of nucleated cells in BM)

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

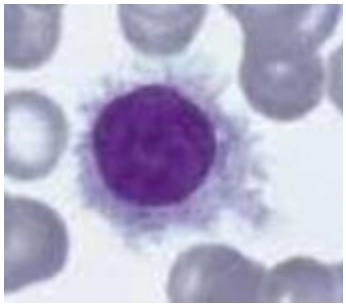


CLINICAL AND LABORATORY FINDINGS

- **Very high ESR.**
- **CRAB (hyperCalcemia, Renal failure, Anemia, Bone fracture)**
- **Amyloidosis: occurs in few patients, secondary to deposition of light chain Kappa or lambda in the form of (AL-amyloid)→** which causes secondary conditions depending on the site.
- **In advanced disease: pancytopenia, plasma cell leukemia, visceral damage.**
- **Slowly growing, not curable with conventional chemotherapy,** Instead, we give other agents called immune modulators:

  1-Lenalidomide: inhibits oncogenic proteins.
- **Proteasome inhibitors: inhibit degradation of misfolded proteins→ When accumulate→ cause apoptosis in plasma cells.**

HAIRY CELL LEUKEMIA



- **Uncommon low-grade B-cell leukemia** (in BM, blood, spleen).
- **Affects older patients, more common in men, smokers.**
- **Characteristic: Leukemic cells are few in number** (unlike all leukemias)**, have prominent cytoplasmic projections** (hair).

- **Splenomegaly, pancytopenia (Leukemic cells heavily infiltrate BM and spleen).**
- **Leukemic cells are biologically active, inhibit hematopoiesis and cause bone marrow fibrosis.**
- **LN involvement is very rare.**
- **Mutation in serine/threonine kinase BRAF gene** (which is important for cell survival and proliferation).
- **Very sensitive to chemotherapy.**

PERIPHERAL T-CELL LYMPHOMA

- **Most common mature T-cell lymphoma**
- **Aggressive, poor prognosis** [T-cell lymphomas are generally aggressive:'(]
- **Neoplastic cells secrete inflammatory cytokines, causing severe inflammation,** even when the tumor is small.
- They express T-cell markers→ **Positive for CD2, CD3, CD5, CD7,** and they are negative for TDT (because they are mature).

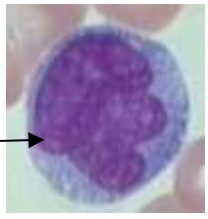
MYCOSIS FUNGOIDES AND SEZARY SYNDROME

Mycosis fungoides→ Because it grows like a mushroom, and they are only in skin.

Sezary syndrome→ subtype of Mycosis fungoides that's leukemic, start in the skin then to peripheral blood then to visceral organs.

❖ **Most common cutaneous lymphoma.**

- **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.**



- **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).**

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 similar to HIV, **and it's transmitted through body fluids (blood, breastfeeding, sexual intercourse).**
- **5% of carrier develop neoplasm, after a latent period of 40-60 years.**
- **Mechanism: Tax protein, which 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.**

GOOD LUCK