- HLS Final pathololgy summary
-Done by: Ola Alahdab

- مليان معلومات مهمة فما قدرت اختصر كتير
- آخر صفحة تجميع للمراجعة النهائية

- BLEEDING DISORDERS:

❍ Pathologic bleeding occurs spontaneously or after a trauma (a prolonged bleeding).

- Caused by defect in either:

• Clotting factors • Platelets • Blood vessels • Endothelium.

- Blood vessels related bleeding:

- Connective tissue diseases.
- Chronic steroid intake (weakens blood vessels, risk of rupture).
- Systemic amyloidosis (amyloid protein can infiltrate through any organ causing damage).
- Vasculitis infections (like spirochetes or fungus, causing rupture & bleeding).
- Vitamin C deficiency (scurvy) (important for collagen in vessels. less common nowadays).
- Symptoms: spontaneous superficial bleeding in the skin & mucous membranes:
- **Petechiae** (in small area) & **ecchymosis** (a large bruise).

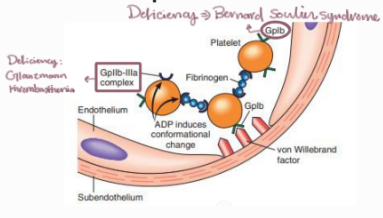
- Platelets related bleeding:

- Thrombocytopenia (ITP, AIDS) (ITP= immune thrombocytopenic purpura).
- It can occur in anemias: **AA, PNH**.
- Thrombocytosis (platelets are large but dysfunctional) is common in **myeloproliferative neoplasms**.
- **Platelets function tests**:

1) Bleeding time test (obsolete: rarely used these days) we make a small superficial cut like in the ear & count time).
2) Platelet aggregation test.
3) Von Willebrand factor test.

The von Willebrand factor is essential for platelets function so we do both tests (2&3):

*Ristocetin Agglutination test: Ristocetin (antibiotic) can cause artificial platelets aggregation by activating VWF to bind to **glycoprotein Ib** (on surface of platelets) causing platelets to clump, so if we add it & platelets do not aggregate, either VWF or the platelets will be abnormal.

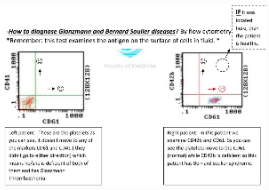


- Glanzmann Thrombasthenia: (Asthenia = weakness)

- Acquired Autoimmune disease.
- Rare autosomal **recessive**.
- Deficiency/Blockage of **platelets' fibrinogen receptors**: glycoproteins IIb-IIIa (CD41/CD61 complex), so fibrinogen cannot bind to platelets = Prolonged hemorrhage (gums, nose, bruising).
- Diagnosis: Flow cytometry

- Bernard Soulier Syndrome:

- Very rare, autosomal recessive.
- Deficiency in **platelets' VWF receptor**: membrane glycoprotein Ib (CD42b), which binds VWF.
- Prolonged hemorrhage.
- Structural abnormalities: Platelets are **large**, can show **thrombocytopenia**.
- Diagnosis: Flow cytometry.



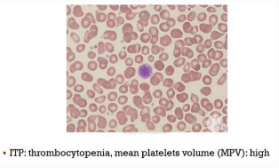
- The VWF is located under the endothelial cells, it is exposed when the endothelium is damaged and removed.

- Heparin Induced Thrombocytopenia:

- Occurs in 5% of patients receiving **unfractionated heparin** (an anticoagulant) where IgG antibody develops, against **platelet factor 4** on platelet's cell membrane (in a heparin dependent matter) causing platelets aggregation = thrombosis.
- The patient has **thrombocytopenia with thrombosis** (like PNH).
- Can also develop in low-molecular weight heparin (fractionated) but less common.

- Immune Thrombocytopenic Purpura (ITP):

- (Purpura = skin bleeding | Immune system destroys platelets = thrombocytopenia).
- Patients have **isolated thrombocytopenia** (sometimes **anemia** of blood loss).
- Most bleeding occurs in skin, mucosal surfaces (petechiae & ecchymosis), GI, urinary tract, CNS.
- Acute ITP: affects children, commonly follows viral infection, self-limited.
- Chronic ITP: affects middle age adults (F>M).



• ITP: thrombocytopenia, mean platelets volume (MPV): high

- IgG auto-antibodies against platelets membrane glycoprotein **IIb/IIIa** (chronic ITP).
- **Splenomegaly** is not always present but patients benefit from splenectomy
- Peripheral blood shows **large platelets**. Bone marrow shows increased number of **megakaryocytes**, spleen shows large aggregates of **B cells & plasma cells**.

- Thrombotic Microangiopathies:

(Microangiopathy: disease occurs in small blood vessels, slows down blood flow, bleeds).

- 2 main diseases cause this syndrome: **Thrombotic Thrombocytopenic Purpura (TTP), & Hemolytic Uremic Syndrome (HUS).**
- **TTP**: we have **thrombosis** all over the body which results in **thrombocytopenia** because the platelets are consumed.
- Symptoms: Fever, microangiopathic hemolytic anemia, neurologic deficits & renal failure.
- **HUS**: similar symptoms as TTP but most dominantly is renal failure, no neurologic symptoms, common in **children**.
- In both diseases, the small circulation in the body is filled with platelets rich **microthrombi**, **without activation of clotting factors** (PT & PTT are normal, these are clotting factors).
- Pathogenesis:
- TTP: deficiency in **ADAMTS13**, a plasma protein required for VWF formation (It converts the precursor of VWF to the actual VWF). So, if this enzyme is absent we will only have the VWF precursor which is a very large multimer (short half-life), it is capable of binding so many platelets together forming **aggregations** = **spontaneous thrombus**.
- HUS: caused by **EHEC** (e. coli) infection in the gut that produces **shiga-toxin**, which reaches the kidneys causing endothelial damage & promotes **thrombosis**.
- Blood film in both diseases: 1) **schistocytes** (cause direct physical damage of RBCs = Traumati) this damage is caused by passing through the thrombi, 2) **thrombocytopenia**.

- Clotting factors related bleeding: (Coagulation disorders)

- Inherited or more commonly acquired.
- Vitamin K deficiency: decreased synthesis of clotting factors related to vitamin K: **II (prothrombin), VII, IX, X** 1972 (due to drugs more commonly **warfarin**, or dietary (rich

in **green leaves** like spinach السبانخ).
- **Liver disease** (site of clotting factors synthesis).
- **DIC** (Disseminated intravascular coagulation).
- **Warfarin.**
- **Autoantibodies** (binds to single or multiple clotting factors, **no true deficiency** but less functionality).
- Diagnosis: How to test clotting factors:
1) **Prothrombin time (PT)**: assesses extrinsic factors (V, VII) & common pathways (X, prothrombin or fibrinogen).
2) **Partial thromboplastin time (PTT)**: assesses intrinsic factors (XII, XI, IX, VIII, V) & common pathways.
- In addition to the possible deficiencies mentioned above, an **autoantibody** (inhibitor) can interfere with the function of clotting factors.
3) **Mixing study**: adding an extrinsic normal serum to the patients serum & repeating the PT & PTT tests. If they are corrected, the patient has a true deficiency., f not, the patient has an inhibitor antibody.

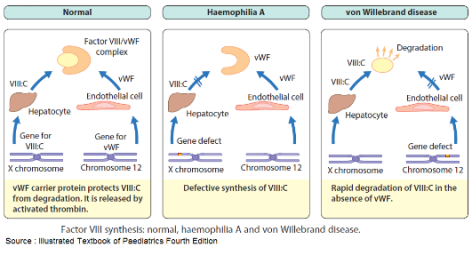
- Von Willebrand Disease: (a Clotting Factors + Platelets Related Bleeding).

- The most common clotting factors-related bleeding & the most common **inherited** bleeding disorder (1% of population).
- Autosomal ***dominant***.
- **Spontaneous bleeding** from mucous membranes, wounds & menorrhagia (excessive menses). (Remember: VWF is important for platelets function).
- VWF circulates the plasma & carries factor **VIII**. VWF is synthesized inside the endothelium (in **Weibel-Palade bodies**), & present beneath endothelium & inside platelets.
- After endothelial damage, the subendothelial VWF binds platelets through glycoprotein **Ib**, forming **platelets plug**.
- Diagnosis: **Ristocetin agglutination test**.
- In VWD (D-disease) there is a compound defect: **non-functional platelets & deficiency in factor VIII**.
- Symptoms: mainly related to platelets defects, (meaning there will be **superficial** bleeding) except in **homozygous** state which is severe & causes VIII deficiency (resembles hemophilia A where bleeding occurs in **body cavities** not superficially, prolonged PTT)
- Type1 VWD: Most common, decreased levels of serum VWF.
- Type IIA: absent high molecular weight multimers of VWF (precursor).
- Type IIB: the high molecular weight multimers are present but have abnormal function (**hyperfunctional with shorter half-life**) which they consume platelets, so patients have **mild chronic thrombocytopenia** (same as TTB but TBB was more severe & widespread) but **with no thrombi** formation.

- Hemophilia A: (classic hemophilia)

- The second most common inherited bleeding disorder.
- X-linked inheritance. Can affect females (random inactivation of X normal chromosome) 70% are familial. 30% are sporadic with new mutations.

- Reduced factor **VIII:**
- If there's mild deficiency, excessive bleeding occurs AFTER trauma (esp in major surgery, or in circumcision of newborn males). If severely deficient (<1% of normal level), life-threatening bleeding may occur.
- 10% have **normal level but non-functioning** factor.
- Characteristic: Bleeding tends to occur in **deep tissues** with mechanical stress (Muscles, joints, body cavities.. not superficially). As a growing child, repetitive bleeding will develop **deformity in joints**. Skin petechiae is absent.
- Prolonged PTT (VIII def), corrected by **mixing study**.
- Specific **assay test** is available.



Factor VIII synthesis: normal, haemophilia A and von Willebrand disease.
Source : Illustrated Textbook of Paediatrics Fourth Edition

- Hemophilia B: (Christmas disease)

- Deficiency in factor **IX**.
- X-linked.
- Much less common than Hemophilia A.
- Clinically similar to Hemophilia A.
- If there's mild deficiency, bleeding occurs after trauma. If severely deficient, life-threatening bleeding may occur (like hemophilia A).
- Prolonged PTT, corrected by **mixing study**.
- Factor **assay test** is available (to differentiate from Hemophilia A).
- Endothelial Related Bleeding:

- Disseminated Intravascular Coagulation (DIC):

- Normally when forming a clot, there's an equilibrium between the formation of the new clot & the lysis of this clot (**fibrinolysis** is needed to stop the clot from getting too big & to get rid of it when the time is right).
- Pathogenesis:
- In DIC, there's an <u>unbalance</u> between the two mechanisms & we have a favor in **formation of new clots**. This occurs **secondary to sepsis, malignancy, trauma, obstetric complications (pregnancy complications), or intravascular hemolysis** all which release a procoagulant/prothrombic agent (like tissue factors, LPS from bacteria, or enzymes) causing **widespread endothelial damage & DIC**. Rapid consumption of clotting factors (prolonged PTT, PT) & platelets, exceeding replacement process. So we have **disseminated clots** which will cause **thrombocytopenia,** so in the other end patients develop life-threatening bleeding.
- Peripheral blood shows **schistocytes**, anemia & thrombocytopenia.
- Causes of DIC:
- **Endothelial damage**: <u>septicemia</u>, <u>viremia</u>, <u>snake venom</u>, <u>complicated labour</u> (placenta produces tissue factor which forms thrombi. So, the tissue factor not only comes from the endothelium), <u>advanced cancer</u> (leukemia or epithelial cancers containing mucin), <u>severe trauma</u>, <u>severe inflammation</u> (acute pancreatitis).

Lec 6 | **WBCs DISORDERS:**

- Disorders include deficiency (leukopenia) & proliferation.
- **Leukocytosis**: increased number of WBC in peripheral blood (any cause). If benign, it is called **reactive** leukocytosis.
- **Leukemia**: increased number of WBC in peripheral blood secondary to neoplastic disease.
- Leukocytosis is more common than leukopenia.
- Reactive leukocytosis is more common than leukemia.

- Neutropenia / agranulocytosis:

- Patients become susceptible to infections (namely bacterial & fungal).
- If neutrophil count drops below 500 cells/uL ➡️ spontaneous infection.
- Decreased production: **aplastic anemia, myelophthisic anemia, myelodysplastic syndrome, advanced megaloblastic anemia, chemotherapy, drugs** (anti-epileptic, anti-hyperthyroidism)
- Increased destruction: **immune mediated, splenomegaly, overwhelming bacterial, fungal or rickettsial infections**.

- Reactive leukocytosis:

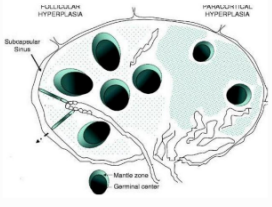
- **Neutrophilia**: infections (with liquefactive necrosis), inflammation (with coagulative necrosis, results from ischemia).
- **Lymphocytosis**: viral infections, **Bordetella pertussis** infection, chronic infections (TB, **brucellosis**).
- **Monocytosis**: chronic infections, rheumatologic diseases, **inflammatory bowel disease**.
- **Eosinophilia**: asthma, allergic diseases, drug sensitivity, parasitic infections, **Hodgkin lymphoma**.
- **Basophilia**: rare, seen in **myeloproliferative neoplasms**.

- Reactive lymphadenitis:

- **Antigenic** stimulation in lymph nodes.
- Causes lymph node enlargement (lymphadenopathy).
- Can be localized or generalized.

- Acute non-specific lymphadenitis:

- Swollen, enlarged & painful lymph nodes.
- Overlying skin is red & may develop a sinus tract.
- The germinal centers in the lymph node are enlarged, infiltrated by neutrophils. With severe infection, **liquefactive necrosis** develop & may enlarge to form an **abscess**.



- Chronic non-specific lymphadenitis:

- Chronic enlargement of lymph node, **painless**.
- **Follicular hyperplasia**: chronic proliferation of **B**-lymphocytes, seen in **rheumatologic diseases, toxoplasmosis, & HIV infection.**
- **Paracortical hyperplasia**: proliferation of **T**-lymphocytes, seen in viral infections (example **EBV**), after vaccination & drug reaction.
- **Sinus histiocytosis**: proliferation of macrophages in lymph node sinuses, seen in **adjacent cancer.**

- Cat-scratch disease:

- **Bartonella henselae**.
- Transmitted from cats (bite, scratch, infected saliva).

- Most commonly in **children**.
- Causes **acute lymphadenitis** in **neck/axilla** area.
- Symptoms appear after **2 weeks** of infection.
- Bacteria causes **liquefactive necrosis** & **necrotizing granulomas** in lymph nodes.
- Mostly **self-limited** in 2-4 months, rarely can **disseminate** into visceral organs.

- Hemophagocytic lymphohistiocytosis (HLH):

- HLH is an uncommon disease.
- Viral infection or other inflammatory agents activate **macrophages (histiocytes)** throughout body to engulf normal blood cells & their precursors in bone marrow.
- Patients have **defective genes related to the function of cytotoxic T-cells & natural killer cells**, thus they are engaged with their target (virus-infected cells) for a long period & release **excess interferon-γ that activates macrophages.**
- Activated macrophages release **TNF** & **IL-6** that causes systemic symptoms of inflammation (**systemic inflammatory response syndrome "SIRS"**).

- HLH-types:

1) Infants & young children:
- **Homozygous** defects in gene **PRF1** that encodes **perforin,** an essential enzyme in cytotoxic T-lymphocytes & natural killer cells.

2) Adolescents & adults:
- **X-linked** lymphoproliferative disorder (**males**).
- Defective **Signaling lymphocyte activation molecule (SLAM)-associated protein.**
- Inefficient killing of **EBV-infected B-lymphocyte**.

3) May be associated with **systemic inflammatory disorders** such as rheumatologic diseases.
- Patients have heterozygous genetic defects in genes required for cytotoxic T-cells

4) **T-cell lymphomas**: malignant T-cells produce aberrant cytokines leading to dysregulation of normal cytotoxic T-cells

- Symptoms:

- Fever, splenomegaly & pancytopenia | High ferritin | High triglyceridemia | High serum IL-2
- Low level of blood cytotoxic T-cells & natural killer cells.
- BM: numerous macrophages engulfing RBCs, platelets & granulocytes.

Lec 7 | Neoplastic proliferation of WBCs:

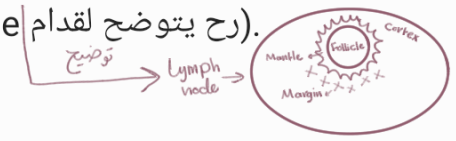
I made up a video explaining the following part, check it here (copy the link): https://youtu.be/9OT89uyGr_g

- Common malignant **fluid** tumors.
- Range from indolent to very aggressive cancers.
- Classified by the 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:

- Neoplastic proliferation of lymphoid cells that forms a mass; may arise in a lymph node or in extranodal tissue. (Neoplasm of **lymphocyte**, **malignant).**
- Divided into **non-Hodgkin lymphoma (NHL, 60%)** & **Hodgkin lymphoma (HL, 40%)**
- NHL is further classified based on cell type (e.g., B and T-cell lymphoma), cell size, pattern of cell growth, expression of surface markers, & cytogenetic translocations:

1. Small B cells - follicular lymphoma, mantle cell lymphoma, marginal zone lymphoma, & small lymphocytic lymphoma SLL (i.e., CLL cells that involve tissue رح يتوضح لقدام).
2. Intermediate-sized B cells - Burkitt lymphoma.
3. Large B cells - diffuse large B-cell lymphoma.



- Called **leukemia** if affects bone marrow or peripheral blood, **lymphoma** if affects lymph nodes or solid organs (**extranodal lymphoma**).
- B-cell lymphomas are more common, involve Ig gene (accidents during class-switch).
- All are malignant, but can be of low-grade (indolent) or high-grade (aggressive).
- Diagnosis is made through morphologic & immunophenotypic (**immunohistochemistry** or **flow cytometry**) examination of biopsy.
- Sometimes a test for **mutations** is performed
- Immunodeficiency is a risk factor for lymphoma, & vice versa.
- Commonly tests immunophenotypes:
- **CD45**: leukocyte-common antigen. (In all WBCs).
- B-cells express **CD19, CD20, CD22.**
- T-cells express **CD2, CD3, CD5, CD7. (**أرقام صغيرة)
- Germinal center lymphocytes express **CD10 & Bcl6**.
- Plasma cells express **CD138. (**More mature = أكبر رقم)
- T-helper lymphocytes express **CD4.**
- Cytotoxic lymphocytes express **CD8.**
- Blasts express **CD34.**
- Lymphoblasts express **TDT** (terminal deoxynucleotidyl transferase) & **CD10.**

extra

Table 6.1: Differences Between Non-Hodgkin Lymphoma and Hodgkin Lymphoma

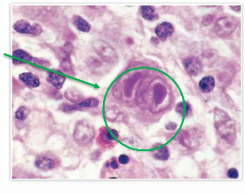
	NON-HODGKIN LYMPHOMA	HODGKIN LYMPHOMA
Overall frequency	60%	40%
Malignant cells	Lymphoid cells	Reed-Sternberg cells
Composition of mass	Lymphoid cells	Predominantly reactive cells (inflammatory cells and fibrosis)
Clinical	Painless lymphadenopathy, usually arises in late adulthood	Painless lymphadenopathy occasionally with 'B' symptoms, usually arises in young adults
Spread	Diffuse; often extranodal	Contiguous; rarely extranodal
Staging	Limited importance	Guides therapy; radiation is the mainstay of treatment.
Leukemic phase	Occurs	Does not occur

- Hodgkin lymphomas (HL):

- Most common type of lymphoma in Jordan, in children & young adults.
- The neoplastic cells are **giant**, different morphology & immunophenotype from normal lymphocytes, forms <10% of tumor mass, while **the rest are normal inflammatory cells** (due to the cytokines' attraction also).
- Arises in a **localized area of lymph nodes** (**neck, axilla, mediastinum**), **then spreads** to anatomically adjacent LN group.
- Mesenteric LNs & Waldeyer ring are rarely involved.
- **Bimodal age distribution** (first peak in children, then in old age groups).
- Classification:
- **Classic Hodgkin** lymphoma (95%):

1) nodular sclerosis 2) mixed cellularity 3) lymphocyte-rich 4) lymphocyte-depleted.

● Cells express **CD30 & CD15**, & **negative for CD20, CD3 & CD45**.



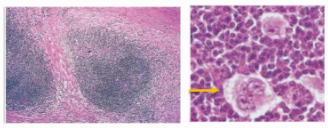
- **Reed-Sternberg cells (the HALLMARK)**: bi or multi-nucleated giant cell, prominent nucleoli, abundant cytoplasm, eosinophilic nuclei.
- Hodgkin cells: mononuclear giant cell. مش ضروري تكون بنواتين
- **B-symptoms**: patients commonly have **fever, night sweats, & weight loss**. (due to the cytokines that are produced by the reed-sternberg cells).
- **Non-Classic** Hodgkin (5%): نوع واحد بس: **Nodular** lymphocyte-predominant.

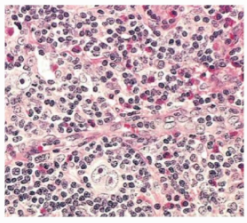
1- Nodular sclerosis HL: sclerotic = hard = fibers

- Common in children & young adults (females).
- **Thick fibrous bands** separating nodules of lymphocytes.

RS = Reed-Sternberg

- RS cells show clear cytoplasm, as a retraction artifact from formalin, called **Lacunar cells.**



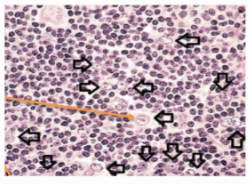


2- Mixed cellularity HL:

- Common in old people.
- Numerous RS cells that prouce **IL-5** ➡️ attract **eosinophils**.
- No fibrous bands.
- Associated with **EBV** مهم.
- Background: mixed neutrophils, **eosinophils**, lymphocytes, plasma cells, & histiocytes.

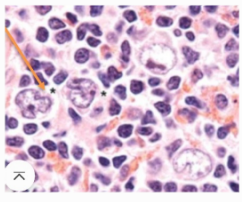
3- Lymphocyte-predominant HL: (non-classic Hodgkin lymphoma)

- Malignant cells are called **lymphohistiocyte** (L&H) variant **RS cells**, or simply **LP cells.**
- **Popcorn cells (the HALLMARK)**.
- **Giant cell** with **multilobated** vesicular nuclear lobes & small blue nucleoli.
- ● Express **normal** B-cell markers (**CD45, CD20**), **negative for CD30 & CD15**.



- Background of lymphocytes, arranged in **nodules**.
- Excellent prognosis.

> Malignant cells in non classic HL are called lymphohistiocyte (L&H) (they are variant RS cells).

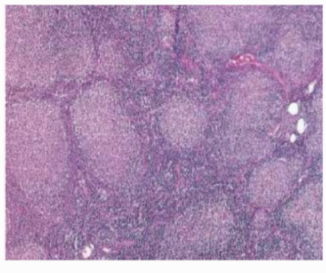


- Pathogenesis & outcome of HL:

- Originate from germinal center B-cells.
- Frequent association with **EBV.**
- RS cells ➡️ more **IL-5**, ➡️ more **eosinophils.**
- Also secrete **IL-13** & transforming growth factor-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.

- Non-Hodgkin lymphomas:

1- 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 & spleen** (80%).

- Pathogenesis:

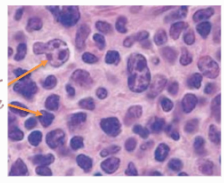
- **t(14;18) (Bcl2 ➡️ IgH):** BCL2 on chromosome 18 translocates to the Ig heavy chain locus on chromosome 14. (MORE BCL2 ➡️ NO APOPTOSIS OF CELLS ➡️ CANCER).

- Overexpression of Bcl2 ➡️ prolonged survival of lymphoma cells.
- 1/3 of patients have mutations in genes encoding **histone-modifying proteins** (**epigenetic** change).

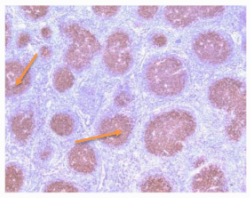
- Morphology:

- The normal architecture of lymph node is effaced by nodular proliferation (follicles).
- The follicles are composed of small irregular **"cleaved" lymphocytes "centrocytes" & large lymphocytes with vesicular nuclei and small nucleoli (centroblasts)**.

cyte = mature | blast = immature | Cenrtro: coz they're in the germinal center.



- In most cases, the **centrocytes predominate (low-grade)**. With time, **centroblasts** increase and the disease becomes **high-grade**.
- Cells express **CD20, Bcl2, Bcl6.** (coz they're germinal center cells [B cells]).



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

↳ Results from a rxn due to infection

- Prognosis:
- **Indolent** course **(low-grade)**.
- Conventional chemotherapy is ineffective لأن العدد بكون قليل بالبداية.
- Overall median survival is 10 years.
- 40% transform to DLBCL (worse than de novo DLBCL).
- Therapy is reserved to symptomatic patients, bulky tumors & transformation (**cytotoxic chemotherapy, anti-CD20, anti-Bcl2**).

Lec 8 | 2- Mantle cell lymphoma:

- Arises from naïve B-cells in mantle zone.
- Most commonly in older men.
- **t(11;14)** that fuses cyclin D1 gene to IgH locus.
- Overexpression of cyclin D1, promote **progression of cell cycle**.
- Affects **LNs, Waldeyer ring**.
- Commonly involve **BM**, **blood** in 20%, sometimes in **GIT**, appears as submucosal nodules (lymphomatoid polyposis).
- Morphology: **small centrocytes**, but in diffuse pattern.

*Recall: cyclin D1 allows the cell to go from the G1 to the S phase in the cell cycle.

3- Exranodal marginal zone lymphoma:

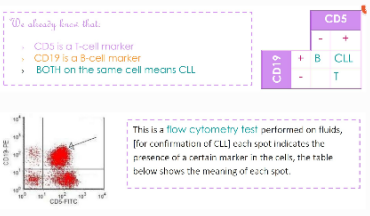
- Indolent B-cell lymphoma.
- Second most common lymphoma in extranodal sites in adults.
- Arises in the setting of **chronic inflammation** (most lymph nodes don't have a marginal zone, marginal zones are formed when there is an activation of the cells (through the germinal centers) this activation occurs in chronic inflam.).
- Can **complicate autoimmune disease** in localized areas (**Hashimoto thyroiditis, Sjogren syndrome**), & can complicate **Helicobacter pylori-chronic gastritis**.
- Infiltrate the **epithelium** & causes destruction.

B-cell = (CD20+ cell)

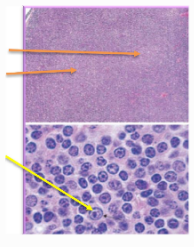
Recall: Patients presents with unilateral enlargement of the parotid gland.

4- Small lymphocytic lymphoma(SLL) & chronic lymphocytic leukemia(CLL):

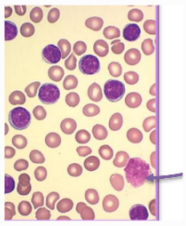
- CLL= Low-grade neoplastic proliferation of **naïve B-cells** that **co-express CD5 & CD20.**
- **SLL= CLL** with involvement of **lymph nodes** that leads to generalized lymphadenopathy.
- CLL is the most common leukemia overall (SLL represents only 4% of NHL).
- Affects elderly, not common in Asia.
- Arises in **LNs & solid tissue (SLL)**, or in **BM & peripheral blood (CLL).**



- Pathogenesis:
- **Increased Bcl2 protein**, secondary to **deletion mutation** in genes encoding micro-RNAs that are negative regulators of Bcl2.
- **B-cell receptor** (BCR) (a surface immunoglobulin), is **autonomously active**, activating a intermediary called **Bruton tyrosine kinase** (BTK) that **activates genes promoting cell survival**.
- Chromosomal translocation is rare.
- Morphology of SLL:
- LN shows effacement of architecture.
- Most of neoplastic cells are **small** in size, round, dark chromatin, along with



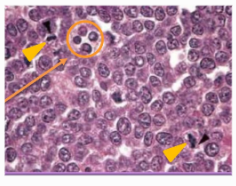
few large cells with central prominent nucleolus (prolymphocyte).
- **Proliferation centers:** focal areas containing large number of **prolymphocytes** & ⬆️ mitosis.
- Morphology of CLL:
- Increased lymphocytes - Leukemic cells appear similar to lymphocytes.
- Occasional prolymphocytes.
- **Smudge cells**.

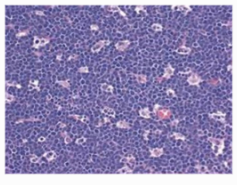


- Clinical features:
- Many patients are **asymptomatic**.
- **Leukocytosis** can reach very high levels (>200,000).
- 50% have generalized **lymphadenopathy** & **hepatosplenomegaly**.
- **Hypogammaglobulinemia** (due to immune dysfunction by suppressing normal B-cells)
*Infection is the most common cause of death in CLL.
- **Anemia:** 15% of patients develop auto antibodies against RBCs & 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**: transformation to **diffuse large B-cell lymphoma**, survival <1 year.

5- Burkitt lymphoma (BL):

- Most common NHL in **children**.
- Three types:
1) Endemic in parts of Africa (**100% EBV+**) ➡️ **jaw mass.**
2) Sporadic in the rest of the world (20% **EBV+**), latent infection ➡️ **abdomen mass.**
3) Immunodeficiency associated BL.
- **Extranodal disease**: **jaw** (endemic), **terminal ileum**, **retroperitoneum**, **ovary**, **CNS** (sporadic), sometimes **leukemic.**
- Pathogenesis:
- **t(8;14) (MYC ➡️ IgH)**.
- Overexpression of MYC transcription factor, potent regulator of **Warburg metabolism** (aerobic glycolysis). **(A LOT OF C-MYC = A LOT OF GRAWTH).**
- Neoplastic lymphocytes are B-cells of germinal center origin (**CD20, Bcl6**).
- Aggressive, but responsive to chemotherapy.
- Morphology:



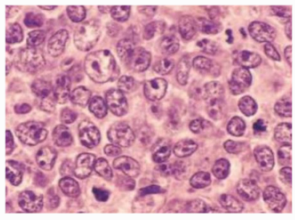


- Intermediate size cells.
- **Monomorphic**.
- **Round or oval, multiple small nucleoli**.
- **Lipid vacuoles** in cytoplasm.
- Very high mitosis, **tangible body macrophages** engulfing nuclear debris.
- **Starry sky appearance** (macrophages look white, surrounded by blue color of other cells).

6- Diffuse large B-cell lymphoma (DLBCL):

- **Most common NHL,** in adults.
- **High-grade** (rapidly growing mass, clinically aggressive).
- Most common **non-cutaneous extranodal lymphoma** (GI most common).
- 2/3 have activating mutation of **Bcl6** promotor gene, which is an important regulator of

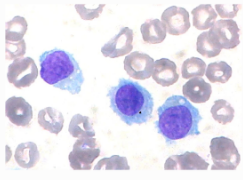
gene expression in germinal center B-cells.
- 30% have t(14;18) (Bcl2 ➡ IgH) ➡ overexpression of Bcl2 protein (anti-apoptotic).
- Few has mutation in **MYC gene**.



- Morphology:
- Cells are **large** (3x normal lymphocytes), **irregular nuclei**, **small nucleoli**, disrupted (no follicles or sinuses), with frequent **mitosis**. **Positive for CD20**.
- DLBCL-subtypes:
- Arise **de novo (sporadically) or from transformation of a low-grade B-cell lymphoma**.
- **Primary mediastinal large B-cell lymphoma**: arises from **thymic B-cells**, most patients are middle age **women**, spread to **CNS** & **visceral organs**. **Females>males** مهم، الوحيد.
- **EBV-associated DLBCL**: arise in immune suppressed patients & in elderly, begin as **polyclonal** B-cell proliferation.
- **Human Herpes Virus-8 (primary effusion lymphoma)**: causes DLBCL **effusion** in pleural cavity, HHV-8 encodes for **cyclin D1** mimicker protein, seen in immune suppressed patients.
- **Chronic leukemia:** = Neoplastic proliferation of **mature** circulating lymphocytes.
- characterized by a high WBC count.

- Chronic lymphocytic leukemia (CLL). شرحناه فوق

- Hairy cell leukemia:



- Uncommon **low-grade** B-cell leukemia.
- Affects older patients, more common in men, smokers.
- Leukemic cells are **few** in number, have **hairy cytoplasmic projections**.
- **Splenomegaly, pancytopenia** (Leukemic cells heavily infiltrate BM & spleen).
- Leukemic cells are biologically active, inhibit hematopoiesis & cause **bone marrow fibrosis**.
- LN involvement is very rare (no lymphadenopathy).
- **Mutation** in **serine/threonine kinase BRAF gene**.
- Very sensitive to chemotherapy.

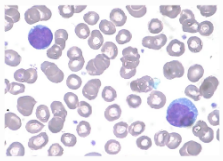
- Adult T-cell leukemia/lymphoma (ATLL):

- Neoplastic **CD4+** T-lymphocyte.
- Caused by a retrovirus; **human T-cell leukemia virus-1** (HTLV-1).
- Endemic in Japan, Caribbean basin, West Africa & 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** & **cyclin D**, **represses** expression of **CDK inhibitors**, & **activates** **NF- kB**, all promote cell survival. - Tax also causes **genomic instability**, inhibiting DNA-repair.
- Symptoms: **skin** lesions (**rash**), **lymphadenopathy**, **lymphocytosis**, **hepatosplenomegaly** & **hypercalcemia**. **(T-CELL LEUKEMIA LIKES TO GO TO SKIN & MAKE A RASH).**
- Neoplastic cells express **CD25 (IL-2 receptor)**.
- Poor prognosis.

Both ATLL & multiple myeloma have **hypercalcemia**, but ATLL has a skin **rash**.

- Mycosis fungoides & sezary syndrome (Cutaneous lymphoma):

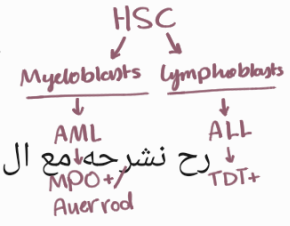
*fungoides = grows like a mushroom.
- Sezary syndrome is a subtype of mycosis fungoides that's leukemic.
- Neoplastic of mature **CD4+** T-cells, that home to **skin**.



- Symptoms: **erythema**, progressive to **plaque** then **tumor**.
- Neoplastic lymphocytes have **irregular nuclear membrane (cerebriform)**, affecting **epidermis** & **dermis**.
- With disease progression, lymphoma disseminates to **LNs & viscera**.
- **Sezary syndrome**: a variant of MF, patients present initially with widespread erythema & blood leukemia of neoplastic cells (Sezary cells, **cerebriform shaped**).

- Peripheral T-cell lymphoma:

- **Most common** mature T-cell lymphoma.
- Aggressive, poor prognosis.
- Neoplastic cells secrete inflammatory **cytokines**, causing **severe inflammation**.
- Positive for CD2, CD3, CD5, CD7.



- **Acute leukemia:** = Neoplastic proliferation of blasts (**immature** lymphocytes).

- Acute myeloid leukemia (AML): myeloid disorders رح نشرحه مع ال

- Acute lymphoblastic leukemia (ALL): precursor B&T-cell neoplasms رح نشرحه مع ال

- **Precursor B and T cell neoplasms:** (Tumors of blasts (lymphoblasts)).

- Lymphoblastic lymphoma when occurs in solid tissue (**T-cell type > B type**).

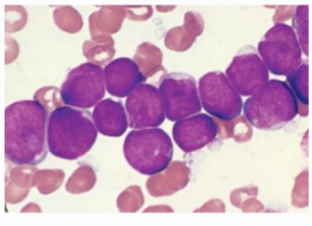
- Acute lymphoblastic leukemia (ALL):

- When circulates **peripheral blood** & involve **bone marrow** (**B>T**).
- **B-ALL** is the most common childhood malignancy.
- Neoplastic cells are lymphoblasts, the most immature lymphoid cell.
- Aggressive neoplasms, express **CD34 &** **TDT.** → a DNA Polymerase, presents in the nucleus of lymphoblasts only.
- T-ALL is less common, presents in adolescents, involving **thymus**, more common in **boys**.
- **B-ALL tends to disseminate to solid organs** (brain, testis, spleen).
- Pathogenesis:
- **Mutations in transcription factors** for genes responsible for maturation of blasts.
- In T-LL: 70% have mutations in **NOTCH1 gene**.
- In B-LL, mutation in **PAX5 gene**.
- Mutations in **RAS signaling & tyrosine kinase proteins** promoting cell survival.
- Most **childhood B-ALL** have **hyperdiploidy** (>50 chromosomes) & **t(12;21)**, involving **ETV6 & TUNX1 genes**, creating new transcription factor.➡️ good prognosis.
- **Adult B-ALL** exhibits **t(9;22)** between **ABL & BCR genes**, similar to chronic myeloid leukemia, creating a new tyrosine kinase protein (**imatinib**).➡️ poor prognosis.
- T-ALL shows mutation in **PTEN gene** (tumor suppressor) & **CDKN2A** (promotes cell cycle).
- Morphology of ALL:
- Blasts are large, high N/C ration, chromatin is open (pale).
- Nucleolus sometimes present, cytoplasm is not granular.
- Clinical features:
- **Anemia, thrombocytopenia**.
- **Damage to solid organs** secondary to leukemic infiltration.
- Favorable prognostic factors in B-ALL: **hyperdiploidy, low WBC count, age btw 2-10 years.**
- Poor prognostic factors in B-ALL: age <2 yrs, age in adolescents/adults, WBC count >100k.

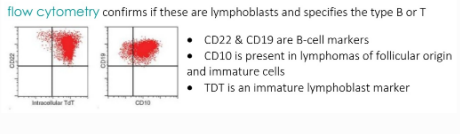
The HALLMARKC marker for a lymphoblasts is that they are TDT +ve.

Interesting info:

Philadelphia chromosome is the first discovered translocation abnormality in human cancer, and Imatinib is the first targeted therapy used in cancer.



*Note: T-ALL= T-cell acute lymphoblastic **lymphoma**
B-ALL= B-cell acute lymphoblastic **leukemia**



Lec 9 |

- Myeloid neoplasms:

- Arises from **hematopoietic progenitor stem cells**.
- Neoplastic cells proliferate & efface normal hematopoietic cells.
- Divided into:

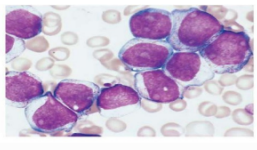
1) Acute myeloid leukemia (AML): **impaired** maturation, **increased** proliferation (myeloblast).
2) Myeloproliferative neoplasms (MPN): **normal** maturation, **increased** proliferation.
3) Myelodysplastic syndrome (MDS): **abnormal** maturation, **normal** proliferation.

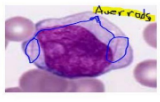
- MPN & MDS can transform to AML.
- BM is hypercellular in all myeloid neoplasms.

- Clonal hematopoiesis of indeterminant prognosis (CHIP): represents a precursor for AML & MDS, patient has normal cell count despite the presence of a clone with a mutation.

- Acute myeloid leukemia (AML): immature immature immature, ok?

- Occur at all age groups, but more common in elderly.
- **Heterogenous**, diagnosis is made by morphologic, immunophenotypic & karyotype studies.
- Prognosis depends mostly on **type of mutations** (molecular & cytogenetic studies).
- Symptoms are accelerated, become significant within few weeks.
- Symptoms are related to anemia, thrombocytopenia & neutropenia.
- Involvement of LN, spleen & solid organs is rare, but when occurs, it is called **myeloid sarcoma** (acute monoblastic leukemia)
- Pathogenesis:
- **Mutations** in genes of **transcription factors** required for maturation & differentiation of myeloblasts.
- Additional mutations in **tyrosine kinase pathways** (RAS)
- **Epigenetic mutation** is common (20%); mutation is **isocitrate dehydrogenase** (IDH) produces an oncometabolite that blocks enzyme of epigenome & interferes with myeloblast differentiation.
- Who-classification:
- **Therapy related AML**: occurs after treatment with chemo or radiotherapy.
- **AML with recurrent cytogenetic mutation**.
- **AML with myelodysplasia**: occurs de novo or complicates MDS.
- **AML-Not otherwise specified**.
- Diagnosis of AML: **20% blasts** in peripheral blood or bone marrow (of nucleated cells).
- Morphology: large cells, high N/C ration, fine granules in cytoplasm, fine chromatin, prominent nucleoli.
- **Auer rods**: small pink rods present in cytoplasm, represent **peroxidase enzyme**.
- Myeloblasts express **CD34, myeloperoxidase (MPO), CD13, CD33**
- Sometimes: monoblast, erythroblast, megakaryoblast.





- Outcome:
- Generally poor, <30% responds to chemotherapy.
- **Worse than ALL**.
- **P53 mutation**: worse outcome.
- IDH inhibitors are new promising drugs.

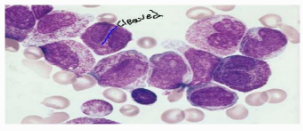
Recall: pigenetic mutation: A mutation that affects the function of the DNA without any changes in the codons.

- Acute promyelocytic leukemia (AML-M3): (a classic type of AML)

- Maturation is **arrested** at promyelocyte stage.
- Leukemic cells appear similar to promyelocytes (heavy cytoplasmic granules, numerous Auer rods, negative for CD34).
- Carry recurrent mutation: **t(15;17) fusion** between PML gene (chrom 15) with alpha retinoic acid receptor (RARA) (chrom 17). **Chimeric fusion gene produces a protein that blocks promyelocyte maturation by inhibiting the action of retinoic acid**.

-NO RETINOIC ACID RECEPTOR ➡️ NO MATURATION ➡️ PROMYELOCYTE ACCUMULATION-

- All trans-retinoic acid (ATRA) (a vitamin A analogue), **overcomes this block**. Effect is synergistic with **arsenic trioxide** (degrades oncoprotein).
- Malignant promyelocyte secrete tissue factor, causing DIC.
- ((Auer rods in the promeylocytes can activate the coagulation cascade ➡️ DIC)). للتوضيح
- APL: malignant promyelocytes show numerous cytoplasmic granules and Auer rods. The nuclei are commonly cleaved.

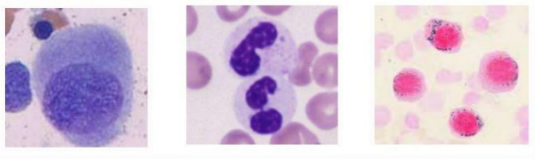


- Myelodysplatic syndrome (MDS): (chronic neoplastic disease)

- AML may arise from **pre existing dysplasia** from prior exposure to **alkylating agents (chemotherapy) or radiotherapy (which cause this myelodysplastic syndrome).**
- It means: Abnormal maturation with increased blasts (**but <20%**).
- If **>20%** ➡️ ACUTE MEYLOID LEUKEMIA (AML) (not MDS anymore).
- Represents **cytopenias** with **hypercellular** bone marrow.

اللي بالأخضر من كتاب باثوما للتوضيح

- Main feature: **defective maturation**, **ineffective hematopoiesis**, high risk for transformation to **AML** (if accumulating more mutations).
- **BM is replaced by** a clonal progenyسلالة of **transformed stem cell** that has a capacity to differentiate into 3 cell lines but with **abnormal** morphology & function.
- Hallmark of MDS: **hypercellular BM**, **peripheral cytopenia, & morphologic dysplasia**.
- Most cases are idiopathic, rarely follows chemo or radiotherapy (therapy-related).
- Most patients are old.
- Pathogenesis:
- **Chromosomal aberration**اضطراب in 50% of cases: monosomy 5, monosomy 7, deletions of 5q, 7q, 20q, trisomy 8.
- Mutations in **epigenetic factors** that regulate **DNA methylation & histone modifications**.
- RNA splicing factors: **abnormal RNA processing** ➡️ **Ring sideroblasts**.
- Transcription factors.
- 10% have **P53 mutation.**
- Morphology:
- **Erythroid**: macrocytic anemia, megaloblastoid nuclei, **ring sideroblasts** (iron accumulation inside mitochondria).

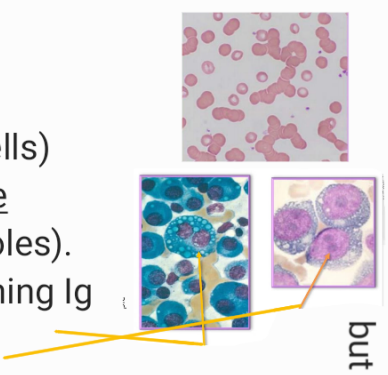


- **Myeloid**: decreased granulation, hyposegmented nuclei of neutrophils.
- **Megkaryocytes**: small, hypolobated nuclei.
- **Myeloblasts**: can be increased, but <20% of nucleated cells.
- Symptoms:
- **Refractory anemia**, **thrombocytopenia**, **neutropenia**. Survival 9-29 months.

- Plasma cell disorders (Dyscrasias):

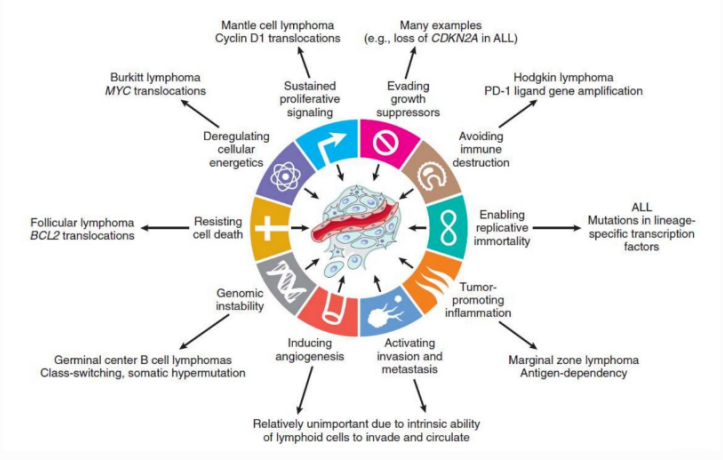
- Plasma cell myeloma (multiple myeloma):

- 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.
-Sometimes **only light chain (kappa or lambda) are detected in urine** (**Bence Jones proteins**).
- Pathogenesis:
- **t(11;14)** IgH-cyclinD1 & cyclinD3.
- **MYC gene mutation** occurs **late** in disease.
- **IL-6** is important is plasma cell survival, secreted from BM macrophages & 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 because Ca2+ gets out of the bone matrix & pathologic fracture because of thin bone).
- Malignant plasma cells **suppress normal B-cell function**.
- Directly **inhibits erythropoiesis** (early onset anemia).
- **Renal failure**: obstruction to distal collecting tubules by **proteinaceous cast** (Bence Jones protein, immunoglobulin, albumin). Hypercalcemia produces kidney stones, causing further obstruction & renal infection.
- Morphology:
- Peripheral blood: RBCs show **rouleaux formation.**
- BM: **increased number of plasma cells** (>10% of bone marrow cells)
- Morphologically might resemble normal plasma cells, or become abnormal (prominent nucleoli, multinucleation, cytoplasmic vacuoles).
- **Abnormal figures** with multinuclei & cytoplasmic vacules-containing Ig
- **prominent nucleoli** instead of the normal cartwheel chromatin appearance of plasma cells' nuclei.



Both ATLL & multiple myeloma have **hypercalcemia**, but ATLL has a skin **rash**.

- Clinical & laboratory findings:
- **Very high ESR**.
- **CRAB** (**hyperCalcemia**, **Renal failure**, **Anemia**, **Bone fracture**).
- **Amyloidosis**: in few patients, secondary to deposition of **light chain** (**AL-amyloid**).
- In advanced disease: **pancytopenia, plasma cell leukemia, visceral damage**.
- Slowly growing, not curable with conventional chemotherapy.
- **Lenalidomide**: inhibits oncogenic proteins.
- **Proteasome inhibitors**: inhibit degradation of misfolded proteins. When accumulate, cause apoptosis in plasma cells.



Lec 10 |

1. Myeloproliferative Neoplasms
   - ♣Chronic Myeloid Leukemia
   - ♣Polycythemia Vera
   - ♣Primary Myelofibrosis
   - ♣Essential Thrombocytopenia
2. Langerhans Cell Histiocytosis
   - ♥Multisystemic LCH
   - ♥Unisystem LCH

- Myeloproliferative neoplasms (MPN):

- Maturation is normal, but proliferation is high.
- **Permanently active tyrosine kinase pathway**, independent from growth factors.
- BM is **hypercellular**, peripheral blood shows **cytosis** (leukocytosis, thrombocytosis, & erythrocytosis).
- Neoplastic stem cells in MPN often seeds to **spleen, liver** & occasionally **LNs**, causing **extramedullary hematopoiesis** & thus **hepatosplenomegaly**.
- Tendency to transform to **AML**.

Remember! we have **cytopenia** in Myelodysplastic syndromes **(MDS)**

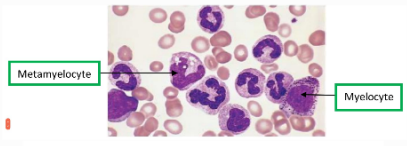
- Chronic myeloid leukemia:

This a counter to Chronic Lymphoid Leukemia (CLL)

- Most common MPN.
- **t(9;22) ➡️ Philadelphia chromosome**, results in **fusion of Bcr/Abl genes** & production of a tyrosine kinase that results in prolonged cell survival.

This translocation also occurs in B acute lymphoblastic Leukemia (BALL), in adults

- Mutation is present in **all BM cells** (myeloid, erythroid, & megs).
- Affects adults 25-60 years.
- Symptoms (non-specific): fatigue, heavy abdomen, weight loss.
- **Imatinib**: **tyrosine kinase inhibitor**, specific for bcr/abl mutation.
- **Accelerated phase**: worsening of symptoms, higher WBC count, **thrombocytopenia**, **resistance to imatinib**.
- **Blast crisis**: transformation to acute leukemia (**AML**>ALL).
- Morphology of CML:
- Leukocytosis, can be >100K | Thrombocytosis | Anemia.
- **Shift to left** | Basophilia | eosinophilia.
- BM: increased myeloid & megs | Spleen: **EMH** | **Blasts: low**.



Shift to left)) - presence of the precursor cells of the myeloid cells (NOT blasts) in the peripheral blood, like myelocyte and metamyelocyte.

-**Leukemoid rxn**(looks like leukemia): high WBC & shift to left, occurs in severe inflammation.

- Polycythemia vera:

- **Mutation in tyrosine kinase JAK2**, normally acts in the signaling pathway of erythropoietin receptor & other growth factor receptors.
- **Hematopoietic cells become less dependent on growth factors**.

Panmyelosis: neoplastic proliferation and maturation of erythroid, megakaryotic and granulocytic elements.

- Excessive proliferation of erythroid, megs, & myeloid (**panmyelosis**), **erythrocytosis** is most prominent, results in **polycythemia** (low erythropoietin level).
- Insidious onset of symptoms: middle age, **plethora** (skin full of erythema), sometimes **cyanosis** (deoxygenated Hb), headache, dizziness, **pruritis**, **peptic ulcer**.
- **Thrombosis** & tissue infarction, **bleeding** is also common (GIT), **gout**.
- **Spent phase**: occurs **after** an interval of **10 years** of symptoms, **BM become fibrotic**, **hematopoiesis shifts to spleen**.

↳ We have a lot of platelets, but with impaired function.

Polycythemia --->Thrombosis

Thrombocytosis --->Bleeding

- **Blast crisis**: transformation to **AML** (rare).
- Treatment: **phlebotomy**, **JAK2 inhibitor**.
- Laboratory findings: High RBC count, hematocrit of 60% & more.
- Leukocytosis | Basophilia | Thrombocytosis.

Remember! we differentiate polycythemia vera from secondary or reactive polycythemia by the **erythropoietin** level. The secondary polycythemia has high erythropoietin level.

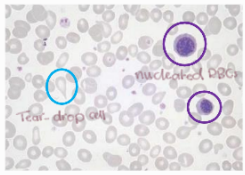
- Primary myelofibrosis:

- **Over BM fibrosis, reducing capacity for hematopoiesis**, leads to cytopenia & massive EMH.
- **JAK-STAT signaling pathway is active** in all cases.
- 50% have **mutation in JAK2**, 5% in **MPL gene** (thrombopoietin receptor).

EMH = extramedullary hematopoiesis

Plethora = overbalanced, excess.

- Neoplastic megakaryocytes secrete TGF-B, which **activates fibroblasts** in BM to deposit reticulin & collagen fibers, also causes **angiogenesis**.
- **RBC production is impaired**, patients have **anemia.**



- Morphology:
- Peripheral blood: **leucoerythroblastic anemia: tear-drop cells, nucleated RBCs, shift to left.**
- WBC: can be normal or increased. Platelets: **high, then low**.
- BM: early: **hypercellular & focal fibrosis**, late: **hypocellular & extensive fibrosis**.
- DOMINENT CELLS: **Megakaryocytes**, they form **clusters**.
- Symptoms(non-specific): weight loss, anemia, massive **splenomegaly**, **gout**, **bleeding**, infection.
- Worse outcome than CML & P Vera. 4-5 years survival. Frequent transformation to **AML.**
- **JAK2 inhibitor**: decreases splenomegaly & symptoms.

- Essential thrombocythemia: Cythemia = Cytosis

- **Predominantly thrombocytosis** (occasional leukocytosis).
- **JAK2 mutation** is sometimes positive, **but NO bone marrow fibrosis**.
- **Splenomegaly** is positive in 50%.
- Good outcome.

- Langerhans cell histiocytosis (LCH):

- **Neoplasm of dendritic cells**.
- Langerhans cells express **CD1a & Langerin**.
- Langerin is a transmembrane protein, attached to **Birbeck granules** (**tennis ricket shape** under electron microscope).
- Proliferating Langerhans cells appear **large & vacuolated, similar to macrophages**.

*LCH is a solid tumor & it develops in tissues, so it is not a leukemia.

- Pathogenesis: **acquired mutation in serin/threonine kinase BRAF**, leads to its hyperactivity.

- Multisystemic LCH:

- Occurs mostly in **children less than 2 years**.
- Multiple **cutaneous lesion**, composed of **LCs.**
- **Hepatosplenomegaly** & **lymphadenopathy.**
- **Pulmonary** lesions.
- **Osteolytic** lesions.
- Extensive bone marrow infiltration leads to **pancytopenia**.
- Treated with **chemotherapy**.

This reminds us of Hodgkin Lymphoma, but in the HL there are a few cancerous cells, while in the eosinophilic granuloma there are numerous cancerous cells

- Unisystem LCH (eosinophilic granuloma):

- Affects a **single organ**, most commonly **bone**, then **skin**, **lung**, **stomach.**
- Unifocal or multifocal:
- Unifocal unisystem disease is asymptomatic, can cause pain.
- Mulfocal unisystem disease in **children**, commonly affects **skull/calvaria bone**, extends to pituitary gland causing **diabetes insipidus**, **exophthalmous** (**Hand-Schuller-Christian triad**).
- Proliferating LCs are **admixed with numerous eosinophils**, **lymphocytes, plasma cells, & neutrophils**.
- Treatment: unifocal: surgical excision, multifocal: chemotherapy, sometimes spontaneous regression!!!

- قال ابن القيم رحمه الله :
« وقد اجمع عقلاء كل أمة على أن النعيم لا يدرك بالنعيم ، وأن من آثر الراحة فاتته الراحة ، وأنه بحسب الأهوال و احتمال المشاق تكون الفرحة و اللذة ، فلا فرحة لمن لا هم له و لا لذة لمن لا صبر له ، و لا نعيم لمن لا تعب له »

Organize your info.:
- Translocations:
• Follicular lymphoma: t(14;18) (Bcl2 ➡ IgH).
• Mantle cell lymphoma: t(11;14) (cyclin D1 ➡ IgH).
• Burkitt lymphoma (BL): t(8;14) (MYC ➡ IgH).
• Diffuse large B-cell lymphoma (DLBCL): t(14;18) (Bcl2 ➡ IgH).
• Acute lymphoblastic leukemia (ALL):
1- Childhood B-ALL: t(12;21) (ETV6 & TUNX1 genes).
2- Adult B-ALL: t(9;22) (ABL & BCR genes), similar to chronic myeloid leukemia (CML).
• Acute promyelocytic leukemia (AML-M3): t(15;17) (fusion: PML gene & RARA).
• Plasma cell myeloma (multiple myeloma): t(11;14) (IgH-cyclinD1 & cyclinD3).
• Chronic myeloid leukemia: t(9;22) ➡ Philadelphia chromosome (fusion: Bcr/Abl genes).
- Shift to left: Chronic myeloid leukemia (CML) & Primary myelofibrosis.
- Tyrosine kinase mutations:
Acute lymphoblastic leukemia (ALL).
Acute myeloid leukemia (AML).
Chronic myeloid leukemia (CML).
Polycythemia vera.
- Gout: Polycythemia vera & primary myelofibrosis.
- Thrombosis+ gout + bleeding: polycythemia vera.
- Splenomegaly + gout + bleeding: Primary Myelofibrosis.
- Thrombocytosis + JAK2 mutation + BM fibrosis + leucoerythroblastic anemia: Primary Myelofibrosis.
- Thrombocytosis + JAK2 mutation only: essential Thrombocythemia.
- Spent phase: Polycythemia vera.
- Accelerated phase: Chronic myeloid leukemia (CML).
- Morphology:
Centrocytes & centroblasts ➡ Follicular lymphoma.
Smudge cells ➡ chronic lymphocytic leukemia (CLL).
Starry sky appearance+tangible body macrophages+lipid vacuoles➡ Burkitt lymphoma (BL).
Auer rods ➡ Acute myeloid leukemia (AML).
Ring sideroblasts ➡ Myelodysplatic syndrome (MDS).
rouleaux formation+Abnormal figures ➡ Plasma cell myeloma (multiple myeloma).
Tear-drop cells, nucleated RBCs, shift to left ➡ leucoerythroblastic anemia (Primary myelofibrosis).
Tennis ricket shape ➡ Birbeck granules in Langerhans cell histiocytosis (LCH).
- myelophthisic anemia + pancytopenia: Multisystemic LCH.
- Hand-Schuller-Christian triad: (1) osteolytic lesion (2) diabetes insipidus (3) exophthalmos ➡ in multifocal unisystem LCH.