		Morphology	Immunophenotype/ genetics	Clinical Manifestation
1)Acute Lymphoblastic Leukemia (ALL). **(look table 2*)**	*Precursor B and T cell lymphoblastic lymphoma/leukemia, commonly called ***B** cell lymphoblastic leukemia - Majority of the cases (85%). The most common malignancy in children. - Peak age: 3 years. ***T** cell lymphoblastic leukemia - Minority of the cases (15%). Called **Thymic Lymphoma** because it presents as a mass in thymus. - Peak age: adolescence.	B-ALL: Hypercellular marrow T-ALL: Cellular thymus or lymph nodes There're large malignant stem cells with small cytoplasm, large nucleus, fine chromatin and prominent nucleoli called **Blasts.** ****Note:** Blasts are the only cells in the hematolymphiod system that have fine chromatin and prominent nucleoli.	**CD19**, CD79, pax5, CD22 and CD20 indicate B cell origin, CD19 is the most specific. - **CD3** is the most specific T cell marker. - TdT indicates early immature B or T lymphocytes, but not myeloid. - CD34 indicates early immature B or T or myeloid cells. For example: if we have a tumor with these markers: CD34+ , TdT+, CD19+, we will diagnose it as B-cell acute lymphoblastic leukemia. **Genetics:** In B-ALL, a translocation mutation may occur between: - (12; 21) genes, which carries good prognosis. - (9; 22) genes, which carries bad prognosis. In T-ALL: (NOTCH, PTEN, CDKN2A) genes are mutated.	**Clinical features:** - Depression of bone marrow. - Mass effect, mostly in T-ALL because it presents as a mass in the thymus. - CNS manifestations, B-ALL cells in children are known to attack the CNS cells and meninges causing vomiting, headache... etc. Acute lymphoblastic leukemia is an aggressive, highly-curable tumor, with 80% cure rate in children, and 40% in adults.
2) Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)	- Chronic lymphocytic leukemia (CLL): When PB count of neoplastic cells is > 5000/microliter. CLL is the most common leukemia in general. - Small lymphocytic leukemia (SLL): When PB count of neoplastic cells is < 5000/microliter, with lymph node involvement	-Small mature lymphocytes that appear like normal lymphocytes with dense chromatin and small nucleoli. A small percentage of lymphocytes show prominent nucleoli, called **Prolymphocytes**.	- CLL is a B-cell neoplasm, so B-cell markers (CD19, CD20, CD22, CD79, pax5) will be positive. - CD5 is positive (although it's a T cell marker). The other CD5 positive B cell lymphoma is	- They are usually old in age. - Asymptomatic. - Nonspecific symptoms like fatigue, anorexia, lymphadenopathy... etc. - Lymphocytosis. - Hypogammaglobulinemia, and 15% of them have autoimmune warm

		If lymph nodes are involved, they will be effaced with sheets of lymphocytes.	mantle cell lymphoma.	hemolytic anemia. - Good prognosis, they live for 10-15 years (prolonged survival). - Not curable without stem cell transplantation, and only in young patients. - Small fraction might progress into diffuse large B cell lymphoma (DLBCL), with a survival period of less than one year.
3) Follicular lymphoma	caused by a translocation mutation between (14; 18) genes, placing BCL2 (antiapoptotic) gene under the control of IgH active gene, inhibiting the apoptotic pathway & causing malignancy.	Lymph nodes are effaced by follicular (nodular) arrangement of centrocytes (small cells with cleaved nucleus), and centroblasts (large cells with nucleus containing basophilic membrane-bound nucleoli).	Follicular lymphoma is a B-cell neoplasm, so B-cell markers (CD19, CD20, CD22, CD79, pax5) will be positive. - CD10 is positive The other CD10 positive tumors are B-ALL , Burkitt lymphoma, and some cases of DLBCL	- Patients are usually older than 50 years. - Generalized lymphadenopathy. - Bone marrow is involved in 80% of cases. - Not aggressive, patients can live 10 years (prolonged survival). - Not curable. - 40% of cases (worse than CLL) transform into DLBCL, with dismal (very bad) prognosis.
4) Mantle cell lymphoma	caused by a translocation mutation between (11; 14) genes, placing Cyclin D1 gene under the control of IgH active gene, increasing uncontrolled cell proliferation and causing malignancy	- Lymph nodes are effaced by sheets of medium sized cells with similar morphology to mature lymphocytes, while a small percentage of cases have blastic morphology.	- B-cell markers are positive. - CD5 is positive (similar to CLL). - Cyclin D1 is positive (CLL is negative for Cyclin D1).	- General nonspecific symptoms. - Lymphadenopathy. - Not curable, patients live for 4-6 years with treatment only.

		From here you can notice that morphology isn't that important in diagnosis; it's all about the Immunophenotyping. - Bone marrow is involved in most cases. - Sometimes results in GI polyps.		
5) external marginal zone of lymphoma	This tumor is a low grade B cell neoplasm arising in tissues such as GI, thyroid, skin, salivary gland and orbit. In these tissues it's associated with chronic inflammation whether infectious or autoimmune	-Lymphoepithelial lesions, tumor occurs usually out of the lymph nodes, in organs with epithelial lining like in GI, where lymphocytes will attack the epithelium. - lymphocytes are small to medium in size with variable cytoplasm.	- B-cell markers are positive. - There's no specific marker to diagnose extranodal marginal zone lymphoma.	- A mass at the site of involvement, like enlarged thyroid, or ulcers in the stomach. - It's a low grade disease, with prolonged survival, without any cure, except gastric MZL secondary to H.pylori infection. Once eradicating H.pylori, the patient will get cured.
6) Diffuse large b cell lymphoma (DLBCL)	the most common lymphoma in adults. It's either de novo (primary) or a transformation from other low grade tumors (secondary), especially CLL and Follicular lymphoma	Hence the name, it presents as large cells with at least double the size of a normal lymphocyte, with diffused arrangement; appears like ALL blasts under the microscope	- B-cell markers are positive. - CD10 in a subset of cases is positive (mentioned before).	- Patients are usually older than 60 years of age, but DLBCL can occur at any age. - Generalized lymphadenopathy. - DLBCL can occur in extranodal sites like in skin or GI, similar to EMZL -DLBCL is very aggressive and rapidly fatal if not treated(With treatment it can be cured in 50% of cases).

7) burkkit lymphoma (Note: Ki67 is a stain used in pathology to determine the percentage of proliferating cells, for example Ki67 for DLBCL (aggressive tumor) is 40-50%, Ki67 for the most aggressive lung tumor is 10-20%. Burkitt lymphoma is the only human neoplasm with Ki67 more than 99% (nearly 100%), which means that Burkitt lymphoma is very aggressive.)	the fastest growing tumor in humans, and presents as 2 types: 1. **Sporadic**: in all over the world, presented by abdominal masses. 2. **Endemic**: in Africa, where it's highly associated with Epstein-Barr virus (EBV) infection, presented by mandibular or maxillary masses. Both are usually extranodal diseases, and are common in young children. Burkitt lymphoma is caused by a translocation mutation involving MYC gene on chromosome 8, the most common translocation is between (8; 14) genes.	- Sheets of medium sized lymphocytes with variable cytoplasm and several nucleoli forming a Starry-sky appearance. - A lot of mitotic figures (Frequent mitosis).	- B-cell markers are positive. - CD10 is positive (as mentioned earlier). - BCL2 is negative. (Remember that BCL2 is positive in follicular lymphoma).	- Patients are usually young adults or children. - Peripheral blood is involved in the majority of cases of burkitt lymphoma, and here we should distinguish between burkitt lymphoma and B-ALL by CD34 or TdT markers (ALL is CD34, TdT positive and burkitt lymphoma is CD34, TdT negative). - As mentioned before, Burkitt lymphoma is very aggressive tumor, and like any other high grade tumor burkitt lymphoma is a curable tumor.
8) Plasma cell myeloma (multiple myeloma) **(look table 3)** Note : -Recurrent bacterial infections is The most common of death. • Renal dysfunction (at least %50 of the patients) – Second most common cause of death	-happens in the bone marrow -we can detect clonality by simple serum test **Electrophoresis**. – Associated with **M proteins**. [The most common M proteins are **IgG, IgA and light chains** (with no association with heavy chains)] – Associated with **lytic bone lesions** – Several translocation involving **IgH, cyclin D1 and D3 as well as *MYC*.** – Cyclin D1 is not specific for mantle cell lymphoma as it can be seen in plasma cell myeloma	-Under the microscope: large basophilic cytoplasm with prominent perinuclear hof, rounded eccentric nucleus with coarse chromatin (clock face) -normal and abnormal plasma cells(binucleated, large and vacuoles in cytoplasm and nucleus contains **antibodies**)	Lab findings: • M protein, but: -1% are non-secretors (they don't secret anti-bodies), they present with the same clinical manifestations but their electrophoresis will be negative. • Elevated creatinine or urea (because of the renal dysfunction). • Elevated calcium levels. • Anemia, thrombocytopenia and leukopenia (if a large portion of the bone marrow is involved)	-Common **lymphoid** neoplasm, present at old age (70 years average) -Light chains (Lambda or kappa) are **secreted in urine{called Bence Jones protein }** (unlike IgG and IgA which are not filtered through the kidney and can be seen only in plasma) - Median survival time for multiple myeloma is 4-7 years. ► No cure (yet).

9) Hodgkin lymphoma **Note: Two major subtypes** • **Classic HL (4 classes):** – Nodular sclerosis – Mixed cellularity – Lymphocyte-rich (very rare) – Lymphocyte-depleted (very rare) • **Nodular lymphocyte predominant HL (NLP HL)[cornpop cells]** ***table 4+5**	One of the **most common diseases**, present at young age and it is curable (majority are benign) *characteristic cells called: **Reed-Sternberg cells (RS cells).** • **B cell origin**	• **RS cells secrete**: – **IL5** recruiting eosinophils (not typically found in the lymph nodes, when you find them search for RS-cells to confirm HL). – **IL13** to promote their own growth. – **TGF-B** resulting in fibrosis. – **PDL1 and PDL2** to inhibit T cell function. • They are **neoplastic B cells**.	***Classic HL** * CD30+, CD15+. * pax5 weakly positive, negative for other B cell markers * Negative for T cell markers * Negative for CD34 **NLP HL** –Negative for CD30 –Negative for CD15 –Positive for B cell markers –Negative for T cell markers –Negative for CD34	*can present in **single lymph node** or a **group of contiguous lymph node.** Cervical and mediastinal are the most common. • Rarely involves tonsils, Waldeyer ring or extra-nodal sites. • Spreads in a contiguous manner.
10) Histiocytic neoplasms (rare) **Remember that**: plasma cell myeloma doesn't occur in young patients, while histiocytosis occurs in very young patients. Both cause lytic lesions especially in the skull.	-The most important one is **Langerhans cell histiocytosis** (previously known as histiocytosis X) • **Langerhans cells**: immature dendritic cells in the skin and other organs, present antigens to T cells.	**Under the microscobe:** *Lytic lesions. *sheets of medium sized cells. *Eosinophils (found in both histiocytosis and HL). *Langerhans cell histiocytosis cells have the appearance of **a coffee bean**.	**Immunophenoty-pe:** • Positive for: **CD68, CD163, langerin** and **CD1a**. *(**CD1a** is the most important one and most specific for Langerhans cell differentiation, you cannot diagnose this disease without CD1a).	• Affects children less than 2 years of age. • Involves skin, bone, lungs, spleen, or bone marrow. • Could be **unifocal or multifocal.** • Associated with **BRAF** mutation (not specific since it is found in melanoma, hairy cell leukaemia, and thyroid tumours).
11) Mycosis fungoides and Sezary syndrome	MF has three stages: 1- erythrodermic rash 2- plaque phase 3- Tumour phase	Lymphocytes invading the epidermis	• **MF:** a form of cutaneous **T cell lymphoma** – neoplastic T-lymphocytes which are **CD4 positive and CD8 negative**. • **Sezary syndrome**: similar to MF with the addition of **generalized**	**Prognosis:** • Prolonged survival if still in early stages. • Tumor stage, visceral involvement or Sezary syndrome have a bad prognosis (1-3 years to live). **Patch**: localized redness **Plaque**: can be felt (palpated)

			exfoliative erythroderma and circulating tumour cells in the blood.	**Tumor**: causes necrosis **Erythroderma:** generalized redness.
12)acute myeloid leukemia (AML) **Diagnosis depends on:** •Morphology •Immuneophenotype •Karyotype (Predictive of prognosis) -Note: Early arrest in the blast cell or immature cell "we call it **acute leukemia**"(in the blast or promyelocyte)	•Mutations arreste myeloid cells at an early stage of differentiation **"inability to differentiate "** **{t(15;17) resulting in fusion of RARA with PML}** Treatment with **all-trans retinoic acid (ATRA, a vitamin A derivative)** which overcomes this protein and forces the cells to **differentiate** into neutrophils and the remission happen in one week, CURE RATE IS HIGH. •Treatment with chemotherapy and possibly SCT (stem cell transplantation) •Prognosis is variable but oveall 5-year survival is~15-30%. (Bad prognosis)	At least 20% blasts -Auer rods "needle shape structure in the cytoplasm"(it is purple in color or magenta color or deep pink color)[its absence does not rule acute myeloid leukemia out. In other words, they are specific for AML but not sensitive.] **CLASSIS :** I.AML with recuurent chromosomal translocation II.AML with multilineage dysplasia III.AML ,therapy related IV.AML, not otherwise classified	**Immunophenotype** •CD34 "marker of stem cell or blasts, myeloid or lymphoid •Myeloid markers •MPO, CD33, CD13, CD117, CD15 **•MPO is the most specific** *Note :the 3rd class (we can diagnose it without tests) previous exposure to =chemo thereby The cytogenetic translocation carries the best prognosis[prognosis of class 1 is better than 2 and 2 better than 3 and so on]	▯ Age of presentation is around 50 can happen0 at any age "6months to 70 y " ▯ Stigmata of **pan**cytopenia "the bone marrow Is replaced completely by neoplastic blasts" ▯ Splenomegaly ▯ Rarely as discrete masses Called **myeloid sarcoma**(rare disease around the mouth) - DIC is a possible complication. •Very similar to ALL (huge overlap), don't depend on the age DON'T •CNS manifestations are less frequent than ALL
13. MDS (Myelodysplastic syndrome)	refers to a group of **clonal** stem cell disorders characterized by maturation defects that are associated with ineffective hematopoiesis with **cytopenias** and a high risk of transformation to AML (no cytosis the cells stay in the bone marrow) Most cases are idiopathic (Some cases are induced by exposure to alkylating agents or ionizing radiation)	**Morphology** •Hypercellular bone marrow •Dysplastic changes •Erythroid: Abnormal nuclear contour and iron deposits (ring sideroblasts) •Myeloid: abnormal segmentation and granulation •Megakaryocyte: small and monolobed	**Pathogenesis** involves genetic and epigenetic(change in the gene and not changing the sequence) mutations that result in inability of the stem cells to have effective poeisis. Still able to proliferate and differentiate but **in a disorderly manner!**	•Age 50-70 •Cytopenia and its effects (if there is a cytosis it is defiantly not MDS) •Does not have to be PANcytopenia •Patients may present with **only** anemia or **only** thrombocytopenia or only leukopenia •transforms to AML in 10-40% of the cases •Survival between 9-29 months

14. MPN (Myeloproliferative Neoplasms)	**Four major neoplasms : 1•Chronic myelogenous leukemia 2•Polycythemia vera 3•Essential thrombocythemia 4•Primary myelofibrosis		mutated, constitutively activated tyrosine kinases or other acquired aberrations in signaling pathways that lead to growth factor independence (uncontrolled growth). Still have the ability to differentiate	These neoplasms have two fates: •Spent phase: fibrosis (extensive) •Blast phase: acute leukemia
15. CML (chronic myelogenous leukemia) **Note**: -Disease course is marked by excessive production of relatively normal blood cells, particularly granulocytes (basophils) and platelets.	- Slowly progressive disease (Median survival is 3 years without treatment) - Can progress to accelerated phase(Anemia, thrombocytopenia and additional genetic mutations) - Progress to blast phase(70% AML 30% ALL) and Rarely progresses to spent phase with fibrosis Myeloid in to lymphoid ?!how? Remember that the mutation is **at the stem cell level**	•Hypercellular bone marrow •Splenomegaly with extensive extramedullary hematopoiesis •High WBC count, often exceeding 100000 (may cause thrombosis -High WBC count secondary to infection or infarction	-BCR-ABL -translocation t(9;22) -The same as in B-ALL -Present in all cells (B, T, myeloid) -It is a tyrosine kinase that results in uncontrolled proliferation **Does NOT inhibit differentiation**	-Age 50-70 -Nonspecific symptoms of fatigue, weakness −Dragging sensation in the abdomen due to splenomegaly −Must be distinguished from "leukemoid reaction" -**The only neoplasm in which the molecular test is mandatory for diagnosis (BCR-ABL)**
16. Primary myelofibrosis	**The hallmark of primary myelofibrosis is :** - **development of obliterative marrow fibrosis, which reduces bone marrow hematopoiesis and leads to cytopenias** - **extensive extramedullary hematopoiesis**	Peripheral blood: •leukoerythroblastosis same as myelophthisic anemia Tear drop RBCs Erythroid precursor cells Immature myeloid cells As you recall this is also found in myelophthisic anemia	JAK2 mutation in ~50-60% of the cases •Neoplastic cells involve the megakaryocytes (always there is fibrosis) Secrete fibrogenic factors resulting in extensive fibrosis • PDGF and TGF-B •Extramedullary hematopoiesis	•Age more than 60 •Anemia and splenomegaly •Fatigue, weakness and night sweats •Lab results •Anemia: normochromic and normocytic •Leukoerythroblatosis •Bone marrow is a must for diagnosis (hypercellularity

		•Abnormally large platelets •Bone marrow: Severe fibrosis Abnormally large and clustered megakaryocytes	with marked splenomegaly (may reach 4 KG and can could be felt on the right side)	,fibrosis, cluster of megakaryocytes) •Median survival is 4-5 years •5-20% transform to AML •Treat with JAK2 inhibitors and possibly SCT

Table (2)

Bad prognostic factors	***Good prognostic factors***
Age < 2, or > 10 WBCs count > 100,000	Age between (2 and 10) Low WBCs count
Normal ploidy or hypodiploidy Translocation mutation between (9; 22) genes	Hyperdiploidy Translocation mutation between (12; 21) genes

****Some notes:**
-**Leukemia**: neoplastic leukocytes circulating in the peripheral bloodstream.
-**Lymphoma**: a neoplastic process in the lymph nodes, spleen or other lymphatic tissue.
These sites are the most common but they're not exclusive, i.e. we may have lymphoma with neoplastic cells circulating in the blood, or we may have leukemia presenting as masses.
-**Acute**: The neoplastic process involves early immature precursor cells.
-**Chronic**: The neoplastic proliferation is presented by some degrees of differentiation (mature precursor cells).
We have three major types of WBCs neoplastic disorders:
I. Lymphoid neoplasms

II. Myeloid neoplasms

III. Histocytic neoplasms

** -Normal lymph node cells are derived from different stem cells which means they show different types of antigens; therefore, they're **Polyclonal** = not malignant. -All lymphoid neoplasms are derived from a single transformed cell, so they're **monoclonal** = malignant.
Assessment of clonality can be done by:
a- Immunophenotying (expressing only kappa or only lambda gene), or by

b- Genetics (receptor gene rearrangement).

**In the table above the Neoplasm which number from 1 to 8 are lymphoid neoplasm And which number from 13-16 are myeloid neoplasm

Remember:
CLL: The most common leukemia.
ALL: The most common leukemia in children.
DLBCL: The most common lymphoma.
-CD5 positive tumors: CLL and mantle cell lymphoma.

-CD10 positive tumors: Follicular lymphoma, B-ALL, Burkitt lymphoma and some cases of DLBCL

**Table 3

.	It affects	
The kidneys	**The immune system**	**The bone**
• Obstructive casts composed of Bence jones proteins (light chains) in the distal tubules. • Deposition of light chain in the glomeruli causing: – Light chain disease. – Amyloidosis. • Hypercalcemia resulting in renal stones. • Bacterial pyelonephritis	• Functional antibodies are markedly decreased (it is true that antibodies are increased in general, but most of them are inactive). – Increase risk of bacterial infections (The most common cause of death in multiple myeloma patients).	• Releases factors such as RANKL that increase osteoclastic activity. • Other factors that decrease osteoblastic activity. • Net result is: – Lytic lesions – Pathologic fractures (sometimes called secondary fractures) – Hypercalcemia (due to the resorption of bones)

Table(4)

Hodgkin Lymphoma	Non-Hodgkin Lymphoma
More often localized to a single axial group of nodes (cervical, mediastinal, paraaortic)	More frequent involvement of multiple peripheral nodes
Orderly spread by contiguity	Noncontiguous spread
Mesenteric nodes and Waldeyer ring rarely involved	Mesenteric nodes and Waldeyer ring commonly involved
Extranodal involvement uncommon	Extranodal involvement common

Table (5)

Stage	Distribution of Disease	Five-year survival
I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or tissue (I_E)	**More than %90 (Most cases are stage I and II)**
II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited contiguous extralymphatic organs or tissue (II_E)	
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (III_S), limited contiguous extralymphatic organ or site (III_E), or both (III_{ES})	**%50**
IV	Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with or without lymphatic involvement	