All our blood cells come from two lineages which are :
1) Myeloid lineage which gives :
- WBCs except lymphocytes (granulocytes , monocytes)
- RBCs
- megakaryocytes which gives platelets

2) lymphoid lineage which gives :
lymphocytes (T + B)

- general concepts :
Acute means it has immature cells (blasts)
chronic means it has mature cells (cytes)
any chronic type can progress to become acute type of the same disease
ex: chronic myeloid leukemia can progress to acute myeloid leukemia.

detailed explanation for each lineage :

myeloid lineage
- chronic diseases :
1- MPNs (myeloprolifrative neoplasms) :
*** granulocyte proliferation (CML – chronic myeloid leukemia)**
*** RBCs proliferation (PV – polycythemia vera)**
*** megakaryocyte proliferation (primary myelofibrosis)**
*** platelets proliferation (essential thrombocythemia)**
2-MDS (myelodysplastic syndrome)—when immature myeloid cells [blasts] in bone marrow account for less than 20% and more than 5%

- Acute diseases :

*** AML (acute myeloid leukemia)—when immature myeloid cells [blasts] in bone marrow account for more than 20%**

[MPNs and MDS can progress into AML]

lymphoid lineage :

- non- hodgkin lymphomas

*** CLL(chronic lymphocytic leukemia)/ SLL (small lymphocytic lymphoma)**

*** ALL (acute lymphobalstic leukemia)**

*** follicular lymphoma**

*** mantle cell lymphoma**

*** diffuse large B-cell lymphoma**

*** burkitt lymphoma**

*** mycosis fungoids**

*** adult T-cell lymphoma/leukemia**

- Hodgkin lymphomas

- plasma cell myeloma

Myeloid lineage :

1) chronic diseases

Type	Subdivision	mutation	Manefistations	Bone marrow cellularity	Prolifrative cell type	Sec. hematopiotic organs	Morphology	Immature cells percentage in bone marrow
MPN	CML	-BCR-ABL fusion (philadelphia chromosome)	- ↑ WBCs - shift to the left - basophilia - anemia - thrombocytopenia	Hyper cellular	Granulocyte mainly + megacaryocytes	splenomegaly	- Granulocytes from various stages of differentiation are seen in blood smear -myeloblast are only slightly increased	<5%
	PV	-JAK-2 kinase mutation in 100% of cases	-High number of RBCs in blood	Hypercellular	RBCs mainly	----------	----------	<5%
	ET	-JAK-2 kinase mutation in 50% of cases	-Hemorrages because of unfunctioning platelets	Hypercellular	Platelets in blood megakaryocytes in bonemarrow	Mild splenomegaly	-Increased number of megakaryocytes - Large mature megakaryocytes with hyperlobated nuclei	<5%
	PM	-JAK-2 kinase mutation in 50% of cases - neoplastic megakaryocytes release : PDGF TGF- beta	-Bleeding - increased susceptibility for infection -cytopenia	Hypocellular + fibrosos	Megakaryocytes	Massive splenomegaly spleen crosses the midline hepatomegaly	-leukoerythroblastic change - tear-drop RBCs	<5%
MDS	--------	chromosomal aberrations affects the ability of progenrator cells to mature	-Refractory Cytopenia -dysplastic bone marrow	hypercellular	Immature cells (blasts)	-------	-RBCs *Megaloblastoid nuclei *There's nuclear-to-*cytoplasmic asynchrony *Multinucleation *Ring sideroblasts -Granulocytes : *Hyposegmented nucleus *Hypogranular cytoplasm -megakaryocytes : *small in size *hypolobated nuclei	20%< blasts >5%

How To differentiate between chronic myelogenous leukemia and leukemoid reaction?

CML	Leukemoid Reaction
Basophilia	Only increased neutrophils
t(9;22) or BCR-ABL fusion gene	No translocation
Mostly asymptomatic	Presents with signs of bacterial infection
Not mentioned but important: LAP (Leukocyte Alkaline Phosphatase) negative this is an enzyme that helps fight bacteria	LAP positive

2) Acute disease

AML

general information about AML

-mutation in the early (progenitor) cells, this
mutation that affects both proliferation and differentiation of the cell so we end up with >>> high number of immature cells (Myeloblasts).
-These myeloblasts will accumulate in the Bone Marrow destroying the
normal hematopoietic cells, so the patient will end up with myelophthisic anemia (bone marrow failure) and pancytopenia.
-AML can come at any age so any person can develop the disease BUT it
commonly increases with age.
-Diagnosis of AML is when blasts reach 20% or more of the total cells either in the bone marrow or in the blood.

**** APL (acute promyelocytic leukemia) and acute monocytic leukemia are special type of AML .**

Type	Subdivisions	mutation	manifestation	morphology	Immature cells percentage in bone marrow	Prognosis	Imp.notes
AML	AML-recurrent cytogenetic abnormality	1- t(8:21) 2- t(15:17) 3- Inversion 11		1- Neuclous : very big neucleous with fine and pale chromatin and neumerous nucleouli which *appears like someone punched out a circle from*it 2- cytoplasm: - the N:C (nuclear to cytoplasm ratio) is very high - Cytoplasm of myeloid cells (neutrophils) has myeloperoxidase enzyme + granules. - Peroxidase enzyme accumulates as needles called Auer rods just 1-2 per cell 3- Antigens (markers): Myeloblasts present CD34 antigen this antigen is present only on immature cells (blasts).	20%< blasts	1- good prognosis 2- intermediate in prognoses. 3- aggressive and has bad prognoses.	1-behaves better than AML not having this translocation. 2-This mutation occurs in APL (M3)
	AML – Myelodysplasia related changes (complicates MDS)	-------				Transformation to AML is gradual , so this leukemia will not be as aggressive as that originated from de novo	
	Therapy related myeloid neoplasm	---------				very aggressive.	MDS also might follow radiotherapy, and it is also aggressive. When MDS is therapy related, there is a big chance to develop AML.
	AML – not otherwise specified	----------				----------	AML- not otherwise specified, and we use FAB classification (back to morphology).
APL	--------	- T(15;17) - RARA +APL fusion	1- DIC (disseminated intravascular coagulation), followed by bleeding because all the platelets are consumed in thrombosis. 2- Disrupting retinoic acid receptor that's why we can manage the disease by giving vitamin A which allows the blasts to mature.	1- Auer rods are highly available in form of sheets 2- twisting in the nucleus 3- Many azurophilic granules	20%< blasts	intermediate grade	When these 2 genes (RARA , APL) fuse they produce a new gene so a new protein. This new protein does 2 things: 1- Binds DNA 2- Blocks maturation of the cell
Acute monocytic leukemia	----------	----------	1- Sudden/ quick onset 2- Bone pain 3- Bleeding 4- Anemia 5- Infection and fever (no neutrophil) 6- Solid organ and soft tissues damage (most important gums infiltration)	1- Monoblasts are larger. 2- Nucleus is more toward the center in Monoblasts. 3- NO granules nor Auer rods.	20%< blasts	----------	This leukemia is found in the bone marrow and goes to the blood (leukemia!) However, it has a special course, This is actually because circulating monocytes give macrophages in the tissues.

**Important note :
Although lymphoblasts resemble myeloblasts, we differentiate between the two by the presence of Auer rods.
We can stain Myeloperoxidase to know if the cell is a myeloblast . If it's +ve, the cell will be a myeloblast.

Lymphoid lineage
- lymphomas
1- T-cell lymphomas

Type	T-lymphoblastic lymphoma	T-cell lymphoma
Maturity of T cells	Immature T cells	Mature T cells
Place	Thymus , so patients come with mass in the neck hence the immature T cells already found in thymus in order to mature	Lymph nodes

2- B-cell lymphomas

Type	B- lymphoblastic lymphoma	B-cell lymphoma	myeloma
Maturity of B cells	Immature B cells	Mature B cells	Mature Plasma cells
Place	Bone marrow hence the immature B cells already found in bone marrow in order to mature	Lymph nodes	Bone marrow (because plasma cells retrain to the bone marrow to secret antibodies)

Diagnosis of both T-cell and B-cell lymphomas :

1-chronic painless lymph node enlargement
2-inflamation and B symptoms which are Fever (↑cytokines), Night sweating, Weight loss, and Anorexia.
3-immune suppression
4- high LDH (lactate dehydrogenase) level
5-abnormal morphology under the microscope
6- overgrowth of lymphocytes
7- surface antigens
***T-cells (both cytotoxic and helper T-cells) express early antigens CD2, CD3, CD5.**
***B-cells express CD19 and CD20.**
8- Terminal deoxynucleotidyl transferase (TdT) enzyme which is only available in Lymphoblasts.

lymphoid leukemia :

Type	Subdivisions	Proliferative cell	CD – marker	Prognosis	maturity of cells	Place of Origin	Age	Mutation	Diagnosis	Clinical manifestations	morphology	Imp.notes
ALL	T-cell ALL	T lymphocytes	CD-3 positive	Very Aggressive / high grade	Immature cells (lymphoblasts)	Thymus then go to blood and other organs	Most common in male adolescence (teenagers)	Mutations that occur in this disease activate proliferation and inhibit maturation of lymphoblasts	- TDT positive -myelophthisic anemia (lymphoblasts count is >=20%	- fever, anemia, bleeding and bone pain due to quick destruction of bone marrow . - solid organs invasion: ALL commonly goes to Lymph nodes (lymphadenopathy) and other solid organs like the liver (hepatomegaly), spleen (splenomegaly), testis, and the Brain.	- High number of lymphoblasts - No granule , Nor Auer rods in lymphoblasts	- if the patient comes with ONLY the lymph nodes affected, it's called (Acute Lymphoblastic lymphoma). - if Only blood and bone marrow affected its called : (Acute lymphoblastic leukemia). - if All (blood, bone marrow and lymph nodes) affected then its called : Acute Lymphoblastic lymphoma/leukemia ** So it's the same disease with different manifestation
	B-cell ALL	B lymphocytes	CD-20 positive			Bone marrow then go to blood then lymph nodes then other solid organs	Most common in children					
CLL/ SLL	----------	B lymphocytes only	1- CD19 2- CD20 3- CD5, which is a T cell marker but these B cells are malignant so they express whatever they want :P	Less aggressive / low grade	Mature cells (lymphocytes)	- In case of CLL it Start in the bone marrow then circulate. - in case of SLL in start in lymph nodes then circulate .		Upregulation (not tranclocation) of BCL2 gene		*Autoimmune Hemolytic anemia *hypogammaglobulinemia (immune dysregulation)	- In blood : *high number of lymphocytes *smudge cells - in lymph nodes: *small & dark lymphocytes and in between them there are large cells called prolymphocytes *the normal architecture of lymph nodes is NOT preserved	- Most commonly it starts in the Bone marrow then circulates, so we call it chronic lymphocytic leukemia (CLL) , But it can affect the lymph nodes first then circulate, so we call it small lymphocytic lymphoma (SLL).

											, we don't see normal follicles and germinal centers .	

- Note about CLL :

**** The course of the disease is chronic which means that the patient will have indolent course i.e asymptomatic and they live for years before they express any complications and we don't treat until they develop complications.**

**** Chemotherapy is not effective when CLL in indolent (in early stages) because most of the cells are not proliferating.**

****How to differentiate between lymphoblasts and myeloblasts ?**

Type	Lymphoblast	Myeloblast
Size	Smaller	Larger
Nucleus to cytoplasm ratio	Very high	Lower
Auer rods (myeloperoxidase)	NO	YES
TDT	YES	NO

Another classification of lymphomas is Hodgkin and non Hodgkin lymphomas

first we will talk about non-hodgkin lymphomas
we had already talked about ALL and CLL types of lymphoid leukemia which both classified as non-hodgkin lymphomas too.
now , non-hodgkin lymphomas either B-cell OR T-cell lymphomas

1) B-cell non-hodgkin lymphomas

Type	Subdivisions	Spread	Age	Place of origin	Prognosis	Mutation	Morphology	Imp.notes
1-Follicular lymphoma	----------	Western countries	Elderly	Follicles in the lymph nodes	Low grade / good prognosis	translocation: t(14:18) - on 14 there is immunoglobulin heavy chain gene - on 18 there is BCL2 gene * this translocation resulting in an increase in Bcl2 production	- Under the microscope we can see numerous follicles occupying the entire lymph node, they are large, crowded, hitting each other and abnormal. - two cell populations can be seen: 1- Centrocytes: small, dark , irregular some have nuclear cleavages 2- Centroblasts: large nucleated immature cells	It is similar to reactive follicular hyperplasia , In order to differentiate between the two we examine the Bcl-2 gene expression by staining the protein itself: ► follicular lymphoma is positive for staining ► Reactive follicular hyperplasia is negative
2- Mantle cell lymphoma	----------	----------	old people	Mantle zone which is the outer circular layer of the germinal center of the follicle	aggressive tumor that is usually disseminated in the lymph nodes and in exratnodal areas	----------	- Looks like the follicular lymphoma, as there are small cells; however they are arranged in a diffuse pattern - there is over expression of: 1- CD-5 2 cyclin D1	How we can diffreniate between CLL/SLL and mantle cell lymphoma although both express CD-5 ? mantle cell lymphoma shows increase expression of cyclin D1 whereas CLL/SLL don't

3-Diffuse large B cell lymphoma	**----------**	**----------**	**The most common lymphoma in adults , but can rise in children**	**- Two types :** **1- denovo** **2- Secondary, following a previous disease, including :** **1. Low grade B cell lymphoma (by transformation).** **2. Immune suppression: ADIS or post-transplant.** **3. Chronic immune activation such as in rheumatologic diseases.** **4. Following *HHV8 infection* which called primary effusion lymphoma**	**Aggressive tumor/ high grade**	**----------**	**- diffuse pattern** **- very large lymphocytes (double the normal cells)**	**----------**

4- Burkitt lymphoma	**EBV assotiated**	**In certain areas of Africa, EBV is endemic causing endemic Burkitt lymphoma These patients are 100% associated with EBV infection.**	**Affects children**	**EBV is transmitted through saliva - oral contact- that's why the manifestation of the associated lymphoma appears in the oral cavity, mostly in the jaws.**	**High grade aggressive tumor that is fatal if not treated**	**translocation t(8:14) - on 8 *MYC* gene which is one of the transcription factors. - on 14 immunoglobulin heavy chain gene * this translocation result in over expression of MYC gene**	**- Diffuse pattern, we see sheets of cells - Cells are intermediate in size - There is very prominent mitosis, and this huge number of mitotic cells is NOT seen in other tumors. - starry sky appearance seen at low power magnification which is very important feature of this lymphoma**	**- It is the fastest human cancer - It appears outside the lymph nodes (extra-nodular). In oral cavity or GI system, most commonly in the ileum.**
	Sporadic type	**worldwide, outside Africa, this lymphoma is sporadic and the association with EBV is much less.**						

2) T-cell non-hodgkin lymphomas :

type	Cell of origin	Place of origin	Clinical diagnosis	CD marker	Morphology	Imp.notes
1- Mycosis fungoides	CD4+ cells (T helper cells)	It is a cutaneous lymphoma that arises in the skin	- diffuse erythema which look like mushroom or fungus - systemic involvement as abnormal T cells are circulating in the blood affecting lymph nodes, spleen, liver and the entire body. It is called in such case *Sezary syndrome.*	It will express CD2,3,4 and 5.	- Very irregular nuclei that look like the brain, thus it is called cerebriform	- *Sezary syndrome* is the same as mycosis fungoides but with systemic involvement. - The disease starts as red patches in the skin of the whole body followed by swelling of these patches so it seems like a mushroom or fungus, hence it is called mycosis fungoides.
2- Adult T-cell leukemia/ lymphoma	CD4+ T cells (T helpercells)	Systemic and skin	- It is associated with human T cell lymphoma virus 1(HTLV-1) - always has systemic involvement and skin lesions	- It will express CD2, 3, 5 and 4 . - in addition to the abnormal one CD-25, which is normally expressed by regulatory T cells.	----------	- The systemic involvement in this disease comes in the early course of the disease, unlike mycosis fungoides in which the systemic involvement might come after the skin involvement (i.e. in late stages),a as in the case of Sezary syndrome. - It is endemic in some areas such as Japan, the Caribbean areas and West Africa.