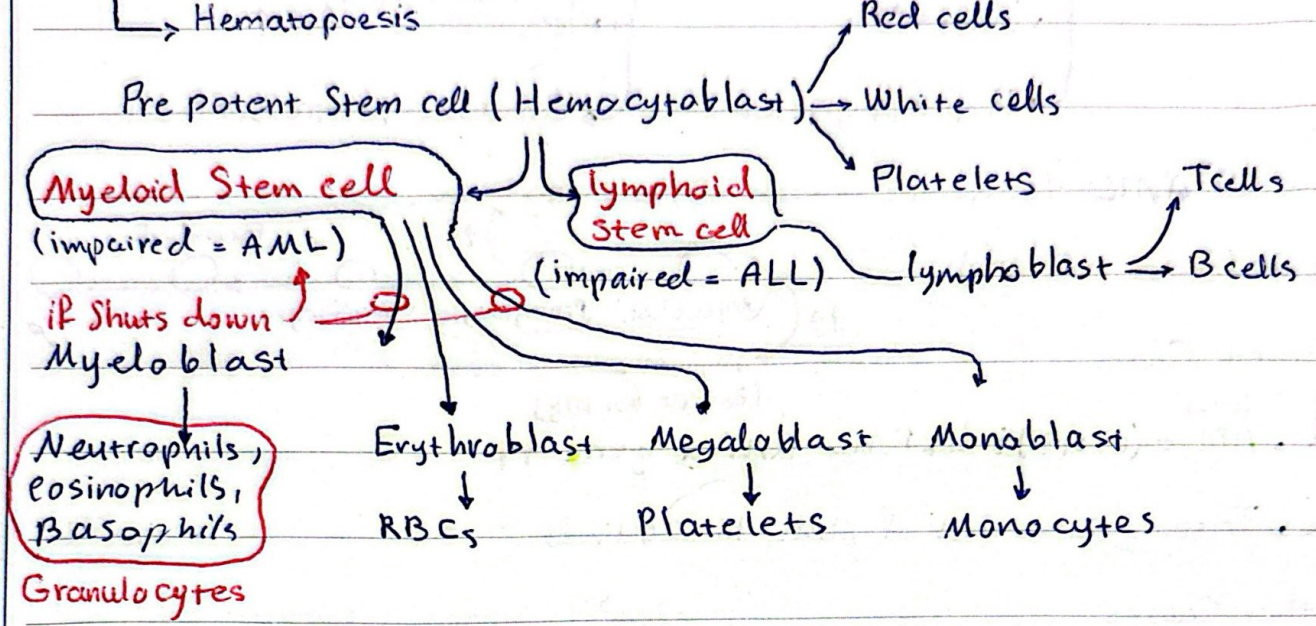
Date: Sub:

Acute leukemia

1) Pathophysiology

↳ Hematopoesis



AML (Acute Myeloid leukemia)

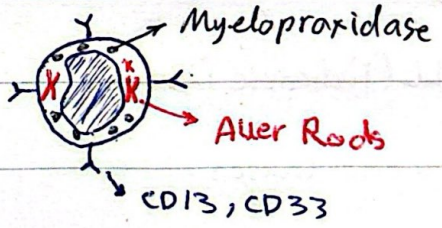
↳ Myeloblast in bone marrow ≥ 20%.

↳ 8 SubTypes (M_0 - M_7) → M_3 Subtype : Acute promyelocytic leukemia (leads DIC)

Myeloblasts in bone marrow biopsy (or pripheral blood Smear)

↳ Auer Rods + Myeloproxidase

+ CD13, CD33 (Not super Spicific)



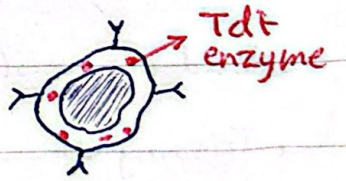
ALL (Acute Lymphoid leukemia)

↳ lymphoblasts in bone marrow ≥ 20%.

↳ 1) T-lymphoblast (20%) → T- ALL

2) B-lymphoblast (20%) → B - ALL

↳ lymphoblast > in bone marrow biopsy (or peripheral blood smear)



T-lymphoblast

Tdt enzyme

CD2-8 → T-lymphoblast

CD 10, 19, 20 → B-lymphoblast

Super Specific for lymphoblasts

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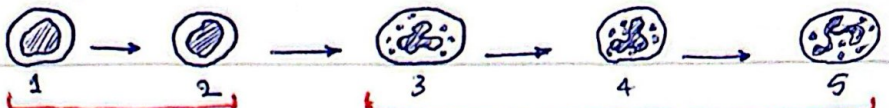
Cell differentiation



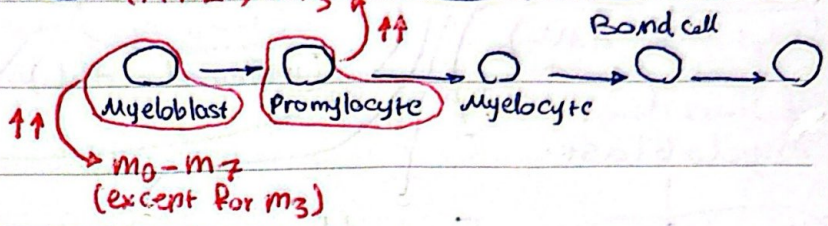
Impairment

Blasts (Early) = Acute
- (non Functional)
- blasts ↑↑
- Rapid progression

Nucleus Segmentation (late) = Chronic
- (more Functional)
- less mature ↑↑
- Gradual progression

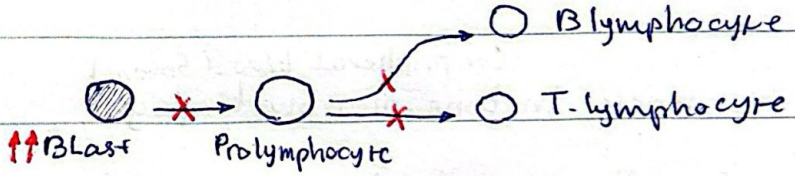
2) Causes of Acute leukemia ~~~ (APL) m_3 ~~~

1) AML (Older patients)



- Genetic Causes
  - (m_3) APL = (15:17)t → PML-RARα gene ↑↑
  - Trisomy 21 → Risk of AML 10-20 times
- Other Causes
  - Chemoradiation
  - Myeloproliferative Disorders)
  - Myelodysplastic Syndrome

2) ALL (Pediatric Disease)



- Genetic Causes
  - Good prognosis (Children) → (12:21)t → EVL-RUNX1 gene
  - Bad prognosis (Adult) → (9:22)t → BCR-ABL1 gene
  - Trisomy 21 → Risk of ALL 10-20 times
- Other Causes
  - Chemoradiation
  - HTLV Infection (Tcell ALL)

Date: Sub:

3) Clinical Findings of Acute leukemias:

1) Pancytopenia → AML (↑↑ Myeloblasts), ALL (lymphoblasts ↑↑) in bone marrow → less space for other cell classes

↳ CBC findings: ↓↓ RBC (Hb ↓) Anemia → fatigue, Pallor, dyspnea

↓↓ Platelets (<150'000) Thrombocytopenia → Bleeding, Bruising (Petechia, Purpura)

Menorrhagie, Gingiva bleeding, Epistaxis

↓↓ Functional WBC (leukopenia) → Frequent infections and fevers

↳ neutropenia (<500) Absolute neutrophil count

not all white blood cells

neutropenic fever

2) Bone pain (common in ALL)

↳ bone marrow expansion (Usually pelvis, femur, Tibia)

↳ Results: Refusal to bear weight on that Limb

+ Limp

3) Mucocutaneous leisians (M_4, M_5 (monoblast)) → AML

Deposition of monoblasts in blood into mucus membranes and tissues

→ Gingival Hyperplasia (like phenytoin)

→ leukemia cutis

4) Complications of Acute lymphoblastic leukemia (ALL):

1) lymphadenopathy (more likely to ALL) → Painless enlargement of lymph nodes (cervical, Axillary, Supraclavicular, Inguinal, Mediastinal)

↳ Release IL-1, TNFα → Fever, Chills => B Symptoms

2) Hepatosplenomegaly (more likely to AML) → Stomach chompression (Early Satiety)

Date: Sub:

3) Mediastinal Mass (Only ALL) → Thymic Enlargement → Mass Effect

→ 1) Dysphagia (in Esophegeal Mass Effect)

2) Dyspnea + Stridor (like Bacterial Treachitis)

3) (in SVC mass effect) (SVC Syndrome) → Int. Jugular V. → head and neck Swelling

→ Subclavicun V. → Chest and arm Swelling

SVC Syndrome (+ Bluish color)

→ ↑ICP

→ Laryngeal Edema

more common in ALL

4) Meningeal leukemia (deposition of leukocytes in meninges)

↳ Symptoms of meningitis → Headache, Nausea, Vomiting, neck pain (nuchal Rigidity), Cranial neuropathy (II, III, IV, VI)

Test - lumbar Puncture

↳ shows lymphoblasts

5) Tumor lysis Syndrome (more common in ALL)

↳ ↑↑ Leukocytosis chemo-therapy → 1) Hyperphosphatemia → ↓↓ Free Ca^{2+} (Hypocalcemia)

AV Block

2) Hyperkalemia (Arrythmias) (Bradycardia)

EKG = 1) Peaked T-wave 2) ↑↑ PR Interval 3) Ø P-wave 4) Wide QRS

3) Hyperuricemia (Acute Tobular Necrosis) + Obstructive Uropathy + ↓↓ GFR

↑↑ Creatinine → AKI

Uremia, ↑↑H^+, ↑↑H_2O, ↑↑K^+

4) Hypocalcemia (Trosso, Chovestak Signs) + Seizures, Oral Paresthesia

mnemonic for Tumor Lysis Syndrome → PUKE T

Elevated calcium

↑ PO_4^{3-}

↑ Uric Acid

K^+ ↑

Ca^{2+} ↓

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Date: Sub:

5) Complications of Acute Myeloid leukemia

1) leukostasis (more common in AML) ∝ Myloblasts Count

↳ if WBC > 100k → ↑↑ Blood Viscosity

↓ Microvascular Occlusion → ↓ O_2 delivery → Ischemia

Brain (1 → Mild → dizzyness, Headache

Severe → (CVA) Infarction, TIA

Retinal Veins (2 → Dilated Retinal Veins → Hemorrhages, Papiledemea → Biwool vision

Palmunary Artery (3 → ↓↓ Alveolar Gas Exchange → Hyporia → Dyspnea, ↑RR, ↑ Work of Breathing

2) DIC (only AML) → M_3 Subtype (APL)

↳ Promyelocytes ↑↑ Secrete → 1) Tissue factor ↑

↑↑ Anexin II → ↑ Plasmin Activity

2) Coagulation factor activator ↑ } ↑↑ Clotting cascade → + Platelets → Microthrombi (1

Microthrombi → Bleeding (GIB, Prolonged Bleeding, Echymosis)

Microthrombi → consumption of Platelets, consumption of clotting Proteins

Bleeding → Worsen → Breaking down of fibrin, fibrinogen

Microthrombi → Schistocytes in peripheral blood smear

Schistocytes ← Shredded RBC's (2

+ ↓↓ RBC, Hb
↑↑ PT/PTT
↑ D-Dimer
↓ Fibrinogen

6) Diagnostic Approach to Acute Leukemia

1) Classic findings →

- Fatigue and Pallor (Anemia)
- Easy Bruising and Bleeding (Thrombocytopenia)
- Frequent Infections and Fevers (Neutropenia)
- Bone Pain (ALL) + Mucocutaneus lesions (AML)

Date: Sub:

Step 1 → Obtain CBC with Diff with Peripheral Blood Smear

CBC Diff : Pancytopenia + ↑ Blasts
Blood Smear : Lymphoblasts

CBC Diff : Pancytopenia + ↑ Blasts
Blood Smear : Myeloblast with Auer Rods

↓

Possible ALL

Possible AML

↳ Bone Marrow Biopsy, Immunohistochemistry, Flow Cyto ↲

ALL ← +20% Lymphoblast (biopsy) → +20% Myeloblast (Biopsy) → AML

Flow cytometry : ⊕ CD19, 20, 10 - Tdt → B cell ALL

" " : ⊕ CD2, 8, Tdt → T cell ALL

Cytogenetics → (12:22)+ → ALL (Good prognosis)

(9:22)+ → ALL (Poor prognosis)

Flow Cytometry - CD13, 33 - MPO

(APL) m_3 ← (15:17)+ ← Cytogenetics

Step 2 → Finding of Oncologic Emergencies

1) AML Stroke Syndrome + Dyspnea/Hypoxia (Leukostatis) WBC ≥ 100k

2) ALL Meningitis Symptoms + CN palsies (Meningial leukemia) → LP

3) ALL Only (T cell) Facial, neck, arm Swelling (SVC Syndrome)

4) AML only (APL) Coagulopathic Bleeding (DIC)

5) ALL AKI + Arrythmias + Gout flare (Tumor Lysis Syndrome)

Uric Acid — K^+

Coagulation Studies (PT, PTT), Uric Acid (INR, D-Dimer)

CMP, CT chest with IV contrast

Clinical diagnosis WBC > 100k + Symptoms → Next Page → leukostasis

Date: Sub:

Meningeal Symp + LP (Leukemic Cells) → Meningeal leukemia

↑PT/PTT, ↓fibrinogen, ↑D-Dimer → DIC

CT chest ↓filling of SVC → SVC Syndrome

K^+↑, Uric Acid↑ PO_4^{3-}↑ Ca^{2+}↓ → Tumor Lysis Syndrome

7) Treatment of Acute leukemia

a) IV fluids → ↑Urinary Solvent, ↓Urate Crystal formation ①

b) Allopurinol → ↓Uric Acid formation, ↓Urate Crystal formation
inhibit Xantine Oxidase, Prophilactic before formation of a lot of Uric Acid molecules

c) Rasburicase → ↑Uric Acid break down into Alantoin, ↓Urate Crystal formation
↳ Tumor Lysis Syndrome

leukostasis ②

a) Hydroxy Urea (Cytoreduction: ↓WBCs) → ↓Organ Ischemia

b) Leukoapherasis (Rapidly remove WBCs from circulation) ↑

DIC ③

a) Transfusion → Treat Coagulapathy

b) ATRA (All-trans retinoic Acid) → Treat APL

Meningeal leukemia ④

a) Metotrexate Injection: Omnaya Resorvior (Into Cerebral Ventricles)
Lumbar meninges

b) Chemotherapy (Long time)

SVC Syndrome ⑤

a) Endovascular Stent

b) Chemoradiation + Steroids

Date: Sub:

a) CVAD Regimen for patients with non-(9:22)+ ALL

- Adriamycin → Dexamethazone
- Cyclophosphamide
- Vincristine

↓ Leukomic Cells

b) Tyrosin kinase Inhibitor for patients with (9:22)+ ALL

↳ ↓ BCR-ABL fusion genes

c) Hematopoetic Stem Cells Transplantation (HSCT)

↳ for All ALL patients if High risk

} ALL

a) Cytarabine + danarubicin → ↓ leukemic Cells in AML patients

b) ATRA + Arsenic Trioxide → ↓ lekemic cells in APL (15:17)+

c) Hematopoetic Stem Cells Transplantation

↳ for All AML patients if High risk

} AML

Date: Sub:

Chronic leukemia

1) Hematopoesis → RBC + WBC + Platelets
→ Red bone marrow

Initial Pluripotent Cell = hemocyto blast → Myeloid Stem Cell
→ Lymphoid Stem Cell

Myeloid Stem Cell → Erythroblast → RBC
→ Megacaryocyte → Platelets
→ Monoblast → Monocyte (Agran
→ Myeloblast —in AML→ Promyelocyte —in APL→ Myelocyte → Metamyelocyte → Band Cell → neutrophil, Eosinophil, Basophils

Granulation
Segmentation of nucleus

↑ myelocytes
in CML → ↑ Metamyelocytes, ↑ Band Cells, ↑ Neutrophils, Eosinophils, Basophils
→ At various stages

⇑ LEFT Shift

Surge in leukocyte count due to Infection, Autoimmunity, Surgery, Stress

	CML	Leukemoid Reaction
WBC Count	WBC >100k	WBC <50k
Left Shift	↑↑↑	↑
LAP Score	Low	High

→ CML: Myelocyte Bulge (+) → myelocyte > Band cells, Neu—
→ CML: ↑ Neutrophils, Eosinophils, Basophils / leukomoid Reaction: ↑ Neutrophils
Basophilia

LAP Score: When a neutrophil releases Leukocyte Alkaline Phosphatase due to "Elevated Inflammation / Infection / Stress", the LAP Score goes high.

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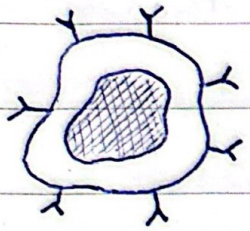
Date: Sub:

Lymphoid Stem Cell → Lymphoblast → ProLymphocyte → B-Cell ↑↑↑ T-Cell in CML

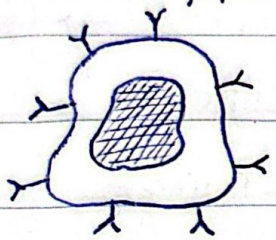
→ Lymphocytosis → >5000/μL (CBC)

Normal Cell



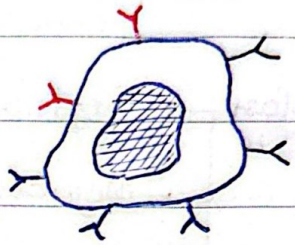
CD19(+) CD20(+)

Mantle Cells (Lymphoma Cell)



CD5(+) CD19(+) CD20(+)

CLL Cells



CD5(+) CD19(+) CD20(+) CD23(+)

↳ In Flowcytometry (We don't need Bone marrow biopsy)

Acute vs Chronic leukemia

Acute

Rapid Proliferation

Do not Differentiate (Blasts)

not functional

Chronic

- Slow Proliferation

Do Differation (Mature)

but not functional

2) Causes of Chronic Leukemia

1) CML → (9:22)t → BCR-ABL1 fusion gene (Philadelphia +)

Older Individuals

↳ ↑ Proliferation ↓ Apoptosis

2) CLL → Brotun Tyrosin kinase Abnormality (BTK Abnormality)

Older Individuals

> 70

Date: Sub:

3) Complications of Chronic Myeloid Leukemia (CML)

1) Splenomegaly → Deposition of (blasts, neutrophils, Prom...) mature appearing cells into Spleen
→ Extramedullary hematopoesis

Palpable LUQ + early satiety (Mass effect on Stomach) + nausea + Vomiting

↳ Severity of Splenomegaly (Bone marrow blasts count)

a) Chronic Phase - CML (most common) → <10% → Mild - Moderate
↑mutation
b) Accelerated Phase - CML → <10 - 19% → Symptomatic (large LUQ, limiting)
↑↑mutation
c) Blast Phase - CML → ≥ 20% → High risk of Splenic Rupture

2) Anemia and Thrombocytopenia → Fatigue, Pallor (Anemia) + Bleeding, Bruising (Thrombocytopenia)

↓ "Cells will crowd out the bone marrow" Menorrhagia, Gingival bleeding, Epistaxis

a) CP - CML → ↑WBC + Anemia + Normal/High Platelets → petechia, purpurae
b) AP - CML → ↑↑ WBC + Anemia + Thrombocytopenia → both groups of Symptoms
c) BP - CML → PANCYTOPENIA → CML → AML

3) Conversion to AML

CP - CML → AP - CML → BP - CML → "Sour Rods" ≥ 20% blasts } AML

if WBC > 100K → ↑↑ Blood Viscosity (Leukostasis) ①

Tumor lysis Syndrome (PUKE calcium) Subsequent to chemotherapy ②

Blasts >>> Functional Cells → ↑↑ Risk of Infections ③

Date: Sub:

4) Complications of Chronic Lymphocytic leukemia (CLL)

1) Lymphadenopathy (Painless Swelling of Lymph nodes)

- Common locations: Cervical, Axillary, Supraclavicular, Inguinal, Mediastinal
- Small Lymphocytic Lymphoma (SLL) → 1) Lymphocytosis (≤ 5000/ML)
  - → 2) Lymphadenopathy
- Richter Transformation → Diffuse Large B cell Lymphoma (DLBCL) (Type of Extensively Invasive non-hodgkin Lymphoma)
  - + Rapid Enlargement of Lymph nodes
  - + B Symptoms
  - + Rapidly Elevated LDH
  - } Poor Prognosis

2) Hepato spleno megaly

↑↑ lymphocytosis → deposition of leukemic cells into Liver / Spleen

→ Presentation →
- Palpable Spleen (LUQ)
- Palpable Liver (RUQ)
- Early Satiety + Nausea + Vomiting

3) Anemia → "Hb must be less than 10"

At first Stage
- + Normal MCV
- + Retic Index < 2%

- like in CML
- Presentation → fatigue, Pallor, Dyspnea, Angina
- Pathogenesis & functional Bcells produce IgG globulins against RBCs and will cause "Extravascular Hemolysis"

Autoimmune hemolytic Anemia (AIHA)

Slightly ↑ LDH, ↓ Haptoglobin, ↑ bilirubin

Direct Antibody Test (Coombs) ⊕ , (↑) Retic I > 2% , Normal MCV

Date: Sub:

4.) Thrombocytopenia → "PLT must be less than 100k"

↳ like in CLL → Presentation: Bleeding, Bruising

↳ like the autoimmune mechanism we have in Anemia, functional cells can produse IgG against platelets and destroy platelets in spleen

Immunogen Thrombocytopeni Purpurae (ITP) → Can't make any diagnosis

* Patient with CLL that appears AIHA + ITP → Evans Syndrome

5) Hypogammaglobulinemia

Abnormal B cells → Abnormal Plasma cells → Less functional Ab

X Complement fixation / Phagocytosis X

X neutralization X ADCC

Sinusitis, Bronchitis, Recurrent Infections

Treatment = IVIG + Antibiotics

5) Diagnostic Approach to Chronic Leukemia

Classical findings of CLS: 1) Fatigue and pallor (Anemia)

2) Easy Bruising and bleeding (Thrombocytopenia)

3) Frequent Infections and fevers (hypo γ globulins)

4) Lymphadenopathy + B Symptoms (CLL)

5) Hepatosplenomegaly (CML)

Next Page ↓

Smudge Cells: Ruptured, fragile Lymphocytes lacking a membrane

Date: Sub:

1st Step → Obtain CBC with Differential + Blood Smear

↑ WBC (>100k) + Anemia + Thrombocytopenia

Diff: Basophilia + Left Shift

Blood Smear: ↑↑ Granulocytes at Various Stages

→ DDx: Leukemoid Reaction → ↓↓ Left Shift

+ LAP Score: Low ←→ LAP: High

Step 2: Possible CML

<10% Myeloblast → CP CML

Bone marrow Biopsy

10-19% Myeloblast → AP CML

≥20% Myeloblast → BP CML

Step 3: Bone marrow Cytogenetics

(+) 9:22 + philadelphia

(+) BCR-ABL 1 gene

Ph(+) CML

↑ WBC (>100k) + Anemia + Thrombocytopenia

Diff: >5000 Lymphocytes/μL

Smear: ↑↑ mature Appearing lymphocytes + Smudge Cells

Possible CLL

Step 2: Peripheral Flow Cytometry

CD5, CD19, CD20, CD23 (+)

CLL

RAI Staging System for CLL

Stage	Modified RAI Stage	Findings
0	Low Risk	Isolated lymphocytosis
1	Intermediate Risk	lymphocytosis + Lymphadenopathy
2	〃	lymphocytosis + hepatosplenomegaly
3	High risk	lymphocytosis + Anemia Hb ≤ 10
4	〃	lymphocytosis + Thrombocytopenia Plt ≤ 100k

Date: Sub:

6) Treatment of CLL

a) Stable No Symptoms (RAI Stage 0/1/2) → Observation

b) Unstable / Symptomatic (RAI 1/2) → BTK Inhibitors (e.g. Ibrutinib)
(RAI 3/4 in Older patients) ↑

b') Unstable / Symptomatic (RAI 1/2) → Fludarabine + Rituximab + Cyclophosphamide
(RAI 3/4 in Young/Fit patients) ↑

c) Hematopoetic Stem cell Transplant → in Refractory CLL
Last option

7) Treatment of CML

Tyrosin kinase Inhibitors (Imatinib) → BCR-ABL CML (Any phase)

+ Hematopoetic Stem cell Transplant → Blast phase of CML
(↳ first TKI + Induction Chemotherapy prior)