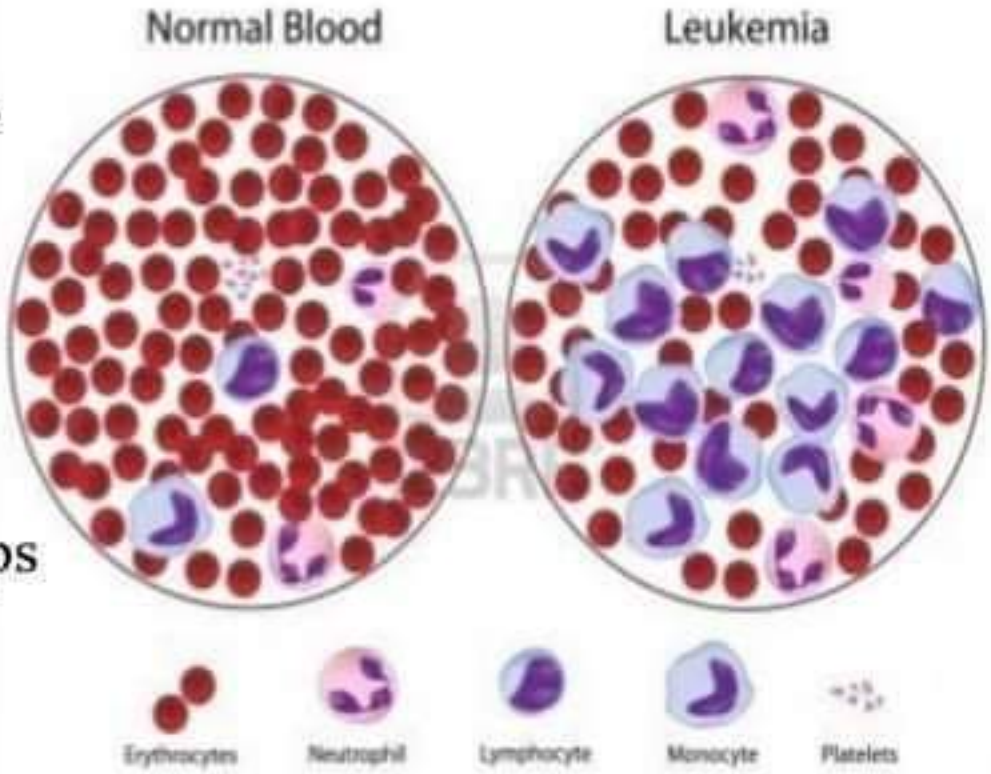
DEFINITION

Leukemia are a group of neoplastic disorders affecting mainly the leukopoietic tissues in the body and characterized by the presence of leukocytosis, immature leukocytes in the peripheral blood and proliferation of these immature cells in the bone marrow resulting in the suppression of normal tissue. The abnormal cells infiltrate several organs in the body.

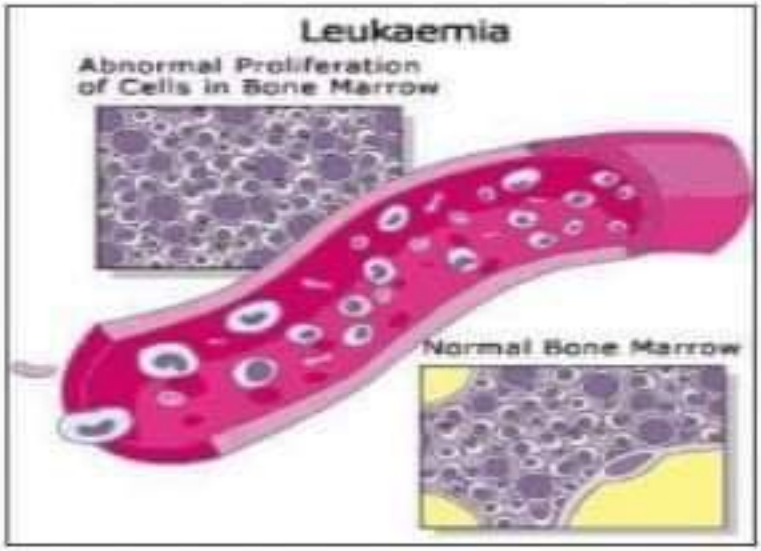
-K.V Krishna Das, Mathew Thomas

Leukemia

- A group of malignant disorders affecting the blood and blood-forming tissues of
  - Bone marrow
  - Lymph system
  - Spleen
- Occurs in all age groups



- Leukemia is a malignant disease characterized by unregulated proliferation of one cell type
- It may involve any of the cell lines or a stem cell common to several cell lines.



TYPES

- **Acute Leukemia**:
  - Affect younger age group frequently
  - Rapid course and the peripheral blood and bone marrow show the presence of large number of blast cells.
  - If left untreated, these are fatal within weeks/ months
- **Chronic Leukemia**:
  - Generally affect older people
  - onset is insidious
  - usually less aggressive
  - the cells involved are usually more mature cells
  - Terminate life within 2-3 yrs of onset.

Types....

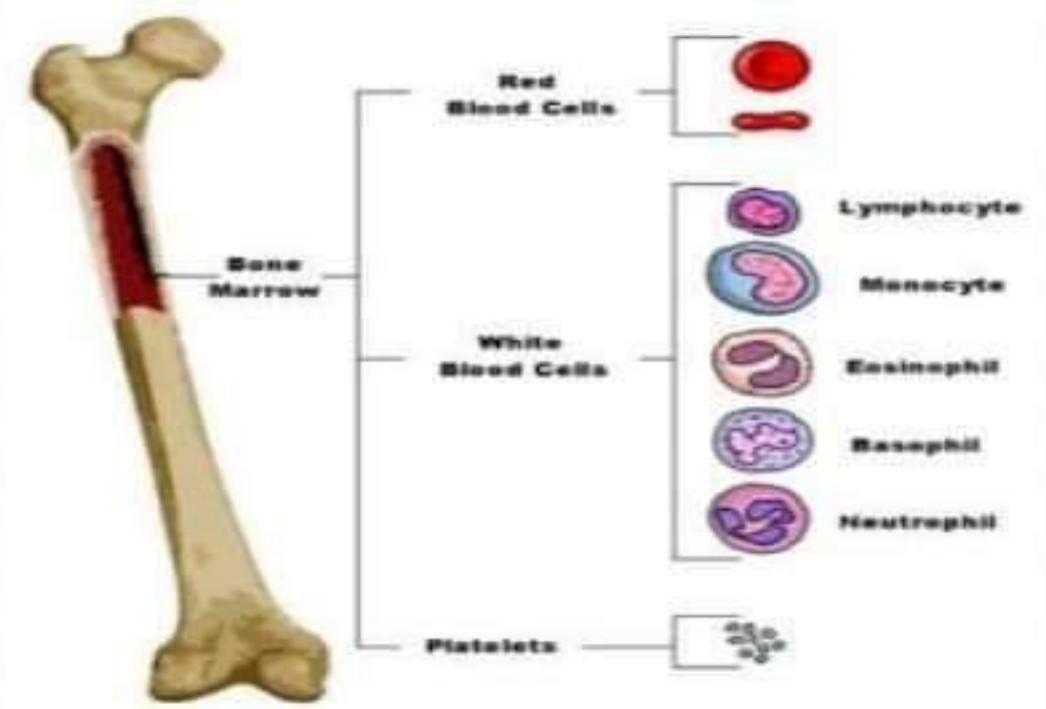
Both acute and chronic leukemias are further classified according to the prominent cell line involved in the expansion:

- If the prominent cell line is of the myeloid series it is a myelocytic leukemia (sometimes also called granulocytic)
- If the prominent cell line is of the lymphoid series it is a lymphocytic leukemia
- Therefore, there are four basic types of leukemia
  - Acute myelocytic leukemia – AML- (includes myeloblastic, promyelocytic, monocytic, myelomonocytic, erythrocytic, and megakaryocytic)
  - Acute lymphocytic leukemia – ALL- (includes T cell, B cell, and Null cell)
  - Chronic myelocytic leukemia – CML - (includes myelocytic and myelomonocytic)
  - Chronic lymphocytic leukemia – CLL - (includes plasmocytic {multiple myeloma}, Hairy cell, prolymphocytic, large granular cell lymphocytic, Sezary's syndrome, and circulating lymphoma)

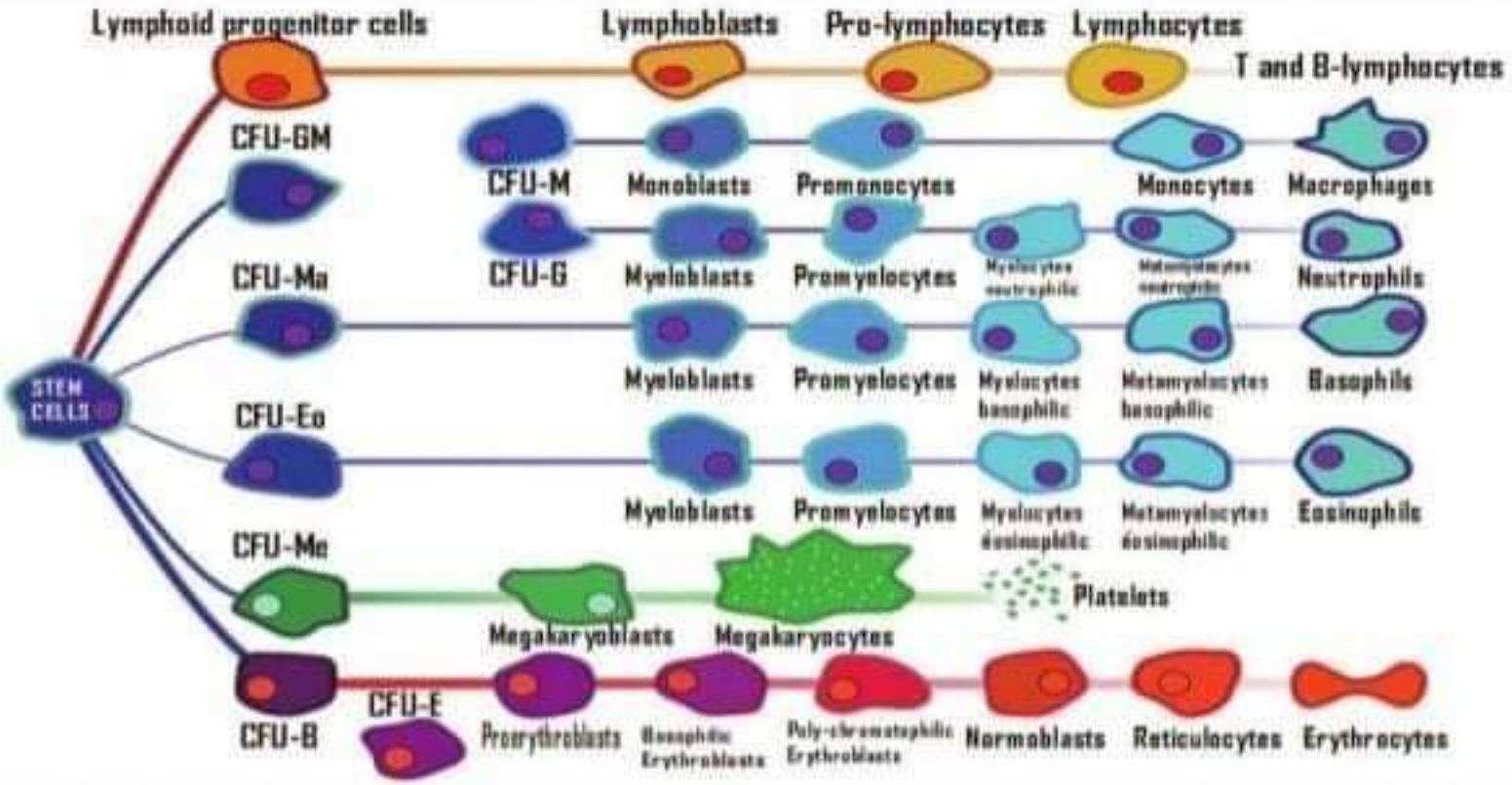
Etiology

- Genetic
- Radiation
- Toxic chemical exposure
- Medication (Alkylating-agents, Topoisomerase-II inibitors, Chloramphenicol, Phenylbutazone, Chloroquine)
- Primary immunodeficiency and infection
- malignancies

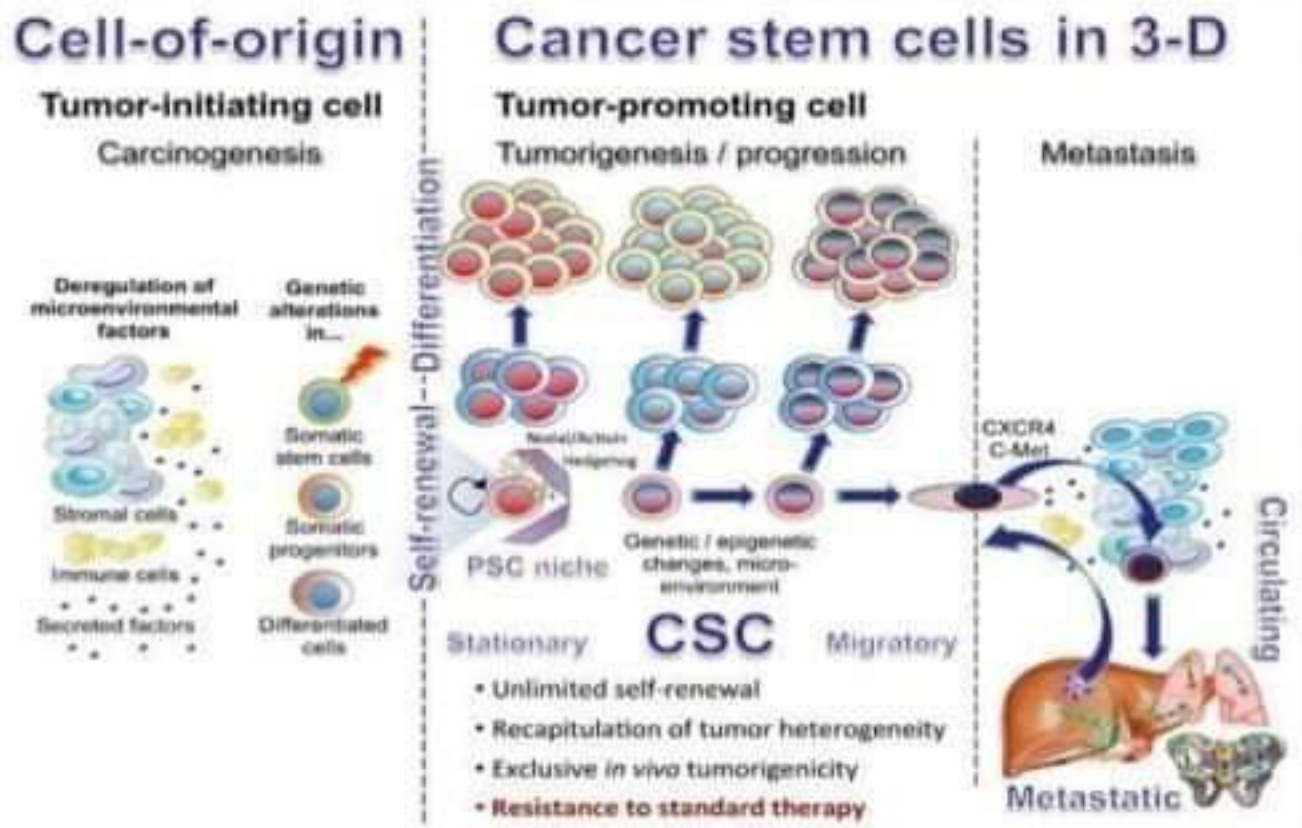
NORMAL HEMATOPOIESIS



NORMAL HEMATOPOIESIS



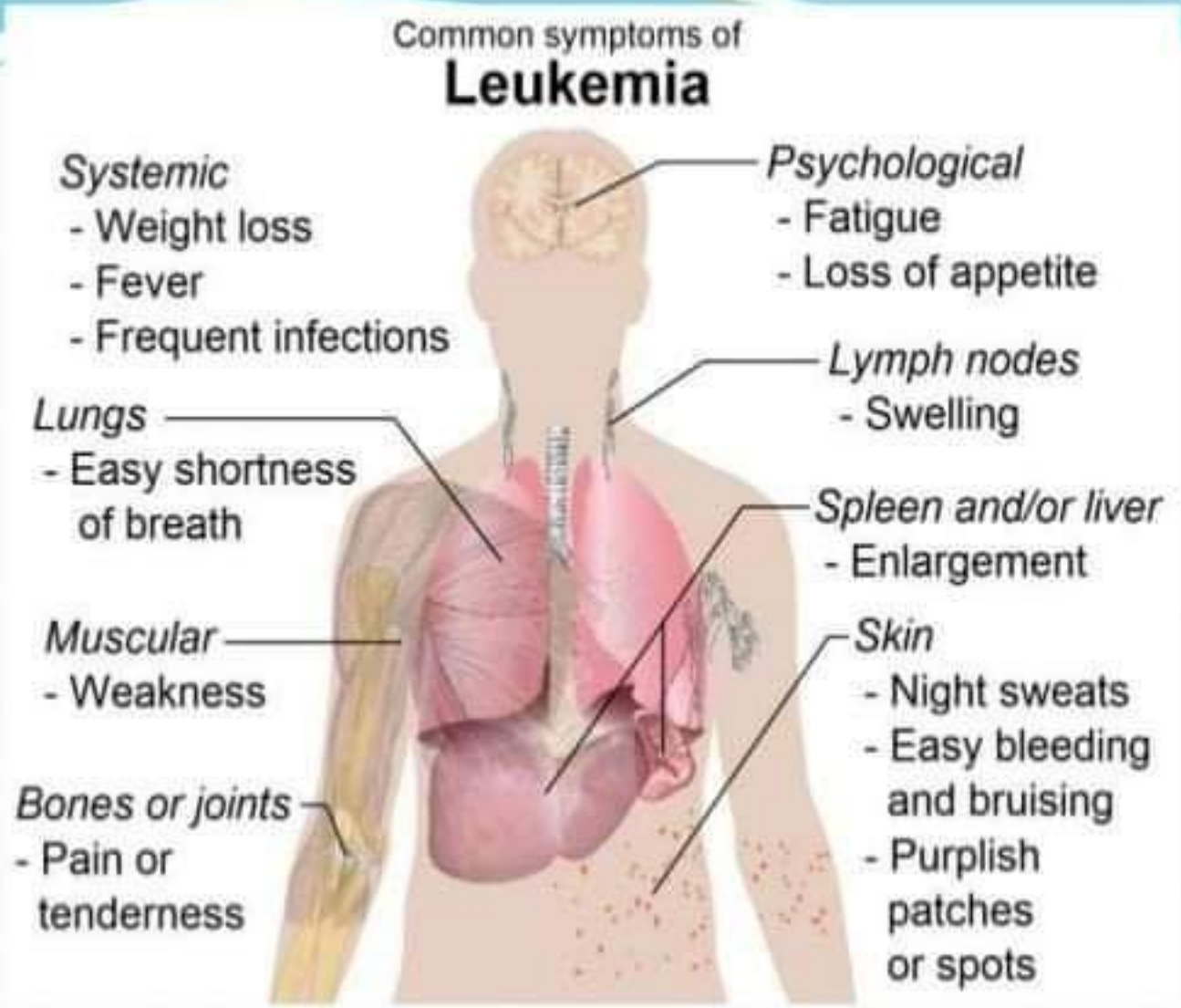
PATHOPHYSIOLOGY



- Acute leukemia –
  - Is a result of:
    - Malignant transformation of a stem cell leading to unregulated proliferation and
    - Arrest in maturation at the primitive blast stage. Remember that a blast is the most immature cell that can be recognized as committed to a particular cell line.
  - Clinical features
    - Leukemic proliferation, accumulation, and invasion of normal tissues, including the liver, spleen, lymph nodes, central nervous system, and skin, cause lesions ranging from rashes to tumors.
    - A humoral mediator from the leukemic cells may inhibit proliferation of normal cells.
  - Failure of the bone marrow and normal hematopoiesis may result in pancytopenia with death from hemorrhaging and infections.

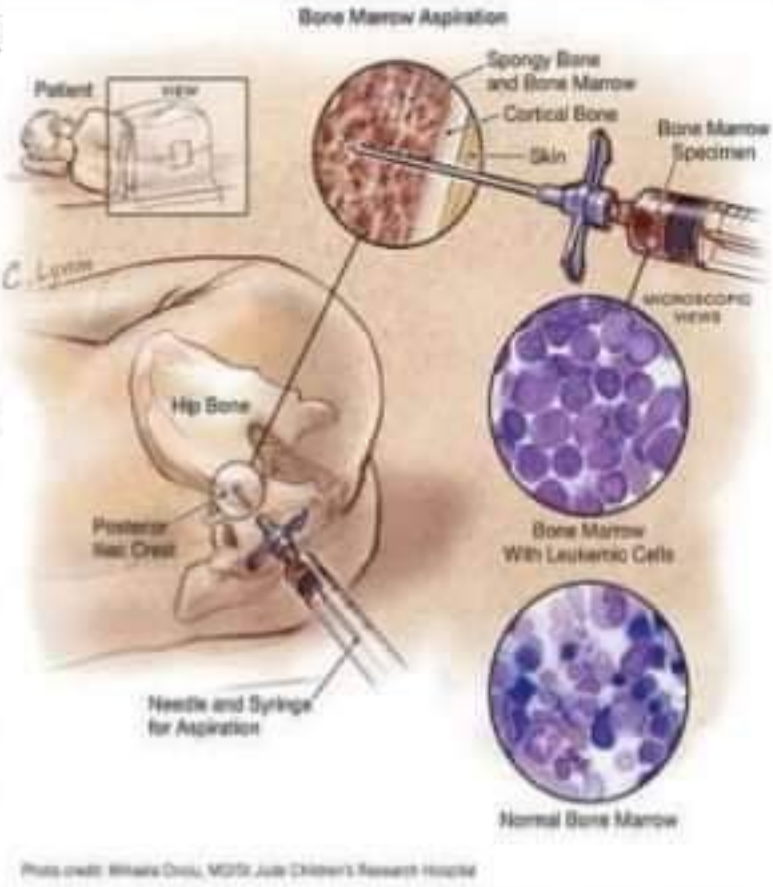
Difference between acute and chronic leukemia

	Acute leukemia	Chronic leukemia
Age	More in first and second decades but can occur in all age groups	Mostly in the 4th, 5th and 6th decades but even young children may be affected rarely
Sex ratio	M:F= 2:1	1:1
Duration of symptoms	Weeks to months	Several months to one year
Presenting complaints	Anemia, fever, infections, hemorrhagic tendencies or complications, especially neurological	Vague symptoms, loss of weight, mass in abdomen, or lymph nodular masses
Organomegaly	Liver, spleen, lymph nodes are moderately enlarged in 70-80% of cases	Moderate to gross splenomegaly is the rule in CML. Moderate to gross lymphadenopathy in CLL
Blood picture	WBC is moderately elevated (15-30×10⁹/L), Blast cells form 10-90% of total. Platelets are often reduced.	Elevated WBC(15-25×10⁹/L)
Bone marrow	Showa depression of erythroid cells, myeloid cellsand megakaryocytes and infiltration by the abnormal cells. Blast cells form more than 30% and may be even upto 90%	CML shows increase in myeloid cells especially myelocytes, metamyelocytes and neutrophils, infilteration by small lymphocytes is seen in CLL. Erythroid and megakaryocytic precursors show variable cellularity
Chromosomal studies	Different pattern for different subtypes	Ph chromosome present in 95% of cases
Course and prognosis	Untreated- fatal within weeks to 6 months due to infections, hemorrhage, anemia and other complications	Untreated- median survival of CML is 18-24 months.CLL has more prolonged survival
Response to treatment	Spontaneous remissions have rarely been reported. With modern treatments, over proportion of 90% of cases go into remission and 60-70% get complete cure.	BMT- cure rate> 50%


Common symptoms of
Leukemia
Systemic
- Weight loss
- Fever
- Frequent infections
Psychological
- Fatigue
- Loss of appetite
Lymph nodes
- Swelling
Lungs
- Easy shortness of breath
Spleen and/or liver
- Enlargement
Muscular
- Weakness
Skin
- Night sweats
- Easy bleeding and bruising
- Purplish patches or spots
Bones or joints
- Pain or tenderness

DIAGNOSIS OF LEUKEMIA

- History and physical examination
- Clinical features
- Blood Examination(work up)
- Peripheral blood examination
- Chest X ray
- Bone marrow studies: BM biopsy, imprint and aspiration.
- Flow cytometry
- Cytological differentiation and immunophenotyping: FISH, RTPCR, chromosome analysis



TREATMENT

- Goal is to attain remission (when there is no longer evidence of cancer cells in the body)
- Chemotherapeutic treatment
  - Induction therapy
    - Attempt to induce or bring remission
    - Seeks to destroy leukemic cells in the tissues, peripheral blood, bone marrow
    - Patient may become critically ill
      - Provide psychological support as well
  - Intensification therapy
    - High-dose therapy
    - May be given after induction therapy
    - Same drugs at higher doses and/or other drugs

TREATMENT……

- Chemotherapeutic treatment (cont.)
  - Consolidation therapy
    - Started after remission is achieved
    - Purpose is to eliminate remaining leukemic cells that may not be evident
  - Maintenance therapy
    - Lower doses of the same drug

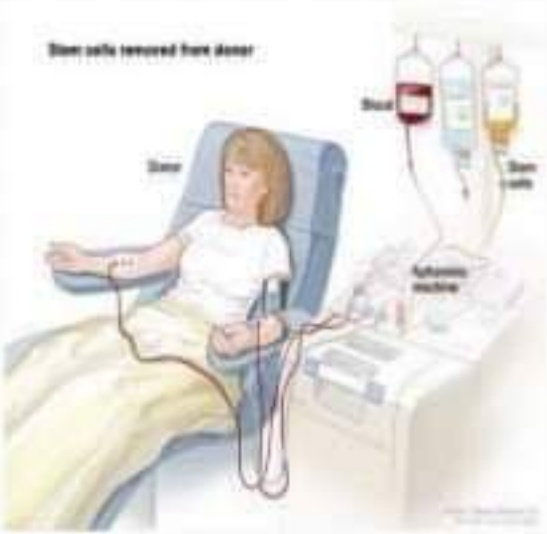
Leukemia

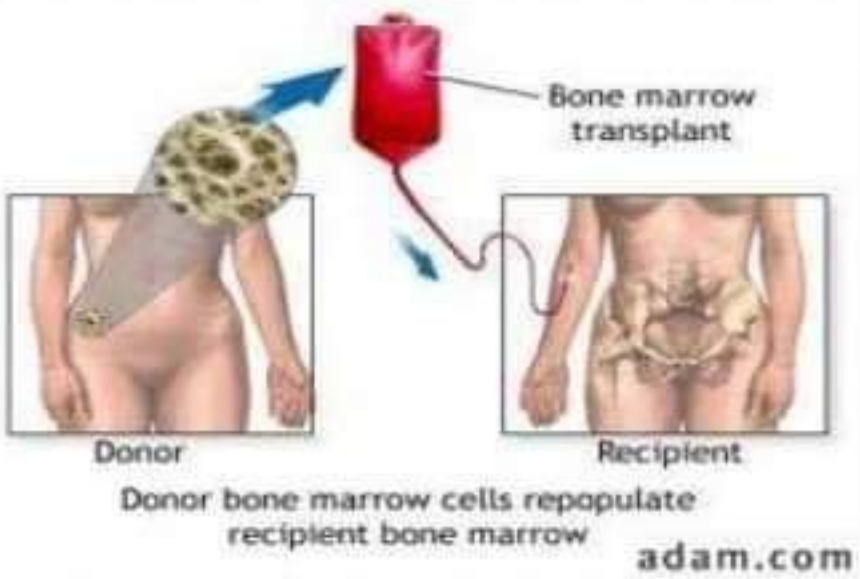
Chemotherapy Regimens

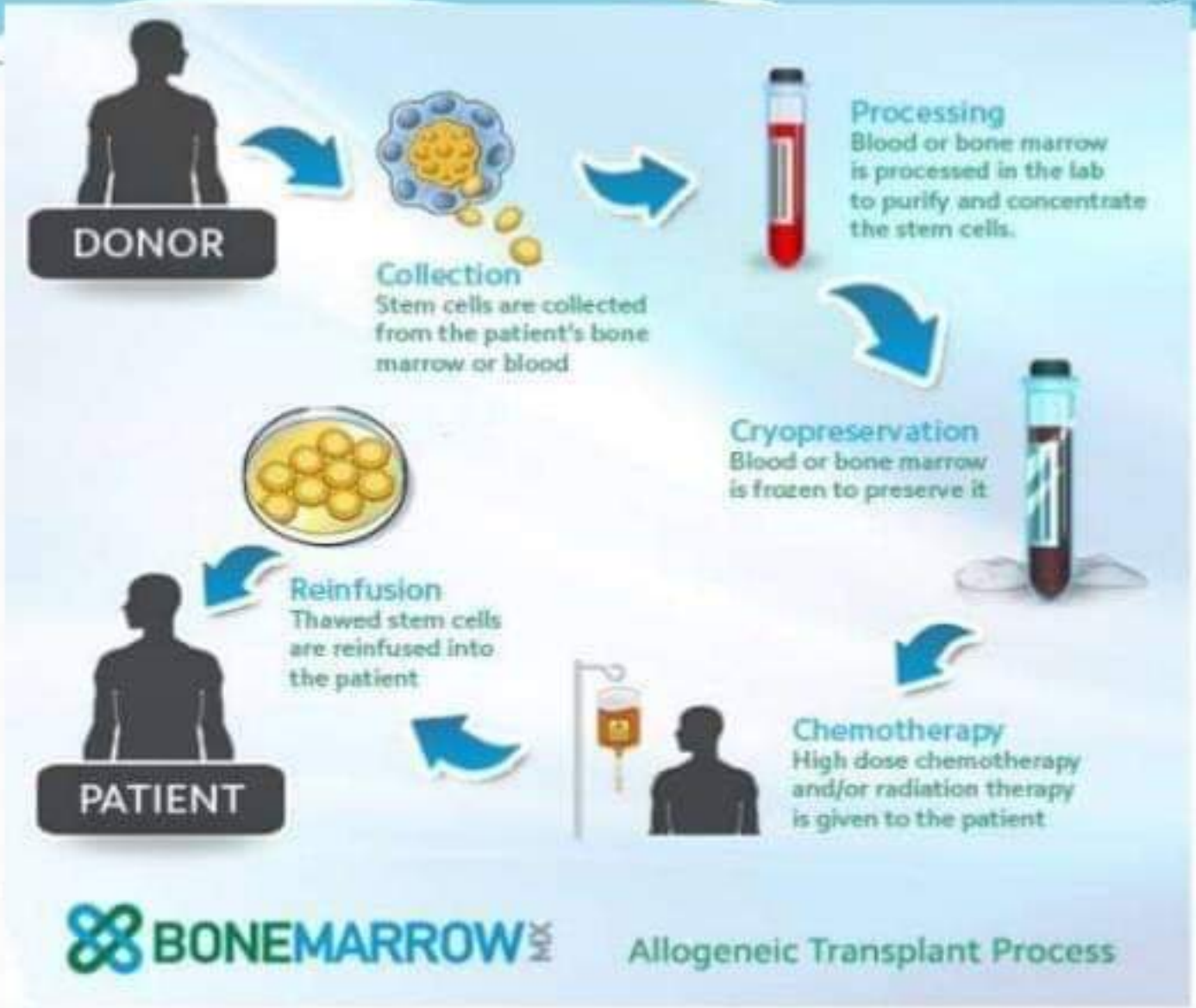
- Combination chemotherapy
  - Mainstay treatment
  - 3 purposes
    - ↓ drug resistance
    - ↓ drug toxicity to the patient by using multiple drugs with varying toxicities
    - Interrupt cell growth at multiple points in the cell cycle

Leukemia - *Bone Marrow and Stem Cell Transplantation*

- Goal
  - Totally eliminate leukemic cells from the body using combinations of chemotherapy with or without total body irradiation



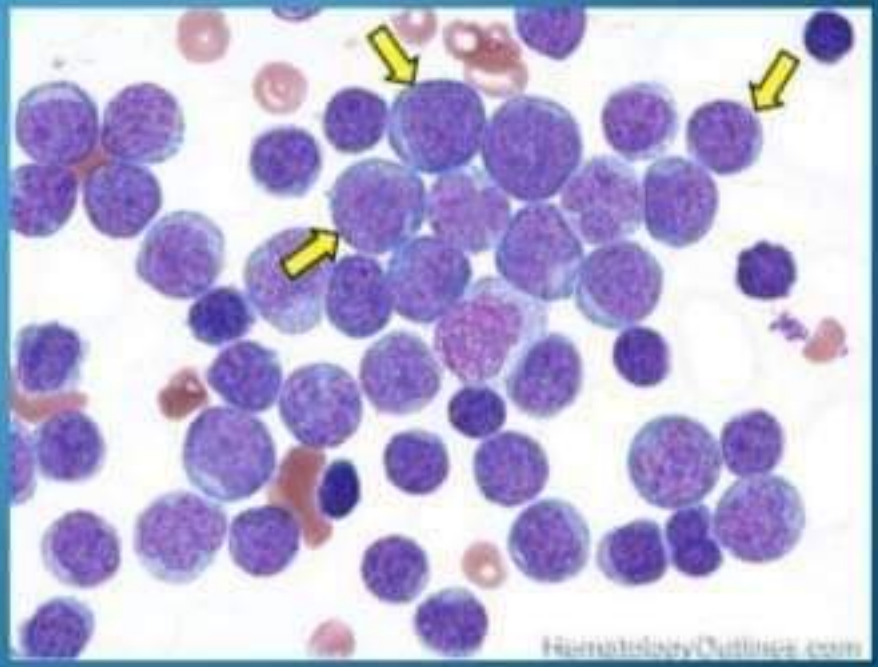



DONOR
Collection
Stem cells are collected from the patient's bone marrow or blood
Processing
Blood or bone marrow is processed in the lab to purify and concentrate the stem cells.
Cryopreservation
Blood or bone marrow is frozen to preserve it
Chemotherapy
High dose chemotherapy and/or radiation therapy is given to the patient
Reinfusion
Thawed stem cells are reinfused into the patient
PATIENT
BONEMARROW MX
Allogeneic Transplant Process

LYMPHOID MALIGNANCIES

ACUTE LYMPHOBLASTC LEUKEMIA (ALL)

- Most common in children
- Arises from lymphoid tissue
- About 75% are null cell type, 20-25% are T cell type and few are B cell type.
- Bimodal distribution
- Male:female= 2:1



ETIOLOGY

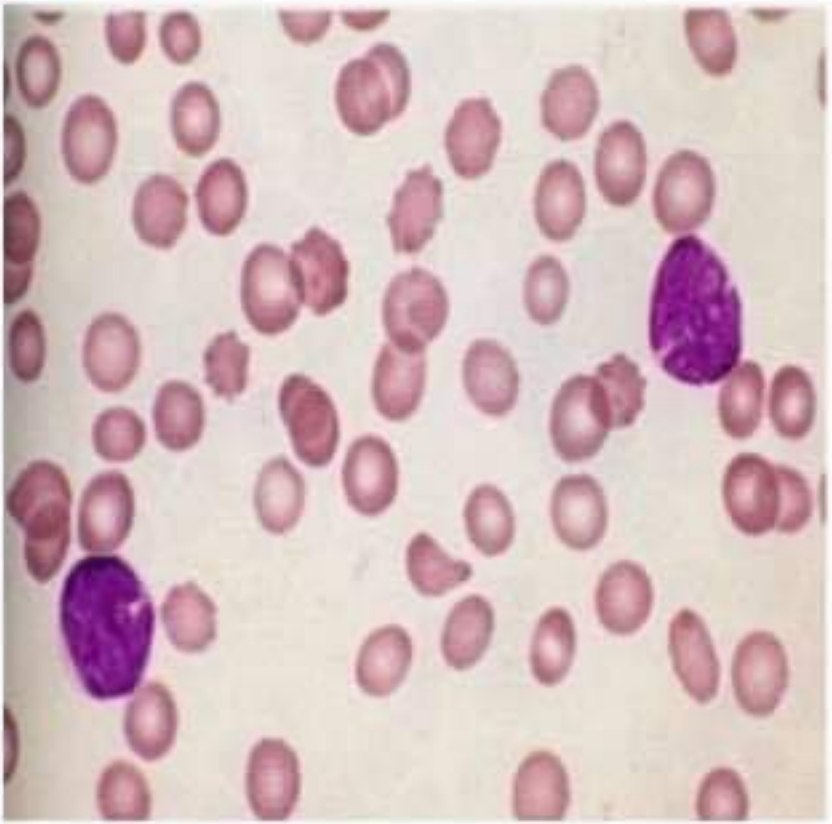
- **Uncertain, but several proposed linkages:**
  - Genetic - Philadelphia chromosome
  - Viral infection (EBV, HIV)
  - Exposure to high energy radiation (T-cell ALL)
  - Toxic chemical exposure
  - Smoking

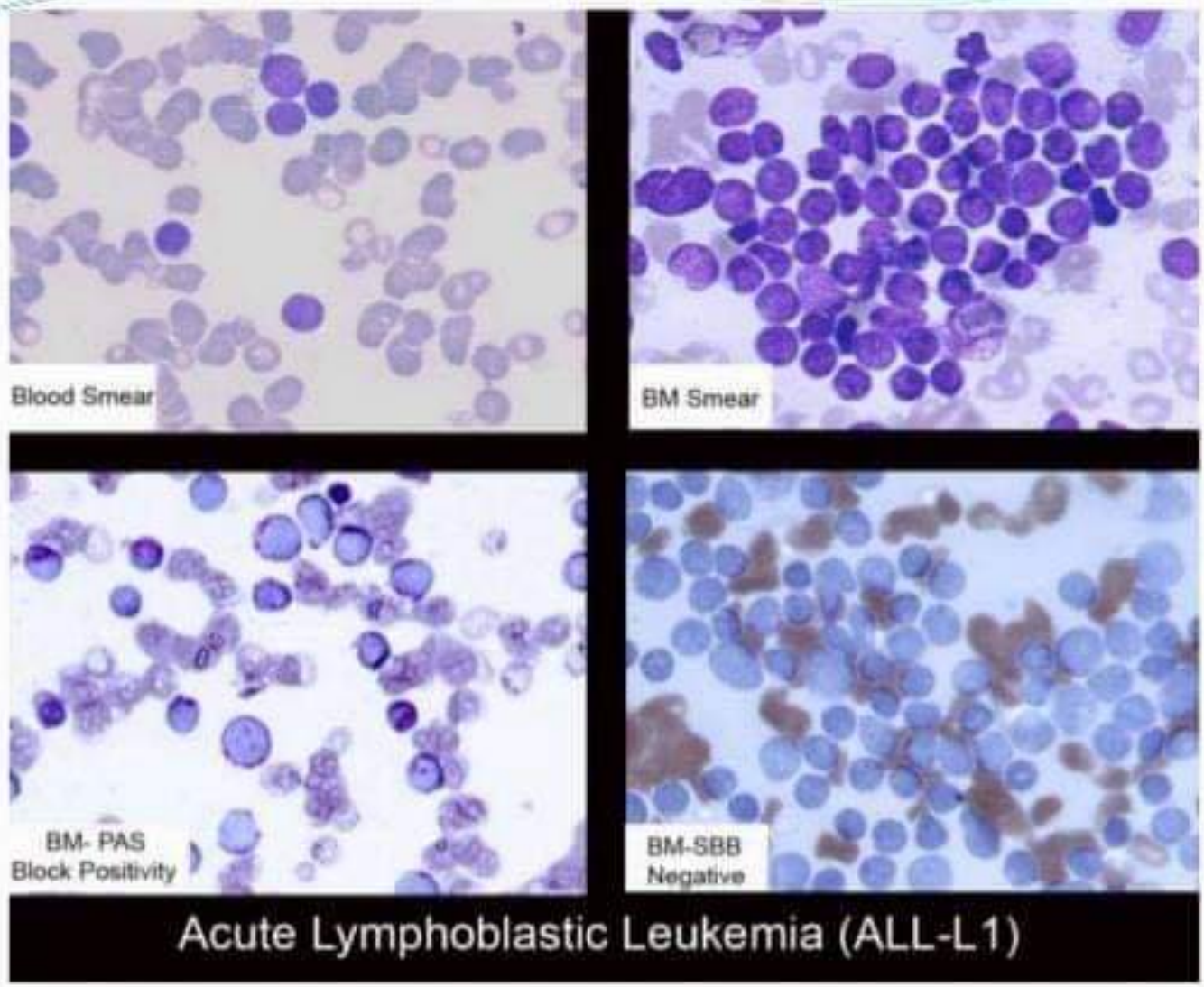
CLASSIFICATION

Immunologic Subtype	% of Cases	FAB Subtype	Cytogenetic Abnormalities
Pre-B ALL	75	L1, L2	t(9;22), t(4;11), t(1;19)
T cell ALL	20	L1, L2	14q11 or 7q34
B cell ALL	5	L3	t(8;14), t(8;22), t(2;8)

Acute leukemias- L1

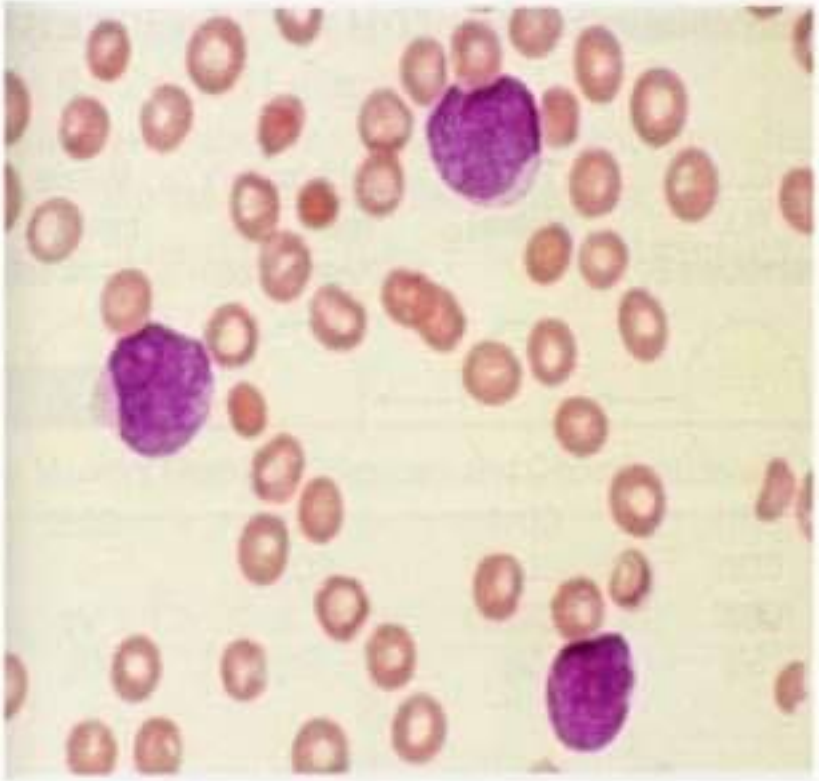
- L1 - This is the most common form found in children and it has the best prognosis.
  - The cell size is small with fine or clumped homogenous nuclear chromatin and absent or indistinct nucleoli.
  - The nuclear shape is regular, occasionally clefting or indented.
  - The cytoplasm is scant, with slight to moderate basophilia and variable vacuoles.

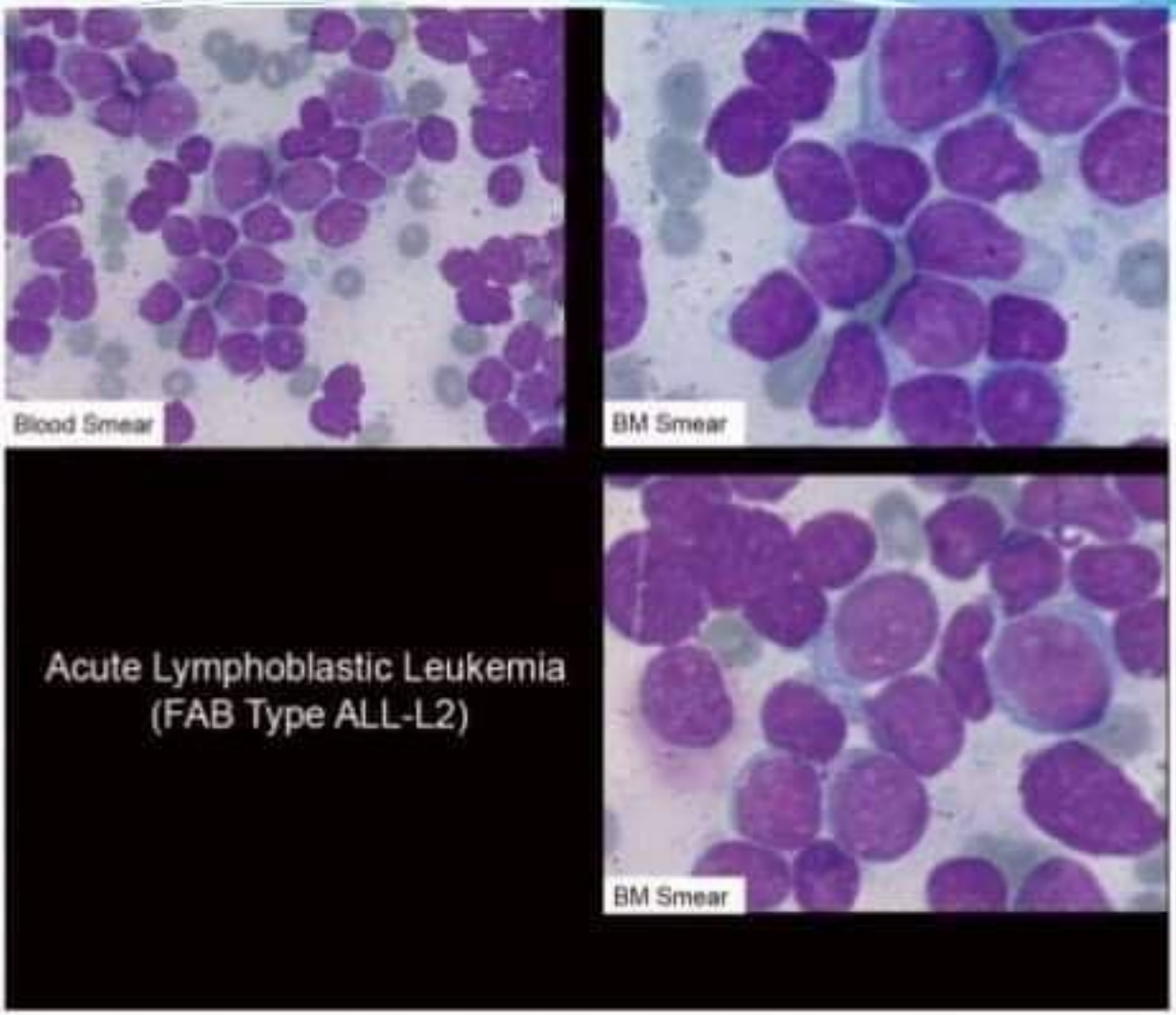



Blood Smear
BM Smear
BM- PAS
Block Positivity
BM-SBB
Negative
Acute Lymphoblastic Leukemia (ALL-L1)

Acute leukemias- L2

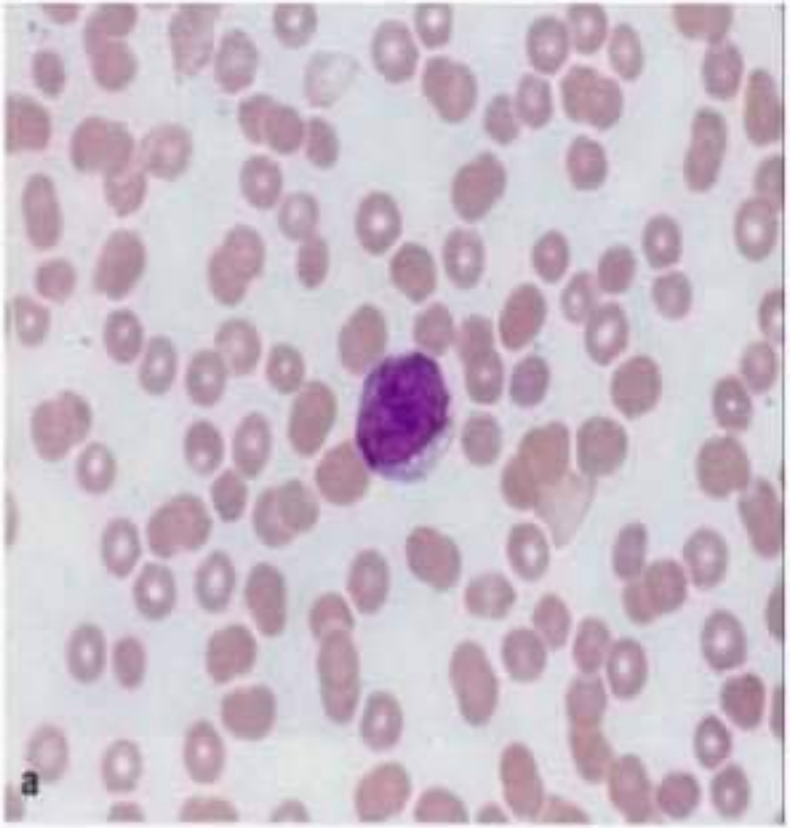
- L2 – This is the most frequent ALL found in adults.
  - The cell size is large and heterogenous with variable nuclear chromatin and prominent nucleoli.
  - The nucleus is irregular, clefting and indented.
  - The cytoplasm is variable and often moderate to abundant with variable basophilia and variable vacuoles.

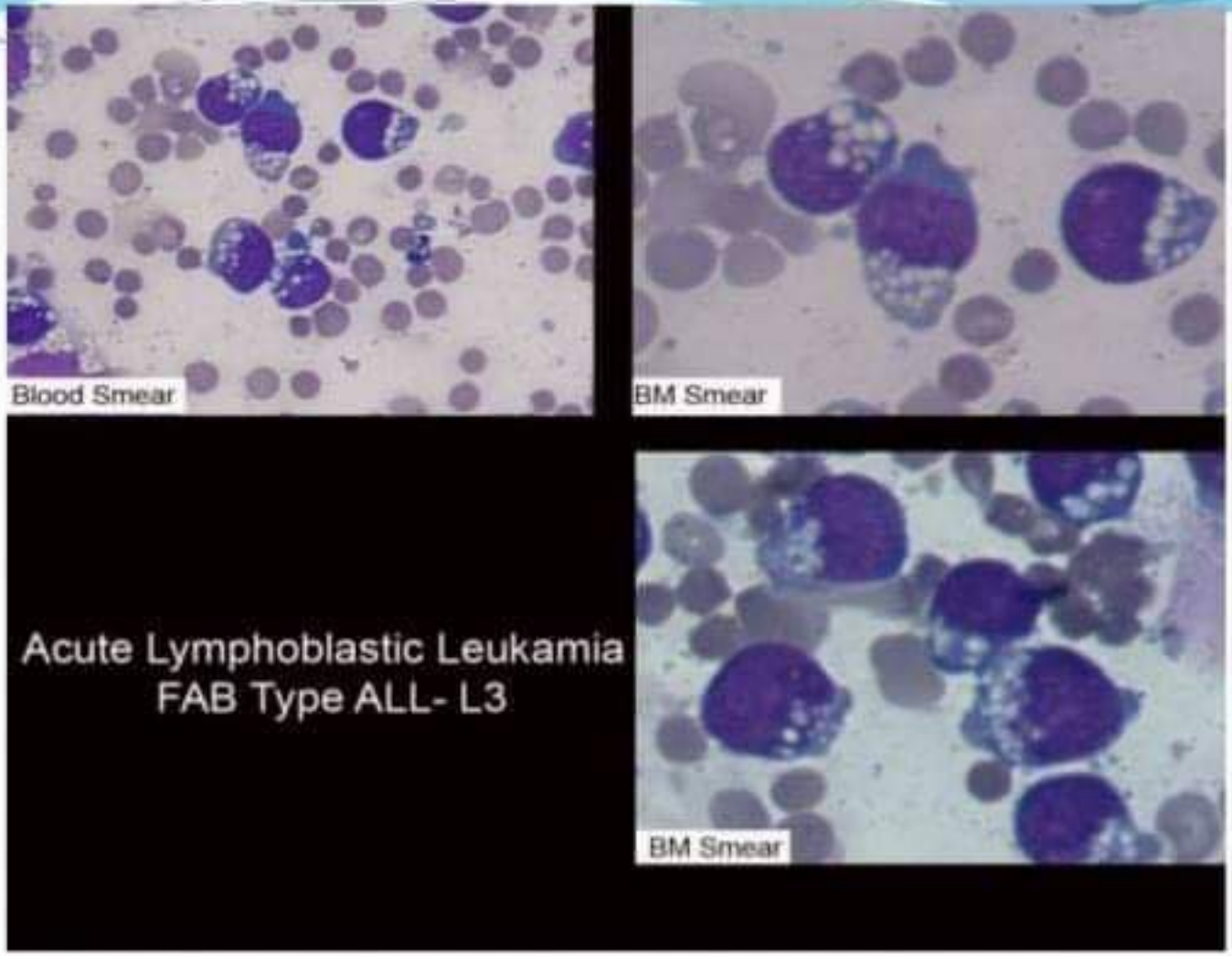



Blood Smear
BM Smear
Acute Lymphoblastic Leukemia
(FAB Type ALL-L2)
BM Smear

Acute leukemias-L3 (BURKITT'S LEUKEMIA)

- L3 – This is the rarest form of ALL.
  - The cell size is large, with fine, homogenous nuclear chromatin containing prominent nucleoli.
  - The nucleus is regular oval to round.
  - The cytoplasm is moderately abundant and is deeply basophilic and vacuolated.

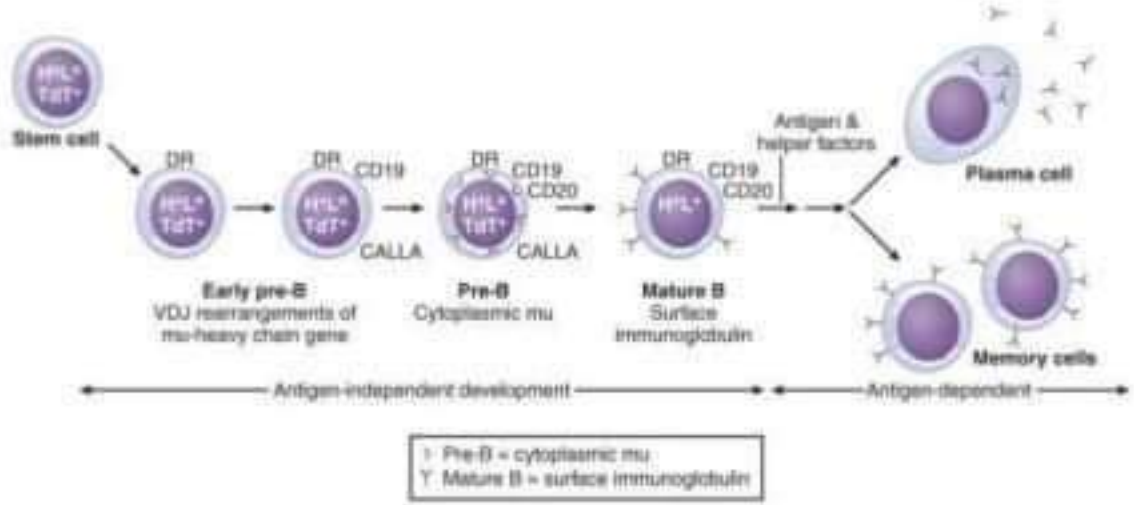



Blood Smear
BM Smear
Acute Lymphoblastic Leukamia
FAB Type ALL- L3
BM Smear

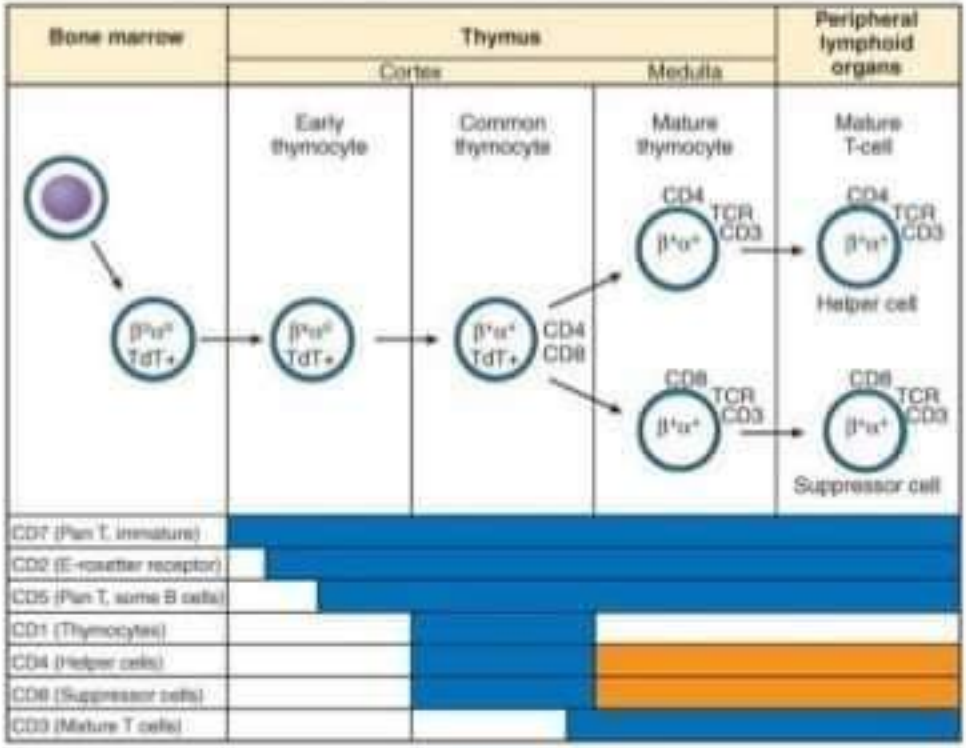
ALL

- ALL may also be classified on the basis of immunologic markers into:
  - Early pre-B ALL
  - Pre-B ALL
  - B ALL
  - T ALL
  - Null or unclassified ALL (U ALL) - lack B or T markers and may be the committed lymphoid stem cell)

B cell maturation

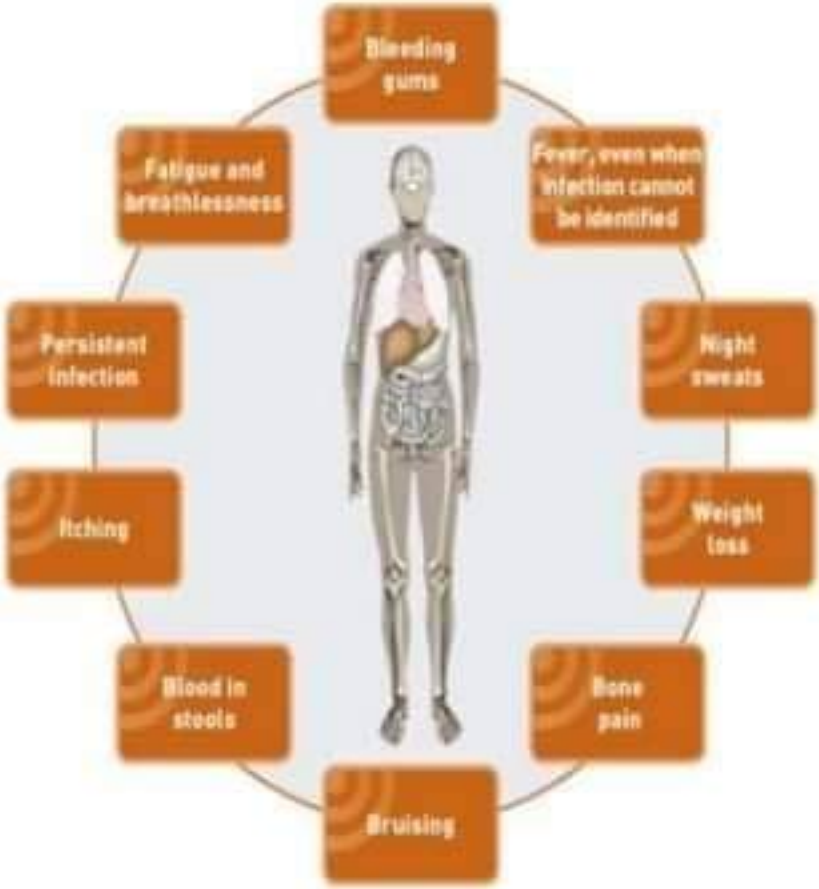


T cell maturation



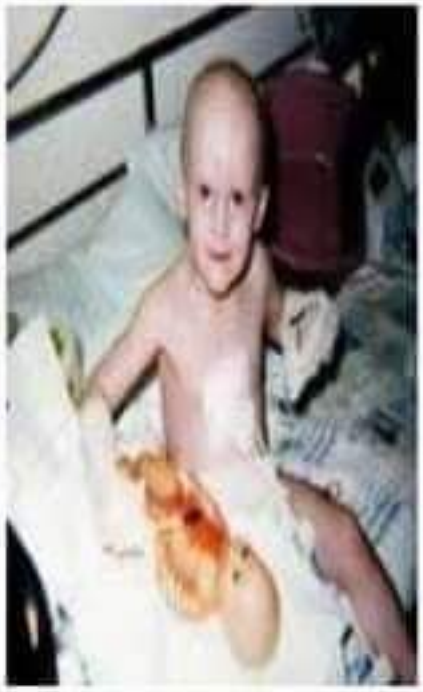
CLINICAL FEATURES

- Bone Marrow Depression (Anemia, neutropenia, thrombocytopenia)
- Fever
- head ache and pappiledema
- Pallor
- Lymphadenopathy
- Bleeding tendencies



CLINICAL FEATURES.....

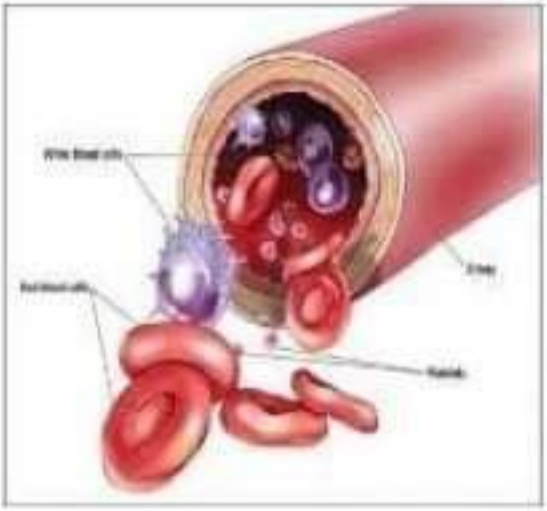
- Malaise, fatigue
- Bony pain
- Anorexia.
- Moderate lymphadenopathy
- Mild spleenomegaly
- Bone involvement
- Neurological involvement.
- Arthralgia, arthritis
- Ophthalmic involvement



DIAGNOSTIC MEASURES

- Complete Blood Count
- Peripheral Smear.
- Bone Marrow
- BM biopsy
- Cytogenetic analysis and flow cytometry
- CSF analysis

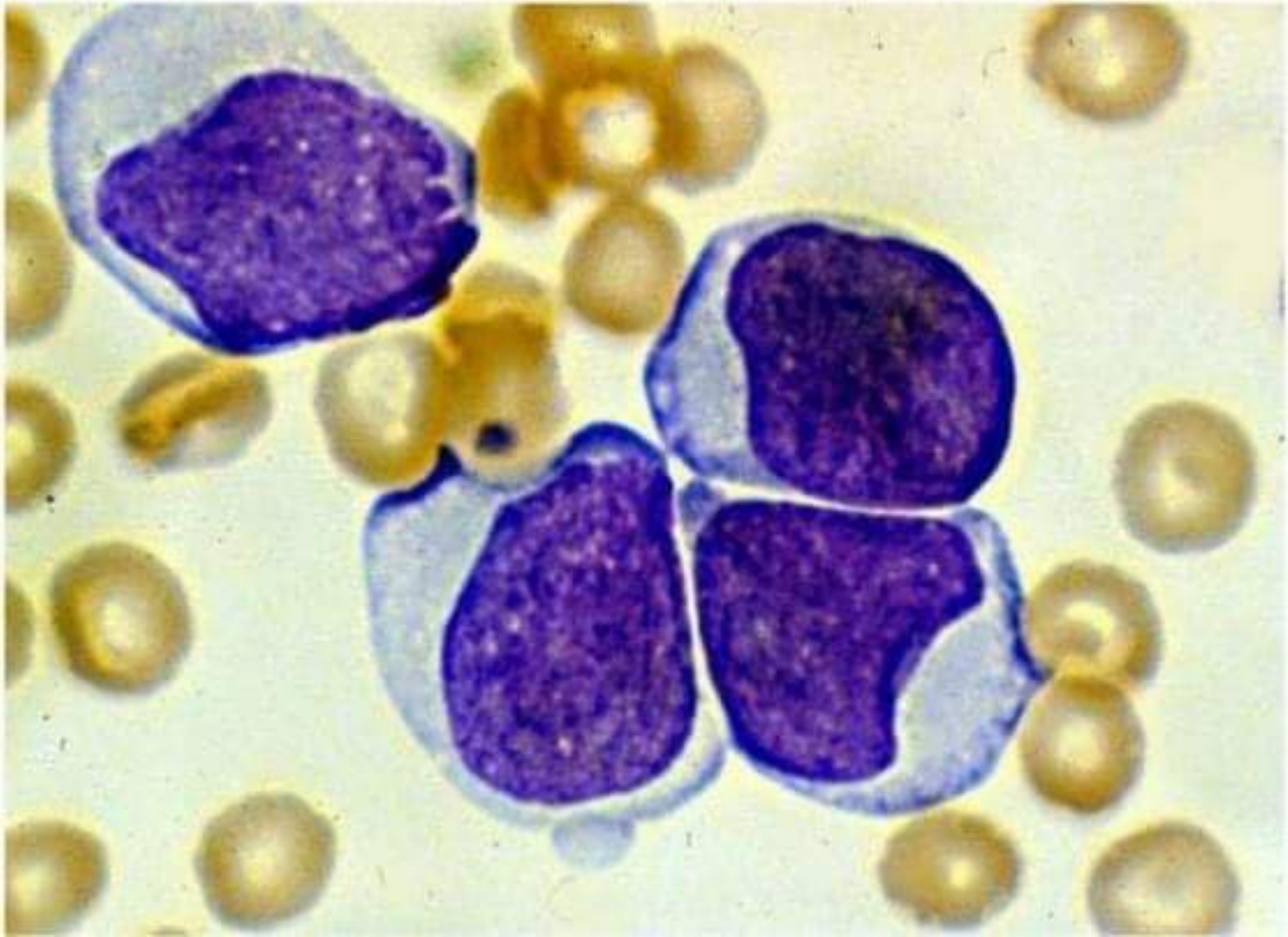
ACUTE LYMPHOCYTIC LEUKEMIA



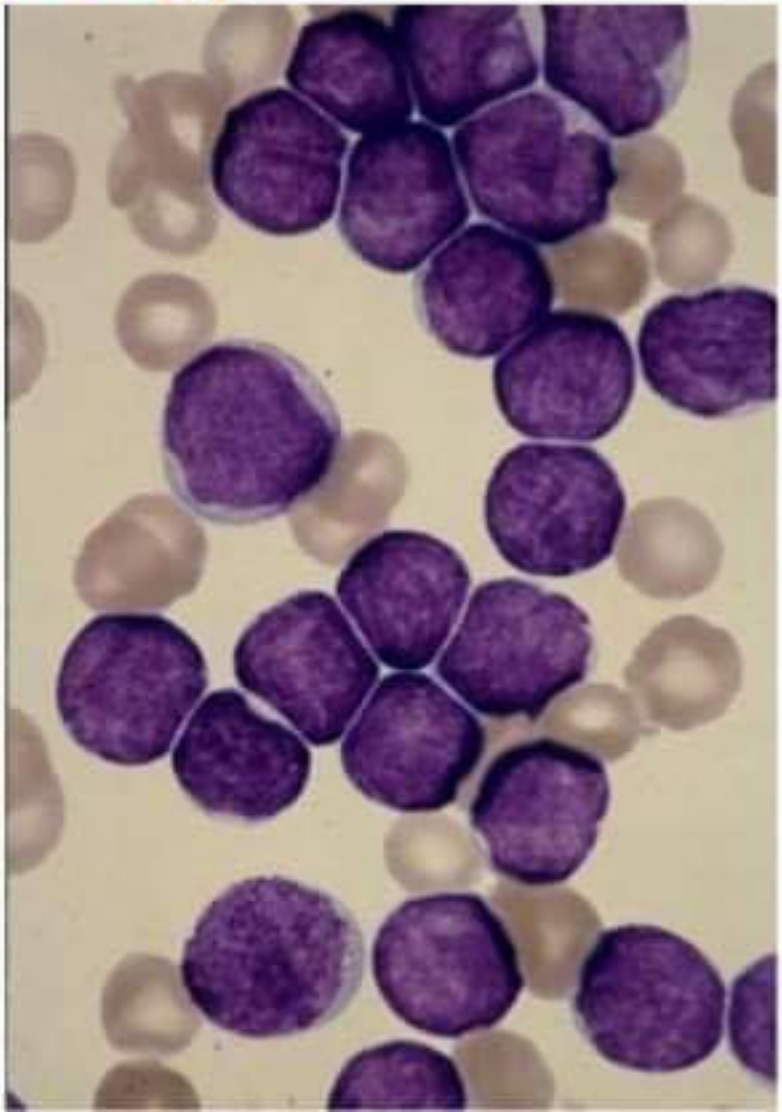
Hematological Findings:

- Anemia (normochromic, normocytic)
- WBC < 5,000 (or > 25,000)
- Leukocytosis (median = 15,000)
- Thrombocytopenia (< 50,000)

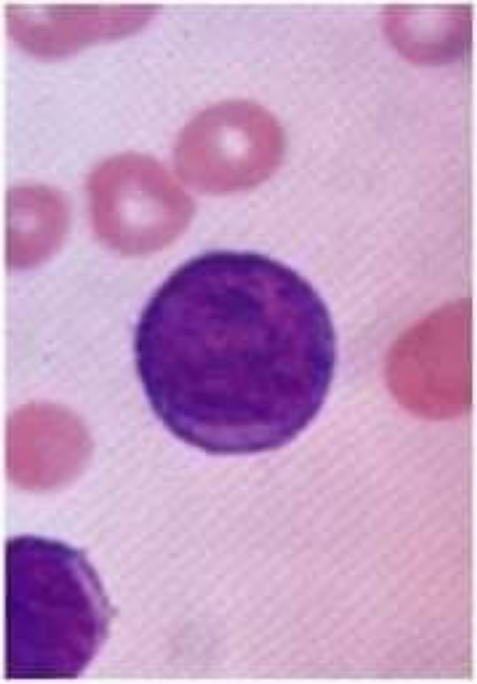
ALL Histology



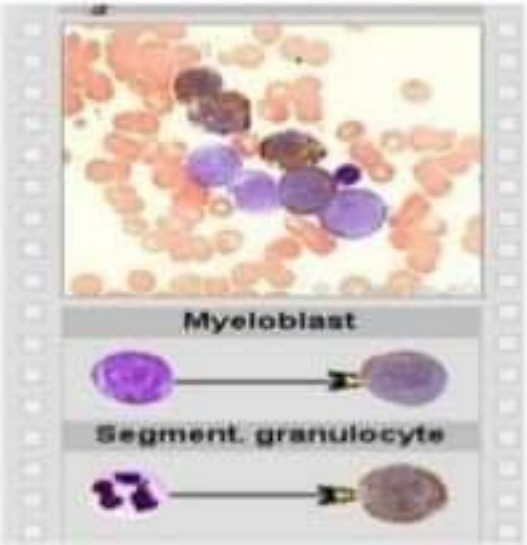
ALL Histology



- ALL – in contrast to the myeloblast, the lymphoblast is a small blast with scant cytoplasm, dense chromatin, indistinct nucleoli, and no auer rods

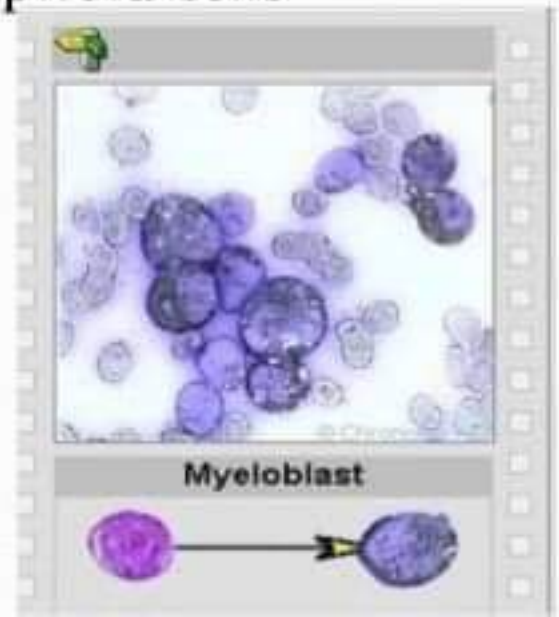


- Cytochemistry – help to classify the lineage of a leukemic cell (myeloid versus lymphoid)
  - Myeloperoxidase – is found in the primary granules of granulocytic cells starting at the late blast stage. Monocytes may be weakly positive.



Sudan black

- Sudan black stains phospholipids, neutral fats and sterols found in primary and secondary granules of granulocytic cells and to a lesser extent in monocytic lysosomes. Rare positives occur in lymphoid cells



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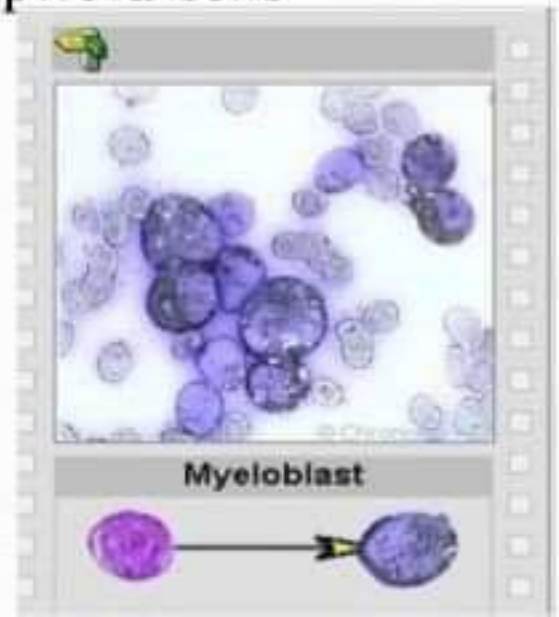
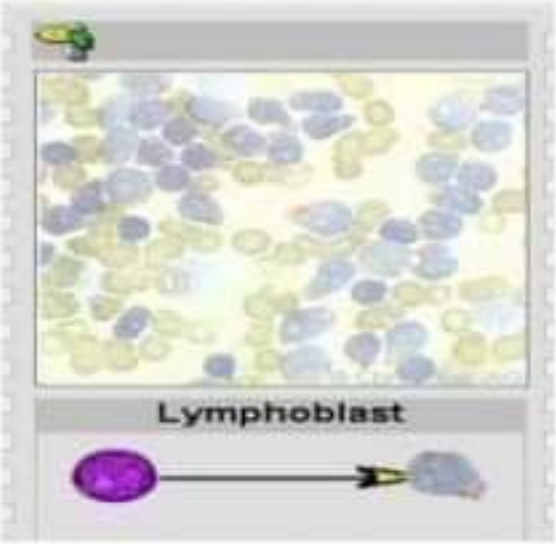


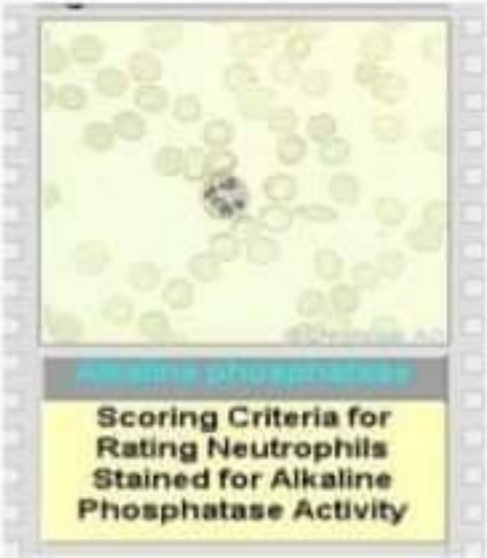
Acid phosphatase

- Acid phosphatase may be found in myeloblasts and lymphoblasts. T lymphocytes have a high level of acid phosphatase and this can be used to help make a diagnosis of acute T-lymphocytic leukemia.



Leukocyte Alkaline phosphatase

- Leukocyte alkaline phosphatase – is located in the secondary granules of segmented neutrophils, bands and metamyelocytes. The LAP score is determined by counting 100 mature neutrophils and bands. Each cell is graded from 0 to 5. The total LAP score is calculated by adding up the scores for each cell.

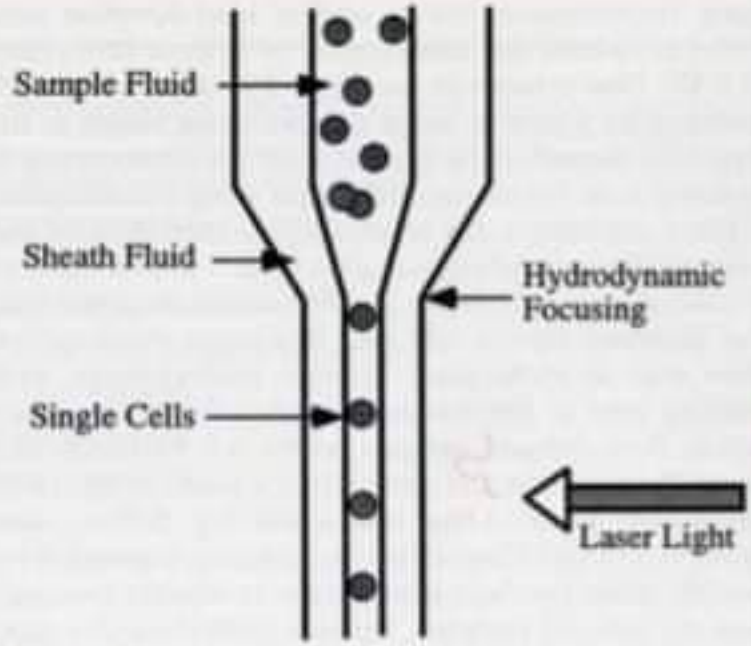


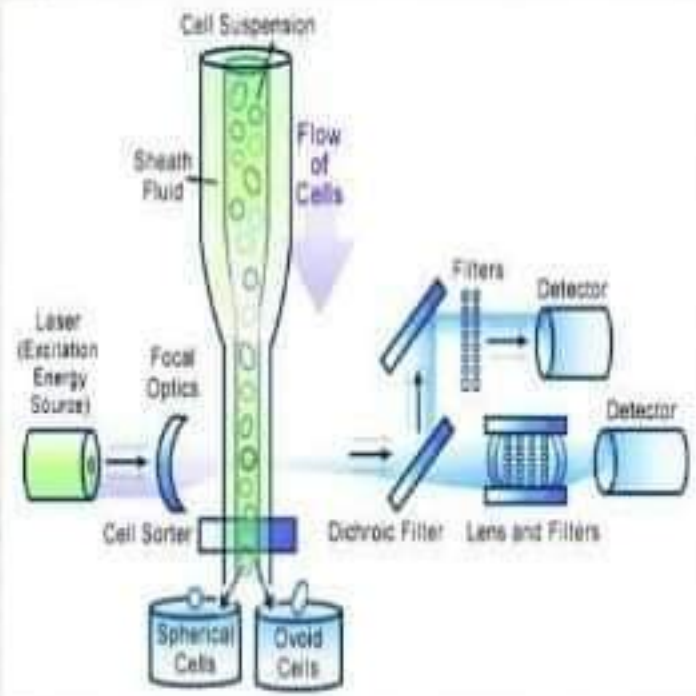
Leukocyte alkaline phosphatase

ALKALINE PHOSPHATASE - Criteria for rating activity			
Intensity step	Intensity of reaction	Normal values	Intensity of staining
0	Negative	80% neutrophilic granulocytes	No reaction.
1	Little positive	18% neutrophilic granulocytes	Single to few granules.
2			Many granules localized.
3	Grand positive	1% neutrophilic granulocytes	Granules diffuse distributed.
4			Cell complete with granules overcast.
5			Maximum number of granules, nucleus frequently no longer visible.

- Immunologic markers (immunophenotyping) – these are used mainly for lymphocytes, i.e., for determining B cell or T cell lineage. These tests rely on antibodies made against specific surface markers.
  - They constitute what we would call the primary antibody and in an indirect assay they are allowed to react with the cells and unbound antibody is then washed away.
  - Fluorescently labeled antibody (secondary antibody) against the primary antibody is added and allowed to react and then unbound secondary antibody is washed away.
  - The cells are then sent through a flow cytometer that will determine the number of cells that have a fluorescent tag and which are thus positive for the presence of the surface marker to which the primary antibody was made.
  - In a direct assay, the primary antibody is fluorescently labeled.

Flow cytometer





■ FIGURE 23-1 Flow chamber. The sample fluid, containing a suspension of single cells, is injected into a stream of sheath fluid. The stream is narrowed and directed through the laser beam (hydrodynamic focusing).

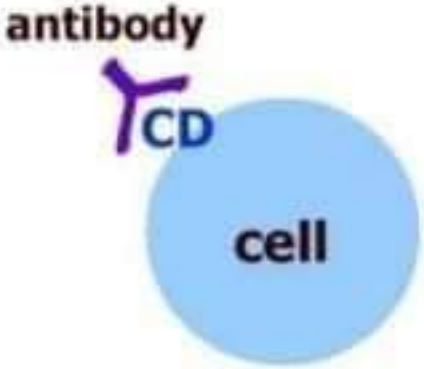
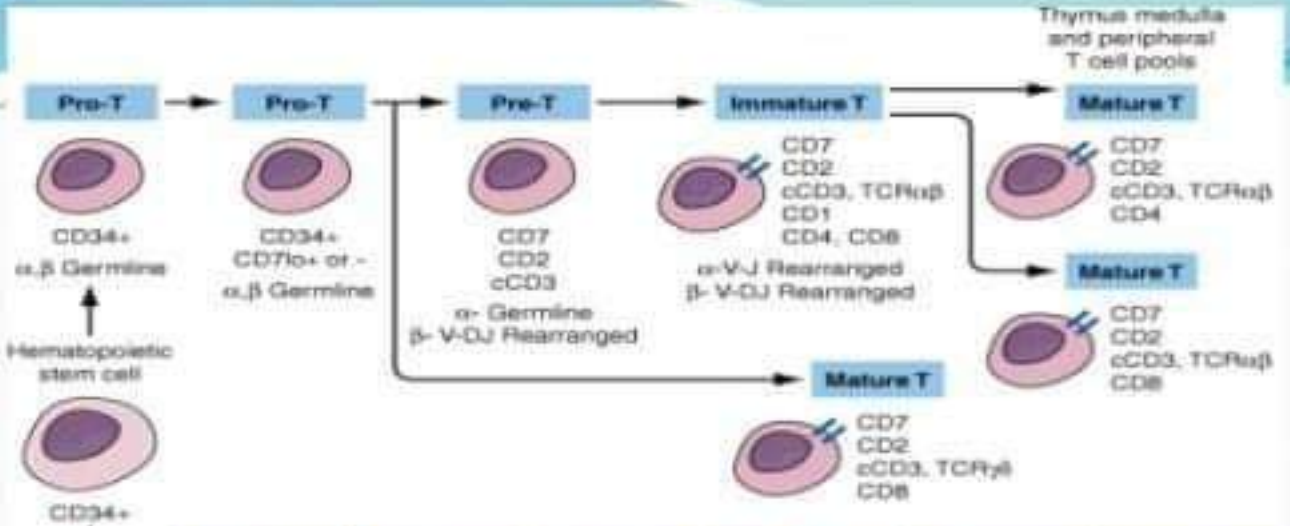


Table 1 : Flow cytometry and common CD markers

All lymphoid cells :	CD45+ (LCA)
Myeloid cells :	Anti-MPO, CD13, CD33, CD14, CD117
Megakaryocytic marker :	CD41, CD42, CD61
B-cells :	cCD22, CD22,, CD19, CD20, FMC7, CD23, CD79a, CD79b, CD10, Smlg, IgM
T-cells :	cCD3, CD3, CD2, CD5, CD7, CD4 or CD8, TCR-a/b, TCR-g/d
NK cells :	CD16, CD56,, CD57
Plasma cells :	CD38, CD138, kappa and lambda light chains
Blasts :	CD34, TdT
Others :	HLA-DR, cyclin D1, CD55, CD59, glycophorin A

Immunophenotype Panel:	Test Code:	Markers Performed:
Mature Leukemia/Lymphoma, Probably B-cell	BCELL	CD3, 5, 10, 11c, 19, 20, 23, 38, 45, Kappa & Lambda
Mature Leukemia/Lymphoma, Probably T-cell	TCELL	CD2, 3, 4, 5, 7, 8, 16+56, 25, 26, 45, 56 & 57
B Cell Clonality Only	SHORTBCELL	CD5, 19, 23, 45, Kappa & Lambda
Acute Lymphoblastic or Myeloid Leukemia	ACUTE	CD2, 3, 5, 7, 10, 11b, 13, 14, 15, 16, 19, 20, 33, 34, 45, 56, 61, 117, 235a & HLA-Dr
Plasma Cell/Myeloma	MYELOMA	CD19, 56, 45, 38, cytoKappa & cytoLambda
Hairy Cell Leukemia	HAIRYCELL	CD3, 5, 10, 11c, 19, 20, 22, 23, 25, 38, 45, 103, Kappa & Lambda
Sezary Staging	SEZ	CD3, 4, 7, 8, 26 & 45
Acute Leukemia in cerebrospinal fluid	ACUTECSF	CD19, 13+33, 34, 45, cytoTdT & cytoCD3
Fluid T Cell Subsets (Bronchoalveolar or other non-blood fluids)	BAL348	CD3, 4, 8, 45



High-chain genes	DJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged	VDJ rearranged
Low-chain genes	Germ line	Germ line	Germ line	VDJ rearranged	VDJ rearranged	VDJ rearranged
Surface Ig	Absent	Absent	μ H-chain at surface as part of pre-B receptor	μ H-chain in cytoplasm and at surface	IgM expressed on cell surface	IgD and IgM made from alternatively spliced H-chain transcripts
Surface marker proteins	CD34 CD10 CD19 CD38	CD10 CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD38 CD40	CD19 CD20 CD40	CD19 CD20 CD21 CD40

Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

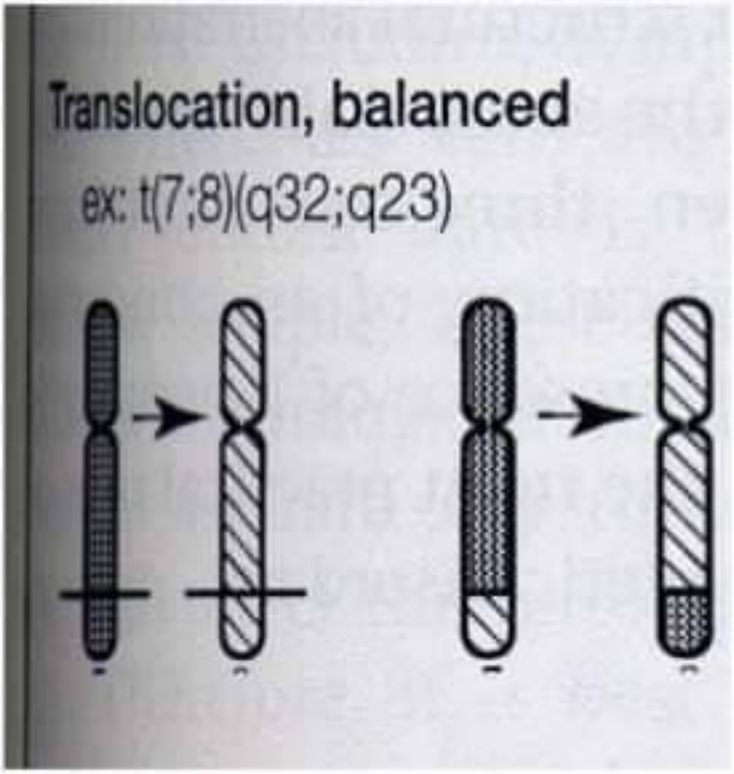
Terminal deoyxtidyl transferase

- This is a unique DNA polymerase present in stem cells and in precursor B and T lymphoid cells.
- High levels are found in 90% of lymphoblastic leukemias.
- It can also be detected using appropriate antibodies and flow cytometry.

Cytogenetics

- cytogenetics studies can now be used for diagnosis and for prognosis of hematologic malignancies.
  - Many leukemias (and lymphomas) are characterized by specific chromosomal abnormalities, including specific translocations and aneuploidy. The specific type of malignancy can be identified based on the specific abnormality or translocation. These may be identified by
    - Looking at the karyotypes of the chromsomes from the abnormal cells
    - DNA based tests – these tests are very useful for following the course of the disease
    - RT-PCR
    - Southern blotting
  - A normal karyotype is usually associated with a better prognosis.

Chromosomal translocation



Chromosome karyotyping

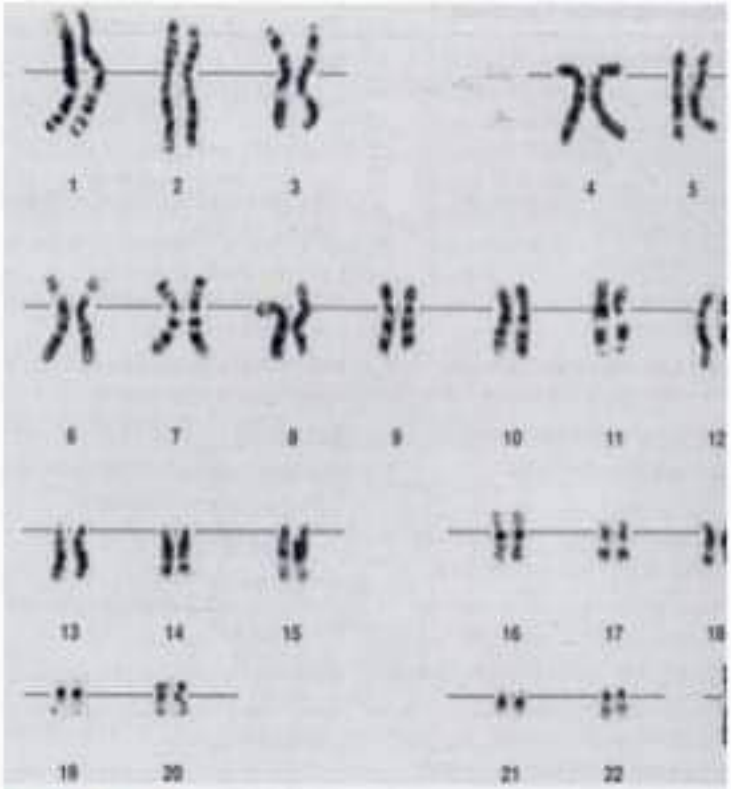
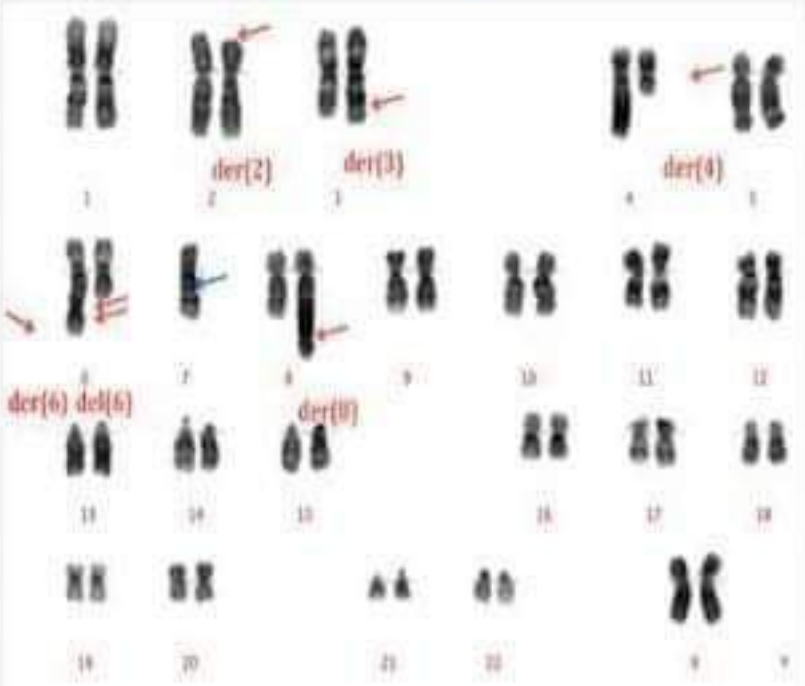


FIGURE 24-6 Karyotype of normal male cell, G-banded.



45,XX,t(2;3),t(4;8),del(6q),der (6q),-7

TREATMENT

- Chemotherapy
- Bone Marrow Transplantation
- Radiation therapy

ALL Treatment:

- Two phases of treatment
  - induction
  - post-remission
- Initial goal is to quickly induce complete remission.
- Combination chemotherapy
- Continued low-dose post-remission therapy must be used to ensure prolonged survival. Otherwise recurrence rates can be as high as 90%

After Induction Chemotherapy:

- Bone marrow biopsy is obtained
- If >5% of blasts with >20% cellularity, then retreatment necessary.
- Stem cell transplant may be necessary if retreatment fails.

Post-remission Treatment:

- Stem cell transplant
- CNS prophylaxis (for ALL)
- Radiation therapy (for ALL)
- Prolonged low-dose chemotherapy for 1-3 years

Continued Supporative Care:

- Transfusions....
  - Platelets >20,000
  - Hgb >8
- Empiric antibiotic treatment when fever present
- Allopurinol for increased uric acid levels

POOR PROGNOSTIC FACTORS

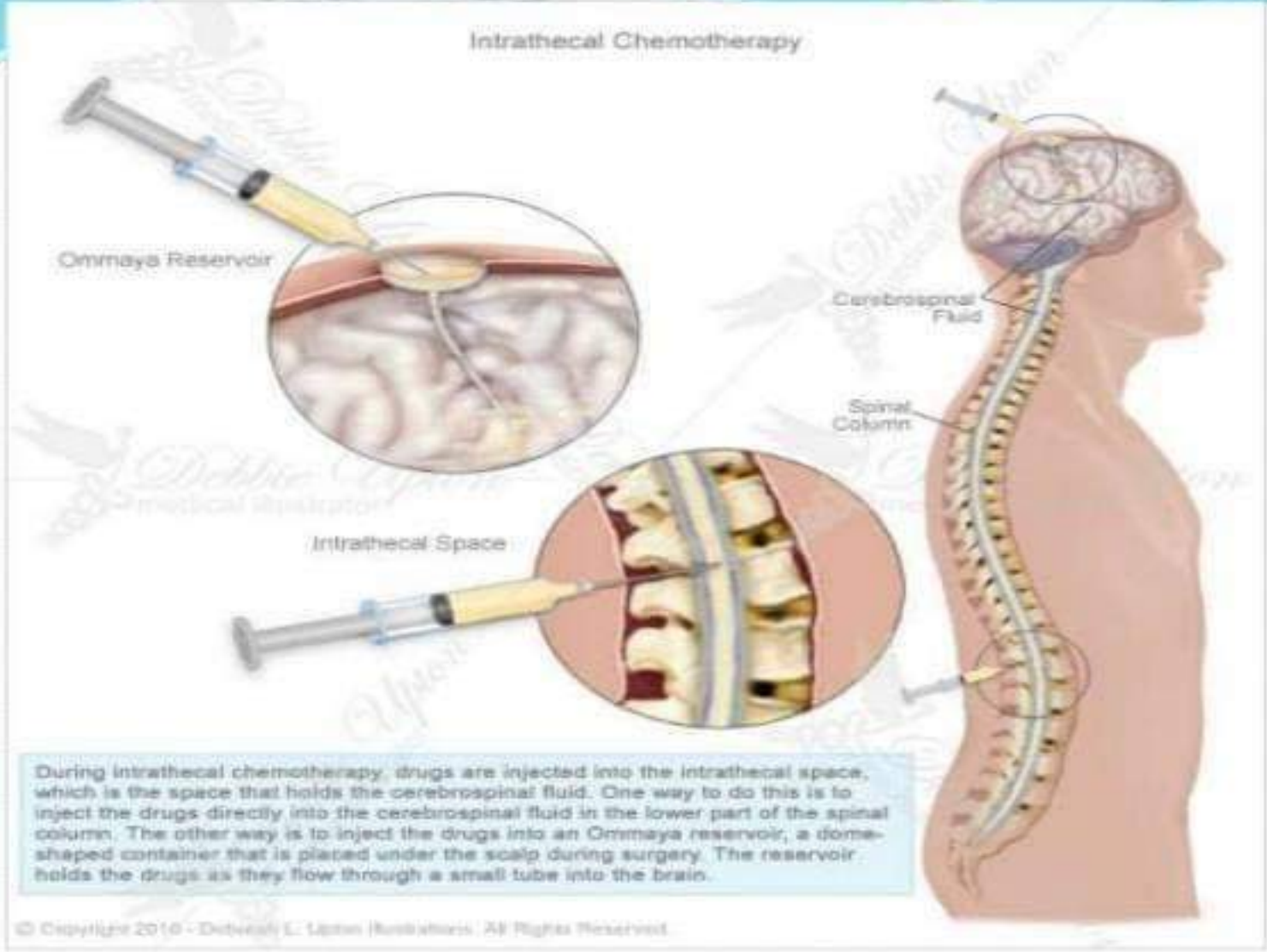
- Age<1 and >20yrs (higher age >50yrs)
- Males
- Presence of mediastinal mass on X ray
- Presence of organomegaly
- Lab results: TC> 50000/cumm in B cell ALL and >100000/cumm in T cell ALL
- Immunophenotype: Blasts are T phenotype and presence of Ph chromosome
- Cytogenetic abnormalities: t(9;22), BCR/ABL or 11q23 abnormalities
- Treatment response: late achievement of cure rate, multi drug resistance, presesnse of blast cells in BM at 14 day.

NEUROLEUKEMIA

- It occurs in 50% of ALL and 10-12% of AML cases, if neuro-prophylaxis is not given along with initial therapy.
- Pathological lesions include infiltration by leukemic cells, hemorrhage, and demyelination.
- Symptoms:
  - raised ICP
  - pappiledema
  - stupor, comma
  - focal neurological symptoms like convulsions
  - cranial nerve palsies
  - spinal cord or spinal root compression
  - intracranial hemorrhage.
  - Hyper viscosity syndrome

TREATMENT

- Neuroprophylaxis:
  - IT MTx :10-12mg/m^2 twice a week for 6 doses. A single dose should not exceed 15mg
  - IT cytosine arabinoside 50mg twice a week for 6 doses
- CNS involvement should be diagnosed when the CSF count > 5/cumm with or without the presence of blast cells.
- Treatment:
  - Cranial or craniospinal irradiation combined with IT MTx/ cytosine


Intrathecal Chemotherapy
Ommaya Reservoir
Intrathecal Space
Cerebrospinal Fluid
Spinal Column
During intrathecal chemotherapy, drugs are injected into the intrathecal space, which is the space that holds the cerebrospinal fluid. One way to do this is to inject the drugs directly into the cerebrospinal fluid in the lower part of the spinal column. The other way is to inject the drugs into an Ommaya reservoir, a dome-shaped container that is placed under the scalp during surgery. The reservoir holds the drugs as they flow through a small tube into the brain.
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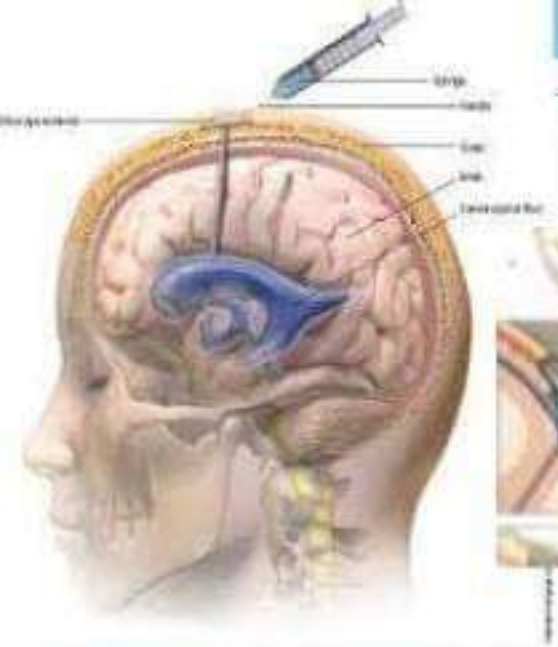
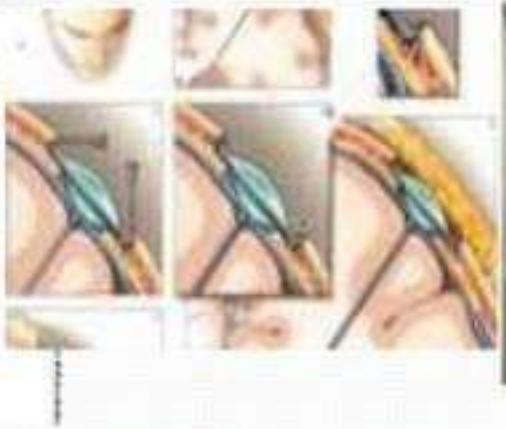




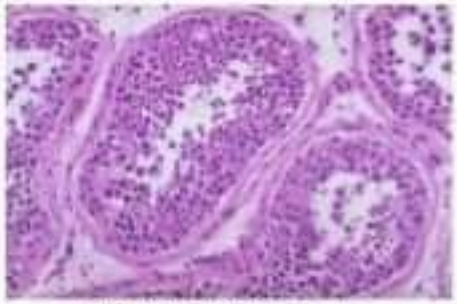
A

B

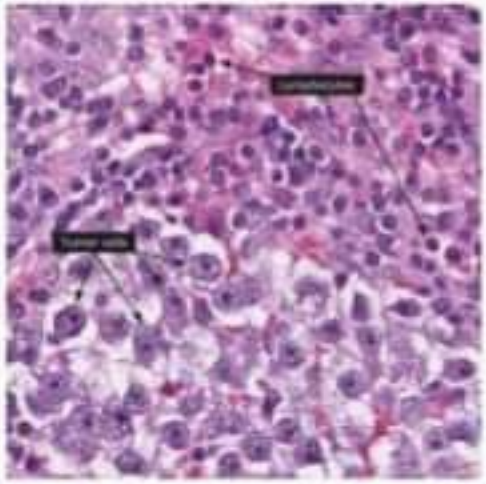
C

TESTICULAR LEUKEMIA

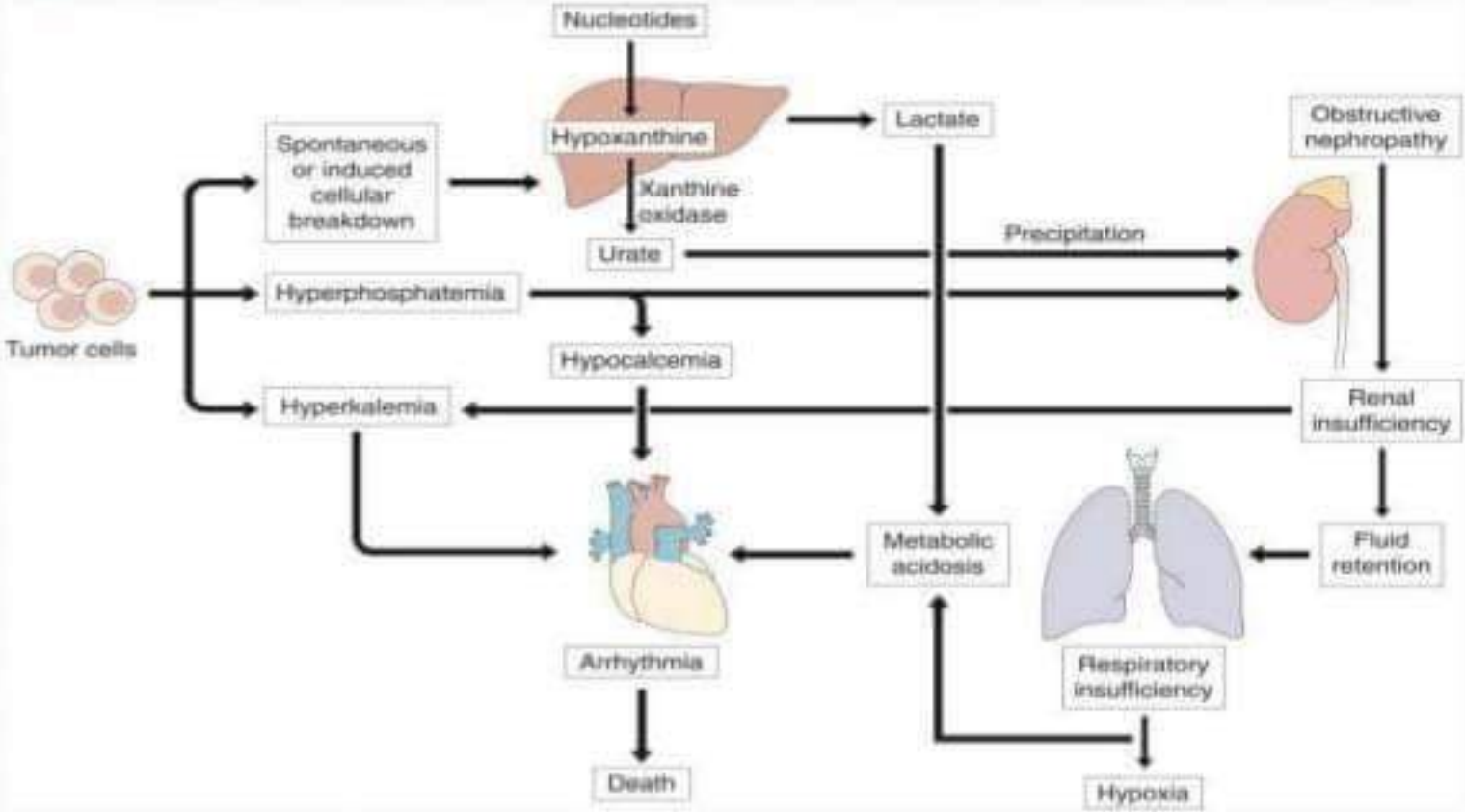
- The testes may be enlarged, firm and tender, or involvement may be clinically inapparent.
- Testicular involvement may leads to relapse.
- Treatment is by irradiation with 1000-2000 rads over a period of 2-10 days.
- Higher incidence of sterility limits its routine application



Normal Testicular Tissue



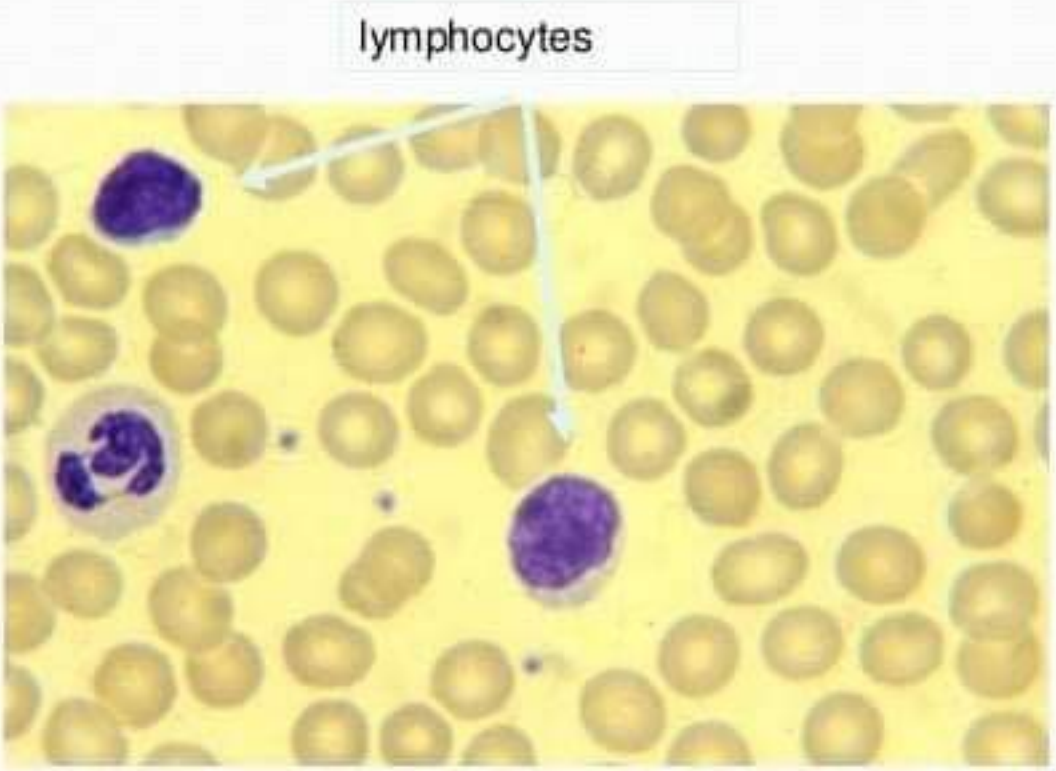
TUMOR LYSIS SYNDROME

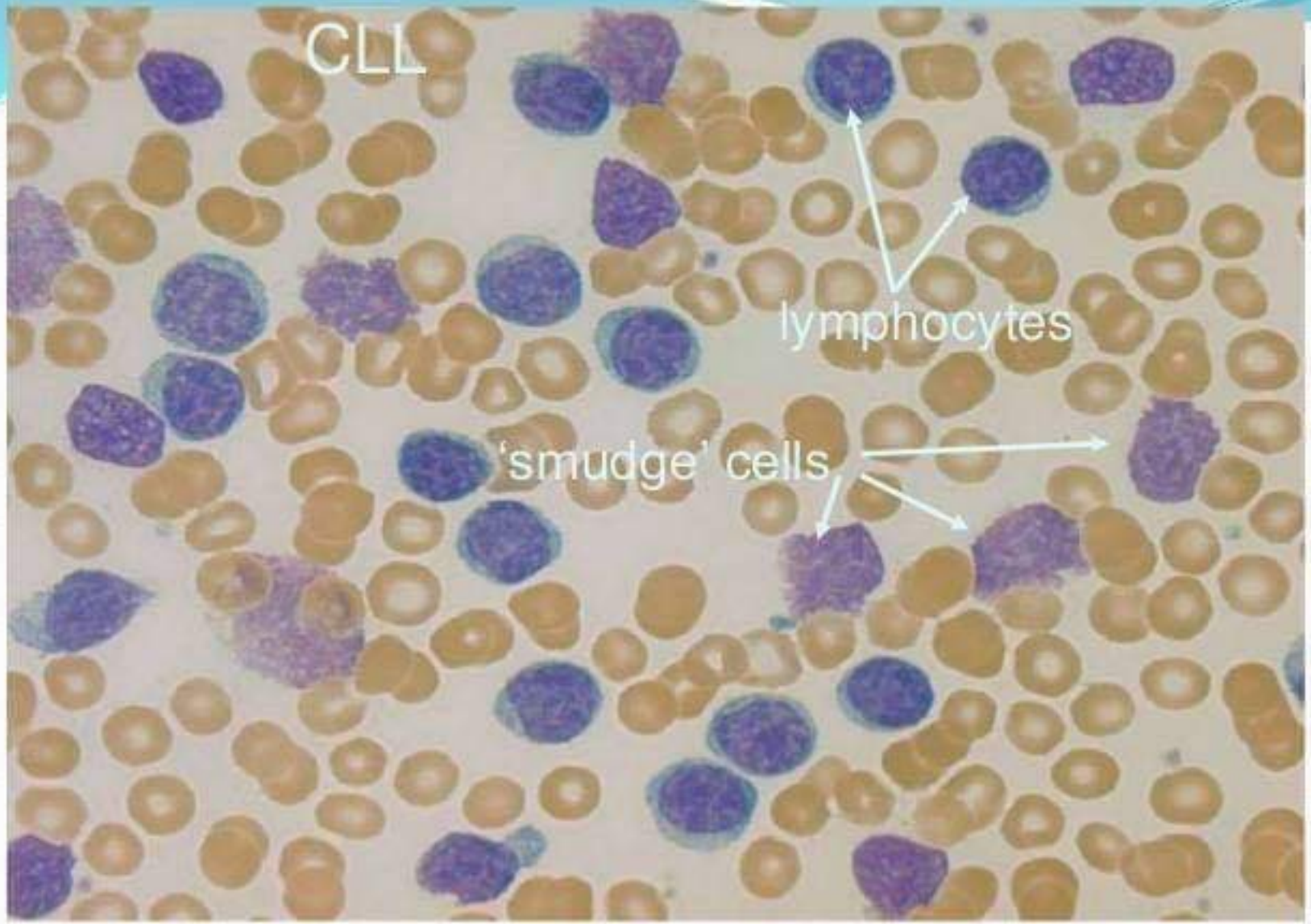


CHRONIC LYMPHOCYTIC LEUKEMIA

- Genetic change in B-cell clone
- Slow proliferation exceeds apoptosis
- Gradual accumulation of neoplastic B-lymphocytes – blood, marrow, nodes, spleen

Normal




CLL
lymphocytes
'smudge' cells

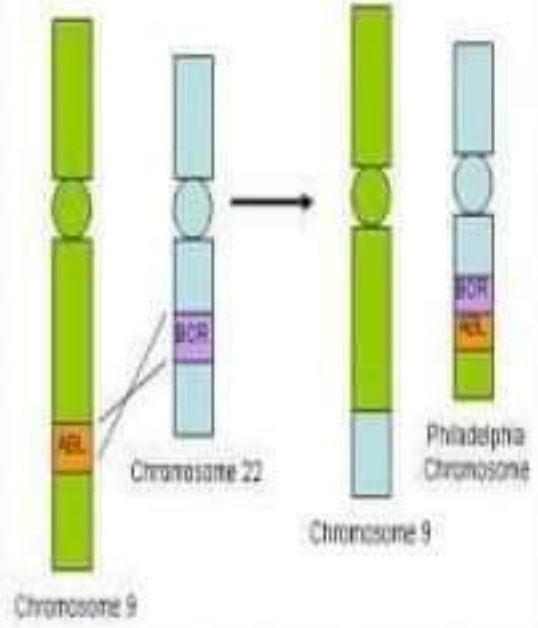
CLASSIFICATION

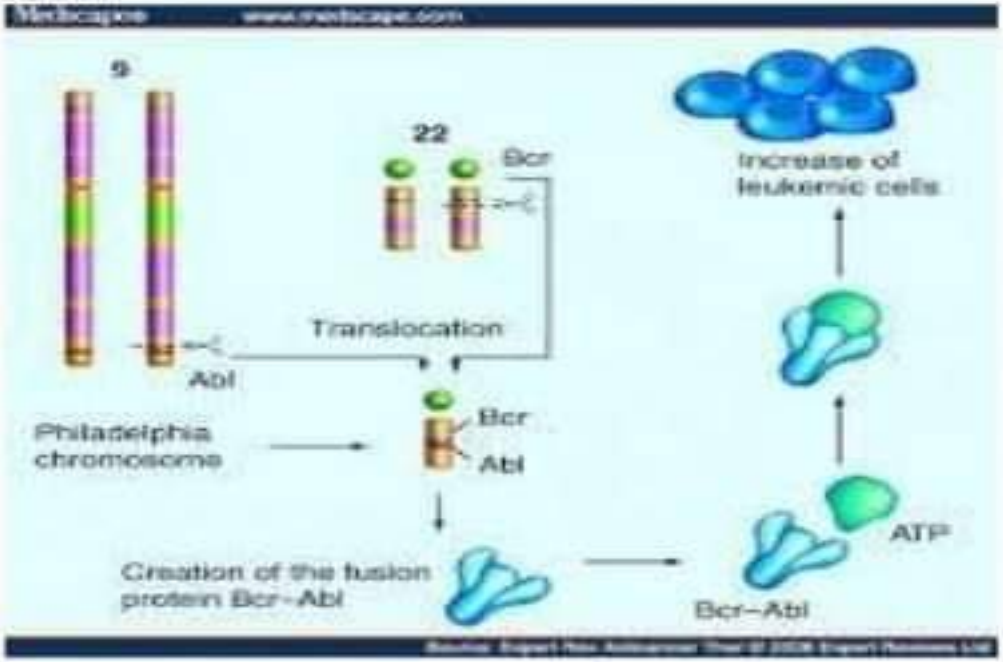
Staging system	Stage	Modified three stage system	Clinical findings	Median survival (years)
Rai	0	Low risk	Lymphocytes in blood and marrow only	>10
	I	Intermediate risk	Lymphocytosis+ lymphadenopathy+splenomegaly±hepatomegaly	7
	II	High risk	Lymphocytosis+ anaemia and / or thrombocytopenia	1.5
	III			
	IV			
Binet	A		<3 node bearing areas	>10
	B		≥3 node bearing areas	5
	C		anaemia and / or thrombocytopenia	2

PATHOPHYSIOLOGY

- Philadelphia chromosome (9:22) in up to 95%

- BCR-ABL protein junction



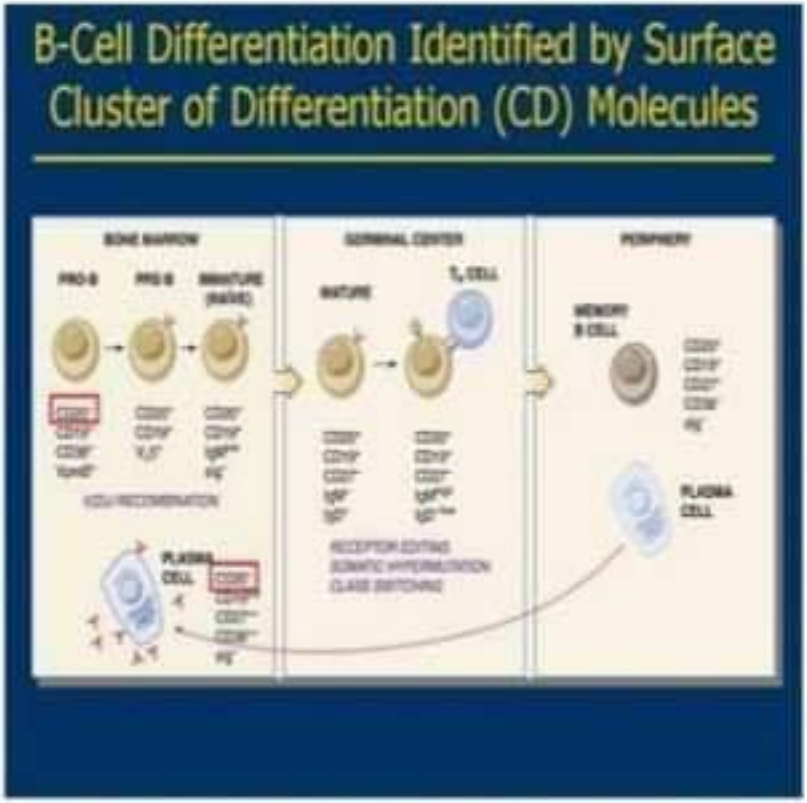


CLINICAL MANIFESTATIONS

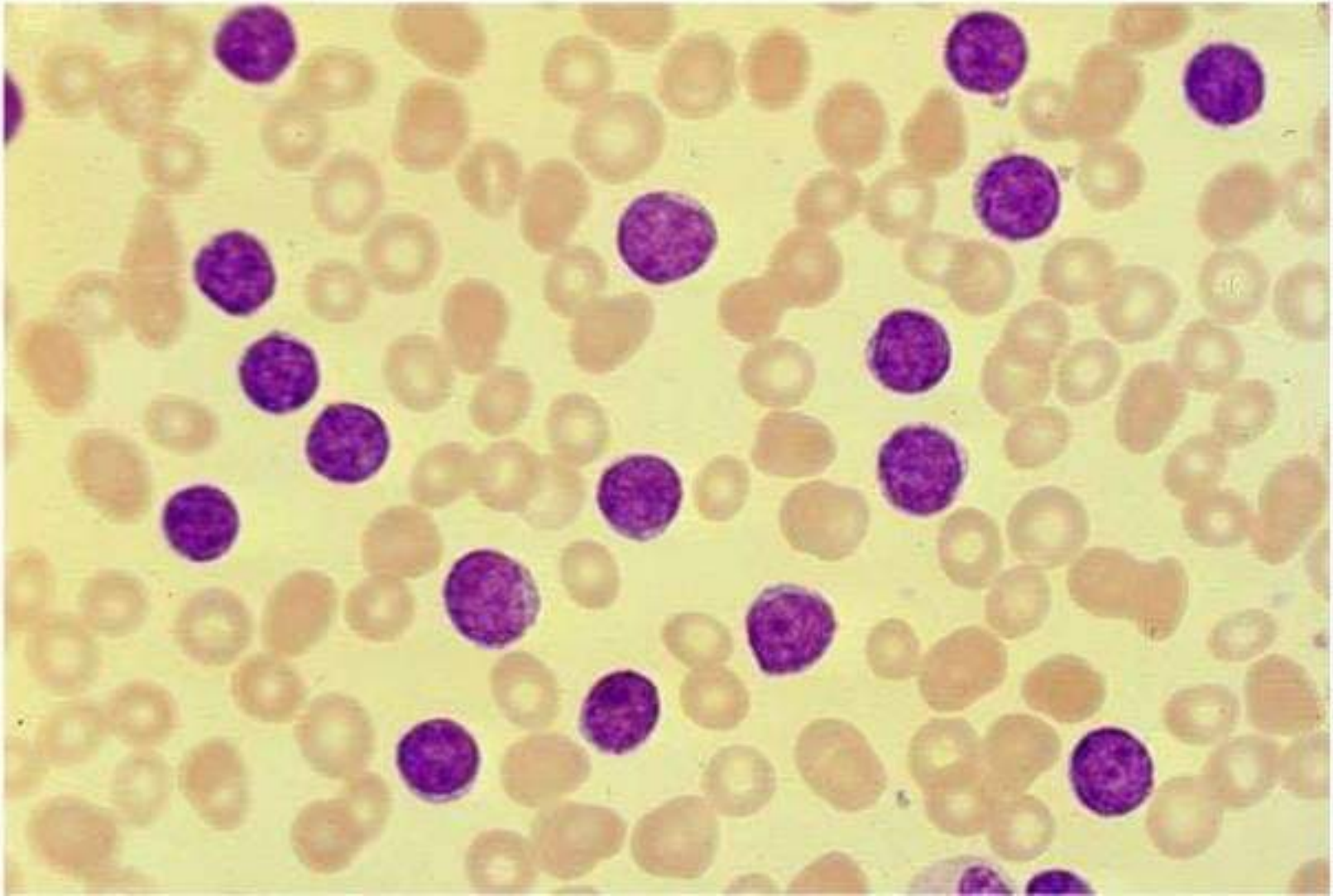
- Asymptomatic lymphocytosis
- Marrow failure
- Lymphadenopathy
- Hepatosplenomegaly
- 'B-symptoms'
- Immunodeficiency

Hematological Findings:

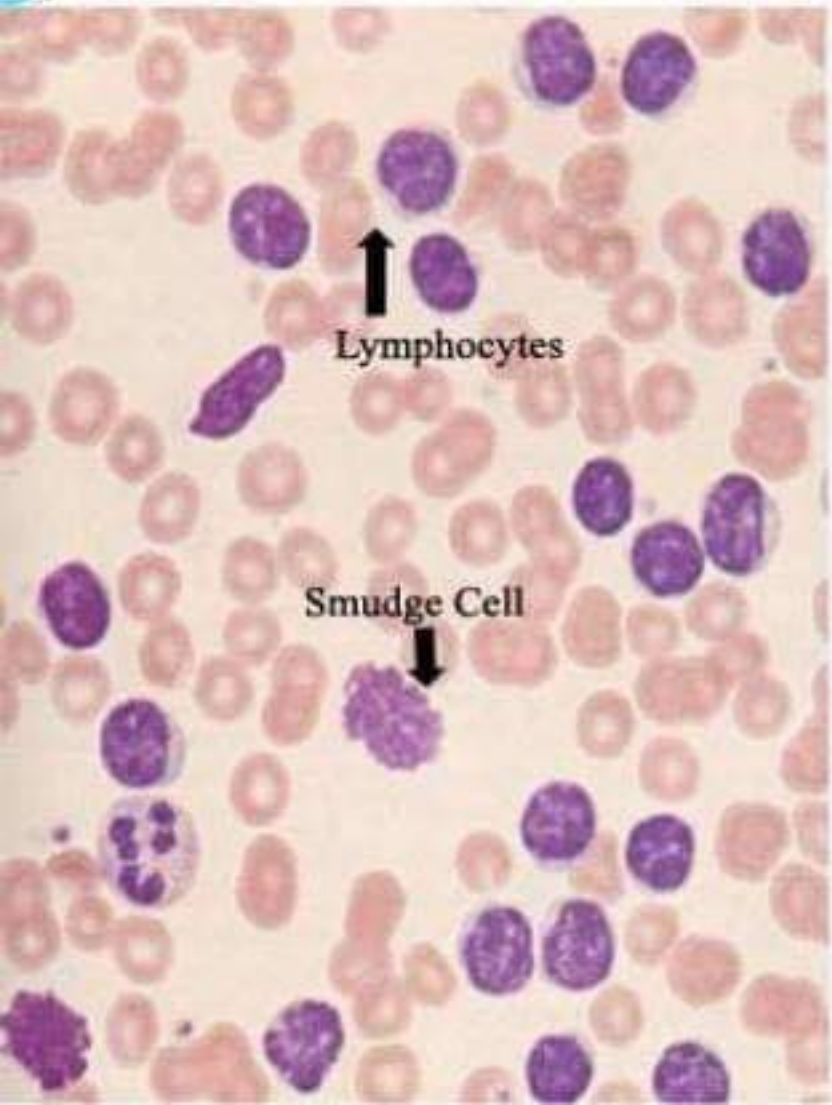
- Increased number of lymphocytes on smear
  - smudge cells
- B-cells with CD 19 and CD 5 on flow cytometry
- Small lymphocitic lymphoma present in histology of nodal biopsy

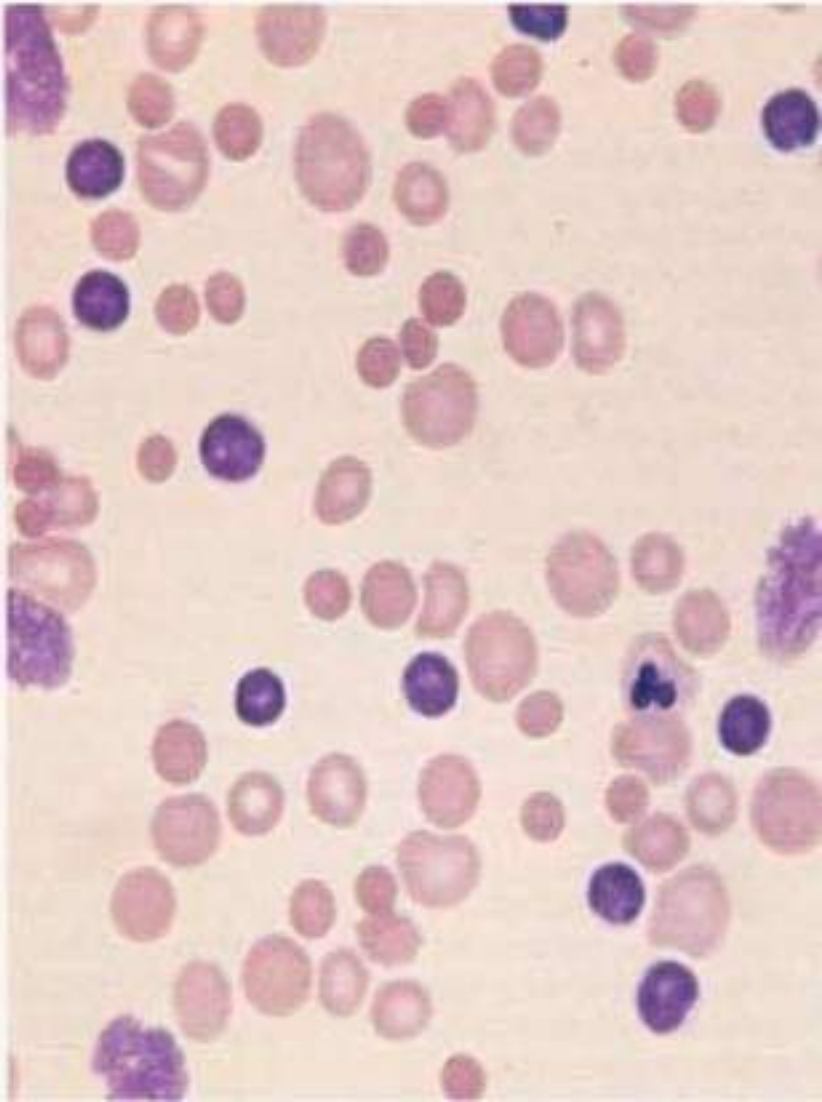


CLL Histology



CLL Histology

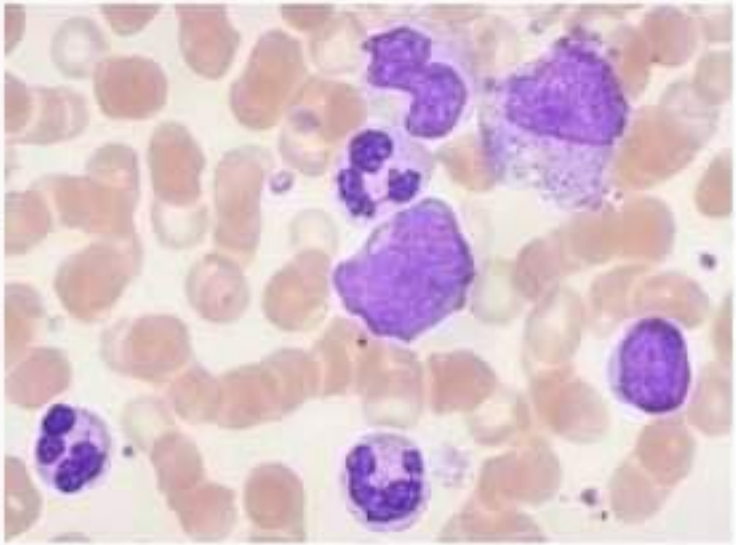


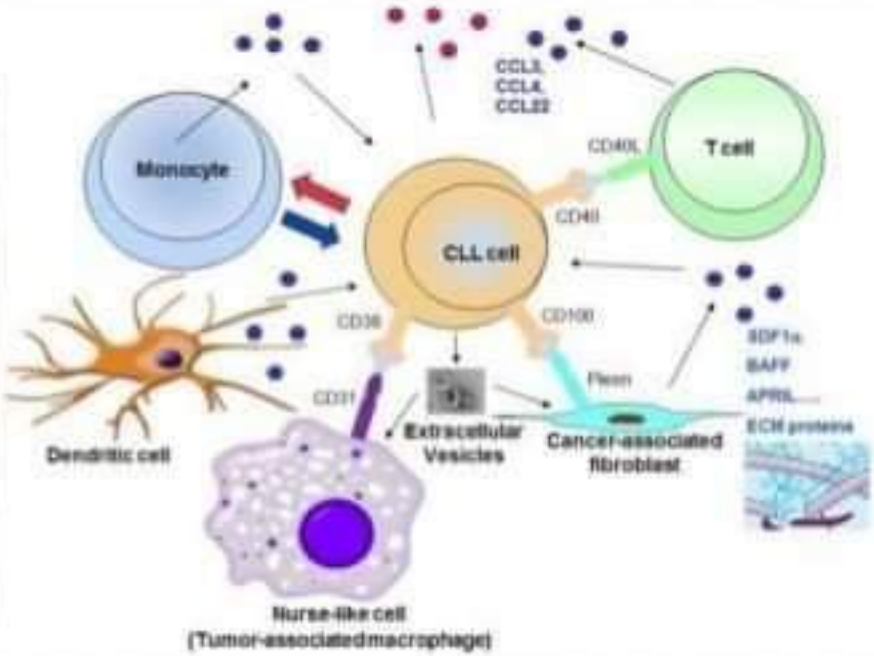


DIAGNOSIS

- Peripheral blood lymphocytosis: an absolute lymphocyte count > 5000/cumm, with cells that appears morphologically mature.
- Immunophenotype of blood lymphocytes that coexpress B cell antigens CD19, 20 and 23, as well as T cell antigen CD5; monoclonal expression of either kappa or lambda light chain; and low density surface immunoglobulin secretion
- BM examination is not a requirement when both of the above criteria are met, but it is useful for prognostic information. Lymphoid cells must constitute more than 30% of cells
- The peripheral blood is sent for flow cytometry to assess immunophenotype of cells

- Increase in blood lymphocyte count
- Demonstrate presence of a B-lymphocyte clone of appropriate immunophenotype
  - *Surface marker analysis – 'flow cytometry'*





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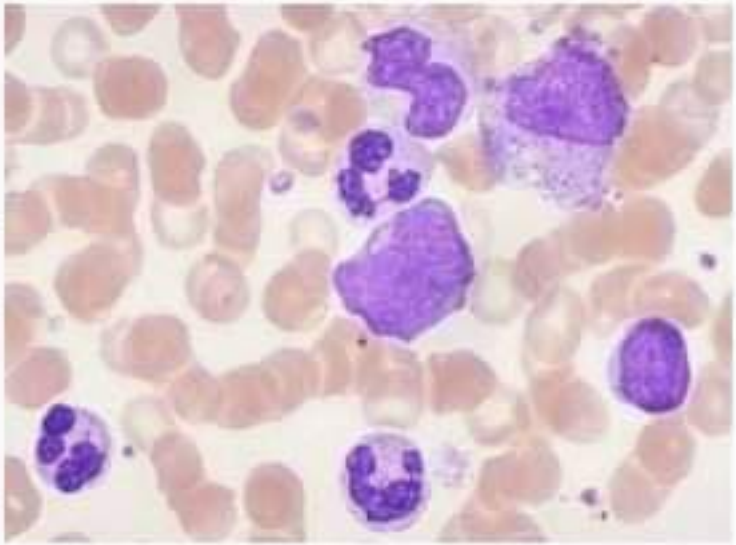
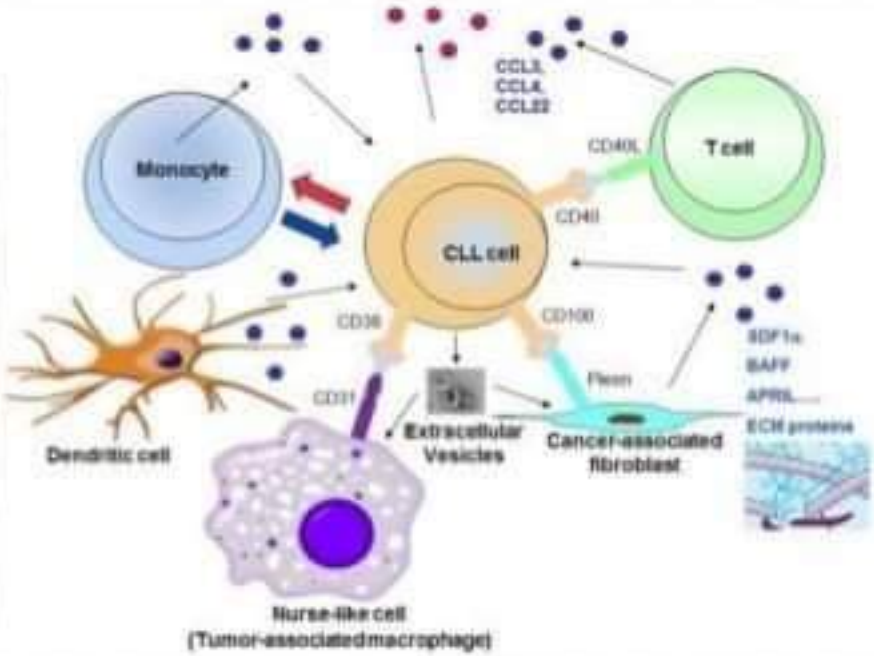
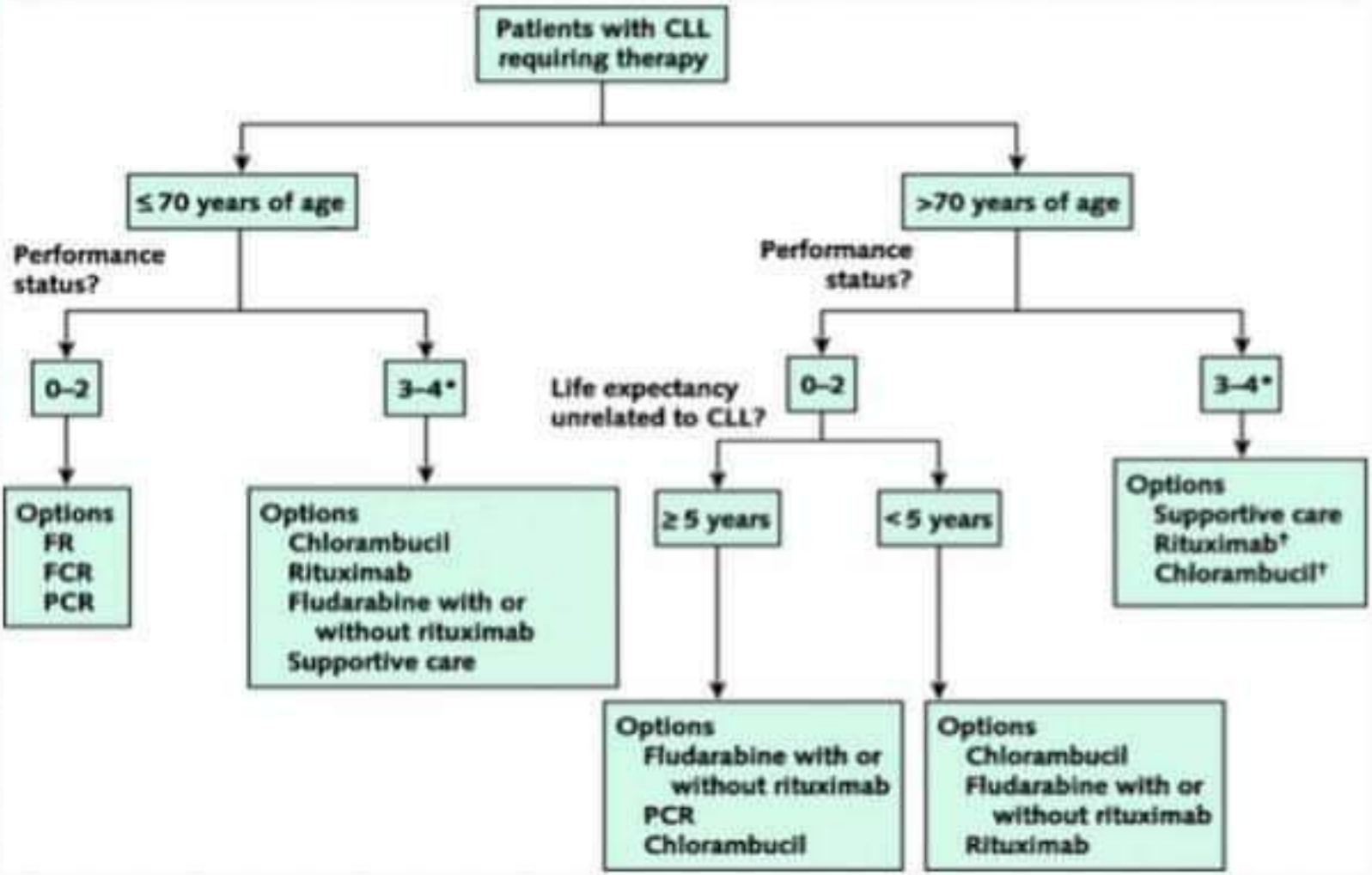




MEDICAL MANAGEMENT

- Single agent chemotherapy: chlorambucil, 6-14mg, PO every 2-4 weeks. PDN increases response rate
- Nucleoside analogue: Fludarabine
- Combination chemotherapy: fludarabine+ cychlophosphamide, fludarabine+ rituxan
- Monoclonal antibody: rituxan+ alemtuzumab
- Stem cell transplantation


Patients with CLL requiring therapy
≤ 70 years of age
>70 years of age
Performance status?
Performance status?
0–2
3–4*
0–2
3–4*
Life expectancy unrelated to CLL?
Options
FR
FCR
PCR
Options
Chlorambucil
Rituximab
Fludarabine with or without rituximab
Supportive care
≥ 5 years
< 5 years
Options
Supportive care
Rituximab†
Chlorambucil†
Options
Fludarabine with or without rituximab
PCR
Chlorambucil
Options
Chlorambucil
Fludarabine with or without rituximab
Rituximab

PROGNOSTIC FACTORS

- Age and sex: increased age, poor prognosis. Female survive more than males
- Lymphocyte doubling time: LDT is the rate at which the lymphocyte count increases, correlate with survival. LDT > 12 months, better outcome
- Beta 2 microglobulin: a low level indicates good survival
- Cytogenetics: most unfavorable abnormality is del 17p and is associated with refractory to fludarabine