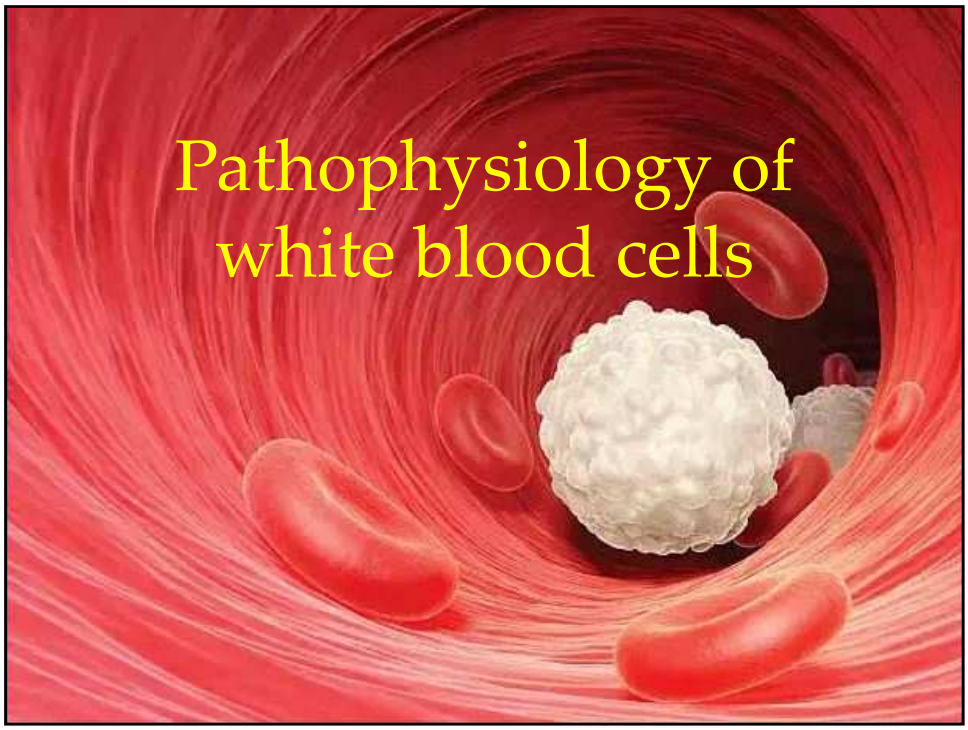
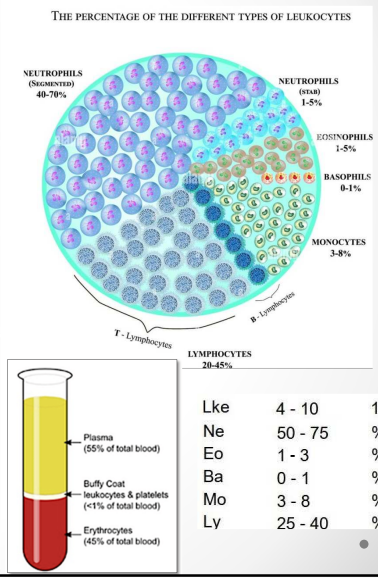


1

White blood cells

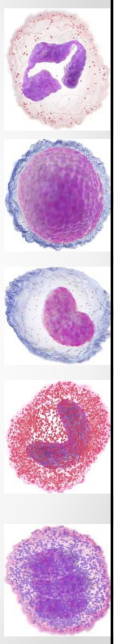
Subtype	Nucleus	Function	Example
Neutrophil	Multi-Lobed	Bacterial or fungal infection. These are the most common first responders to microbial infection.	
Eosinophil	Bi-Lobed	Parasitic infections and allergic reactions (inflammatory).	
Basophil	Bi/Tri-Lobed	Allergic and antigen response (releases histamine causing vasodilation).	
Lymphocyte	Deep Staining, Eccentric	Include B cells, CD4+ helper T cells, and CD8+ cytotoxic T cells. Operate primarily in the lymphatic system.	
Monocyte	Kidney Shaped	Phagocytosis of pathogens. Presentation of antigens to T cells. Eventually, they become tissue macrophages, which remove dead cell debris and attack microorganisms.	



Lke	4 - 10	10^9/l
Ne	50 - 75	%
Eo	1 - 3	%
Ba	0 - 1	%
Mo	3 - 8	%
Ly	25 - 40	%

2

Characteristics of white blood cells lineages



Neutrophils
- count 1.8–7.7×10⁹/l
- more than half of all leukocytes
- phagocytes

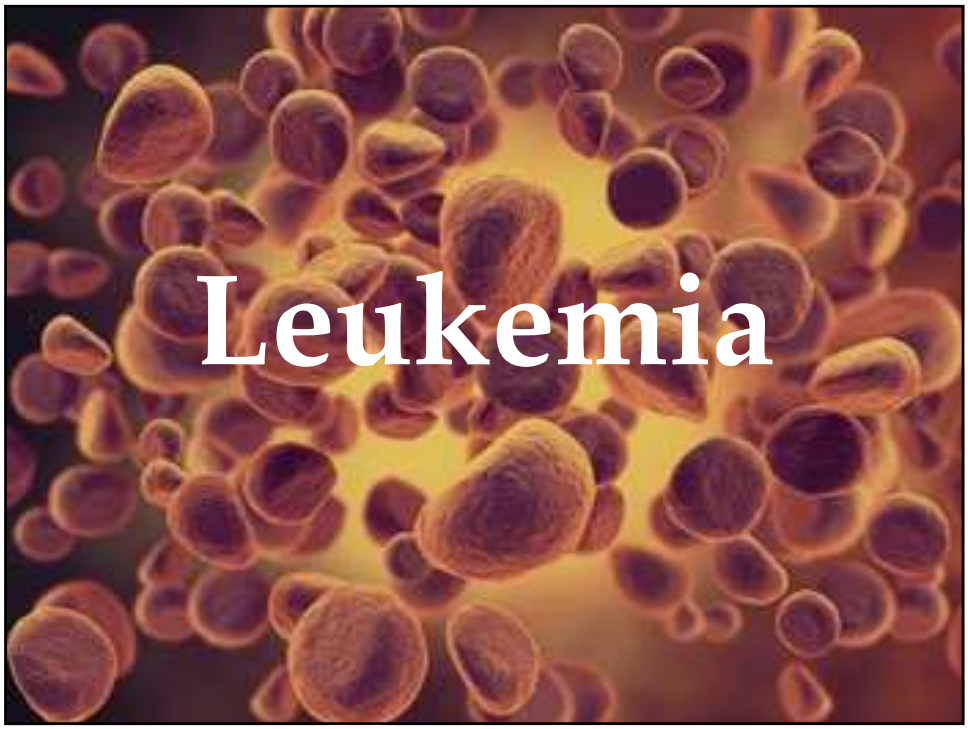
Lymphocytes
- count 1.0–4.0×10⁹/l
- about one third of the white blood cells in the peripheral blood
- T cells : B cells - 2 : 1
- B and T lymphocytes cannot be distinguished morphologically
- 10% of lymphocytes are natural killer cells

Monocytes
- count 0.3×10⁹/l
- 3–8% of circulating leucocytes
- after migration into extravascular tissues, they increase in size and acquire the morphological characteristics of tissue macrophages

Eosinophils
- 0.2×10⁹/l
- 1–5% of circulating leucocytes
- allergic, parasitic, and neoplastic disease processes

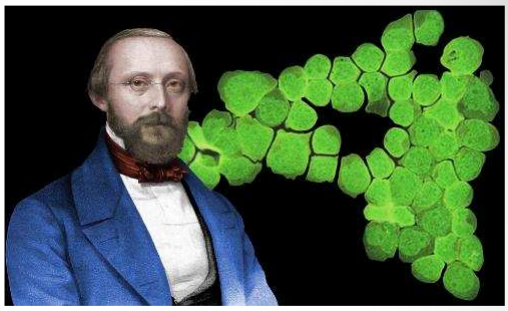
Basophils
- Up to1% of circulating leucocytes
- mast cells are related to, but distinct from, basophils
- both cell types are involved in immediate and cutaneous hypersensitivity reactions including asthma, urticaria, allergic rhinitis, and anaphylaxis

3



4

History

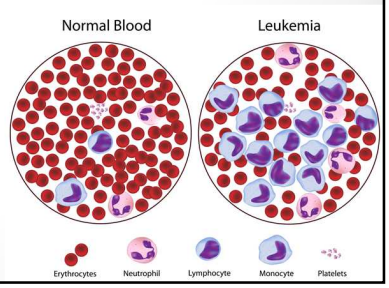


- Rudolf Ludwig Carl Virchow (1821 -1902) was born in the town of Schivelbein, in the German Kingdom of Prussia. Today the town is called Świdwin and lies in Poland.
- Virchow identified and named the disease leukemia and offered the best description of it available. He named the disease by combining the Greek words *leukos* (white) and *aima* (blood).
- Virchow was the first to correctly link the origin of cancers from otherwise normal cells. In 1855, he suggested that cancers arise from the activation of dormant cells (perhaps similar to cells now known as stem cells) present in mature tissue. Virchow believed that cancer is caused by severe irritation in the tissues, and his theory came to be known as chronic irritation theory.

5

Definition

- Malignant neoplasms arising from the transformation of one blood cell line derived from hematopoietic stem cells.
- Production of dysfunctional cells because of a loss of regulation in cell division, these cells are released to circulation and may also infiltrate other organs – spleen, lymph nodes, liver, bones...
- The leukemic cells are immature and poorly differentiated, they proliferate rapidly, have long life span, and do not function normally.
- Progressive diseases
- Occurs in all age groups
- The most common cancer in children but in adults 10x more frequent



6

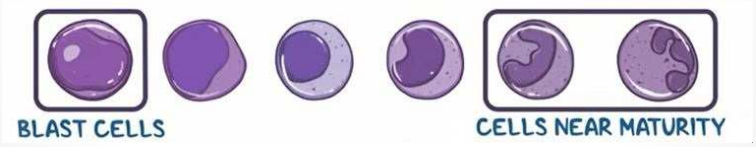
Classification

- Acute versus chronic
  - Disease onset
    - Acute
      - Acute lymphoblastic leukemia (ALL)
      - Acute myelogenous leukemia (AML)
    - Chronic
      - Chronic lymphocytic leukemia (CLL)
      - Chronic myelogenous leukemia (CML)
  - Cell maturity
    - Acute: clonal proliferation of immature hematopoietic cells
    - Chronic: mature forms of WBC; onset is much gradual

7

Acute versus chronic

Acute	Chronic
• Rapid development	• Slow development
• Blasts (immature cells)	• Cells in higher level of maturation



• Abnormal function	• Abnormal function

8

Classification

- Type of white blood cell (WBC)
  - Lymphoid neoplasms
    - Acute lymphoblastic leukemia (ALL)
    - Chronic lymphocytic leukemia (CLL)
    - Lymphomas
      - Hodgkin
      - Non-Hodgkin
  - Myeloid neoplasms
    - Acute myelogenous leukemia (AML)
    - Chronic myelogenous leukemia (CML)
    - Myelodysplatic syndromes

9

Lymphoid versus myeloid

Lymphoid

- Acute lymphoblastic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL)

malignant proliferation of abnormal cells in bone marrow and their presence in the blood

- Lymphomas
  - Hodgkin
  - Non-Hodgkin

solid tumors in lymph nodes

Myeloid

- Acute myelogenous leukemia (AML)
- Chronic myelogenous leukemia (CML)

malignant uncontrolled growth of abnormal cells

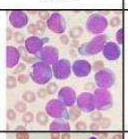
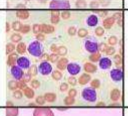
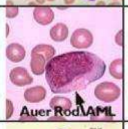
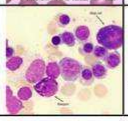
- Myelodysplatic syndromes

ineffective and dysplastic blood cell production in bone marrow that can be malignant or benign

- AML and CML also belong here

10

Classification

condition	picture	etiology	cell involved	morphology	clinical presentation	CBC results	demographic
acute lymphocytic leukemia (ALL)		chromosomal abberation resulting in abrnomal transcription factors that affect development of B and T cells	immature B or T cell (marrow)	condensed chromatin, scant cytoplasm, small nucleoli	stormy onset, symptoms related to depressed marrow function, bone pain, CNS manifestations	anemia, thrombocytopenia, variable WBC's, **>30% lymphoblasts**	children.
chronic lymphocytic leukemia (CLL)		chromosomal deletion or possible somatic hypermutation of postgerminal or naive B cells	peripheral B or T cell (lymph nodes)	**smudge cells,** condensed chromatin, scant cytoplasm	asymptomatic or nonspecific, LAD, hepatosplenomegaly,	sustained abs. lymphocytosis >5000/uL, low platelets in 20-30%	most common leukemia in adults. twice as common in men.
acute myelogenous leukemia (AML)		oncogenic mutations impede differentiation, accumulating immature myeloid blasts in marrow	immature myeloid lineage cells (marrow)	**auer rods** (abnormal lysosomes), myeloblasts, monoblast	anemia symptoms, spontaneous bleeding, petechiae and ecchymoses	anemia, neutropenia, thrombocytopenia, **>30% myeloblasts**, auer rods	adults.
chronic myeloid leukemia (CML)		tyrosine kinase pathway related chromosomal translocation-philadelphia chromosome	pluripotent hematopoetic stem cell (marrow)	hypercellular marrow, elevated eosinophils and basophils	insidious onset, mild anemic symptoms, splenomegaly	asx WBC> 50,000, symptomatic **WBC>200,000-1,000,000,** some blast forms, **increased eosinophils and basophils**	ages 20-50, rare in children.

11

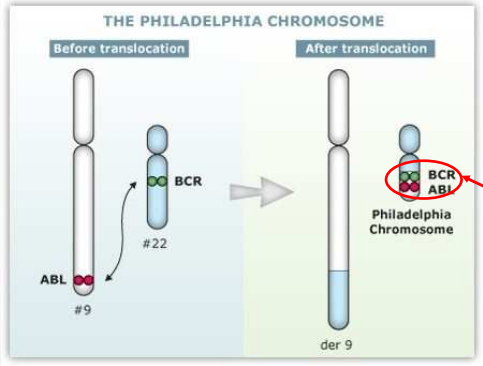
Etiology

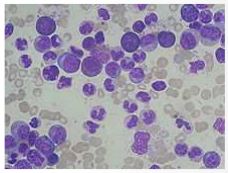
- No single causative agent
- Most from a combination of factors - genetic and environmental influences
  - Radiation
  - Chemical compounds
    - polycyclic aromatic hydrocarbons, chemotherapy...
  - Viruses, bacterias
    - EBV, HIV, HTLV (human T-cell lymphotropic virus), helicobacter (lymphomas from lymph. tissue of GIT)
  - Immunodeficiencies – Wiskott-Aldrich sy.
  - Chromosomal and monogenic disorders – genomic instability
    - Deletions
    - Aneuploidy - Down sy., Patau sy.
    - Translocations (22 and 9, 15 and 17...)
    - Philadelphia chromosome – chromosomal structural aberration
    - Disorders of DNA replication - Bloom syndrome
    - Disorder of DNA repair - Fancony anemia

12

Philadelphia chromosome

- reciprocal translocation of chromosomes 9 and 22
- production of the BCR-ABL fusion gene → oncogenic tyrosine kinase → activation of cell cycle-controling proteins and enzymes activation of cell division
- mainly chronic myelogenous leukemia





BCR-ABL fusion gene

13

Pathogenesis

Genetic or chromosomal mutation

- Somatic mutations affecting hematopoietic stem or progenitor cells
- Chromosomal translocations (e.g., t(9;22) BCR-ABL1 in chronic myeloid leukemia; t(15;17) PML-RARA in acute promyelocytic leukemia)
- Gene deletions or amplifications affecting tumor suppressor genes or oncogenes

↓

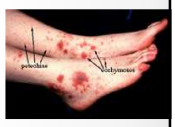
Cell transformation

- Uncontrolled proliferation → activation of oncogenic signaling pathways
- Impaired differentiation → failure of normal maturation
- Resistance to apoptosis
- Clonal expansion
- Bone marrow failure

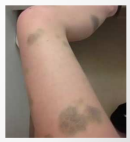
14

Clinical signs

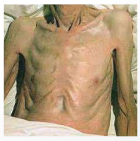
- Bone marrow failure
  - Overcrowding by abnormal cells
  - Inadequate production of normal marrow elements
  - Anemia, thrombocytopenia, ↓ number and function of WBCs
    - fatigue, weakness, frequent infections, fever, nigh sweating, petechiae or bruising, bleeding from nose, bleeding to organs



- Leukemic cells infiltrate patient's organs
  - Splenomegaly
  - Hepatomegaly
  - Lymphadenopathy, swollen lymph nodes
  - Bone pain, meningeal irritation, oral lesions (chloromas)



- Changes in metabolism
  - Anorexia, weight loosing, muscle atrophy



15

Oral, head and neck manifestations of leukemias

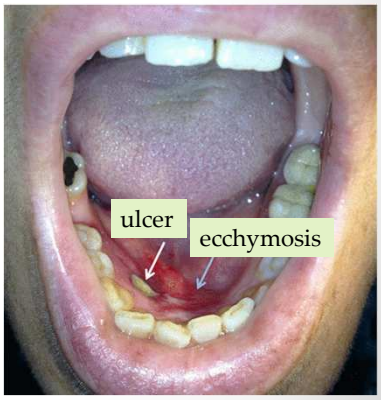
Manifestations in the oral cavity and the head and neck region are common and may represent the first clinical signs of the disease. They occur most frequently in acute leukemias (AML, ALL) and in advanced stages of chronic leukemias.

16

Oral, head and neck manifestations of leukemias

Oral manifestations

- Gingival changes
  - Gingival hyperplasia
  - Gingival edema
  - Spontaneous bleeding or bleeding after minimal trauma
  - Cyanosis
- Hemorrhagic
  - Petechiae and ecchymoses of the oral mucosa
  - Prolonged bleeding after minor procedures
- Ulcerations and Infections
  - Painful mucosal ulcerations
  - Necrotizing gingivitis or stomatitis
  - Secondary infections:
    - Bacterial
    - Fungal (Candida spp.)
    - Viral (HSV)
- Mucosal infiltration
  - Ddiffuse or nodular infiltrates
  - Firm, usually painless lesions
  - Leukemic infiltrates of the oral mucosa
- Other oral findings
  - Xerostomia
  - Halitosis
  - Dysphagia in cases of extensive infiltration

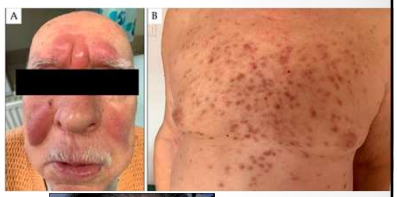


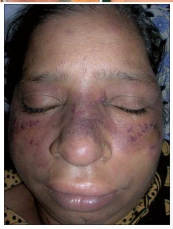
17

Oral, head and neck manifestations of leukemias

Head and neck manifestations

- Lymphadenopathy
  - Enlarged cervical, submandibular, and supraclavicular lymph nodes, typically painless, firm, sometimes matted
  - common especially in ALL and CLL
- Cutaneous manifestations
  - Petechiae and purpura of the face and neck
  - Ecchymoses
  - Leukemia cutis
    - nodules, plaques, infiltrates
    - violaceous to reddish-brown discoloration
- Soft tissue
  - Infiltration of the lips, tongue, or facial tissues
  - Facial asymmetry
  - Mucosal thickening
- Tonsils and nasopharynx
  - Tonsillar hypertrophy
  - Infiltration of the nasopharynx
  - Snoring and obstructive symptoms





18

Acute lymphoblastic leukemia (ALL)

- Most common type of leukemia in children, boys > girls, whites > nonwhites (2x)
- 15% of acute leukemia in adults
- Often influenced by enviromental factors – viruses (HTLV-1, EBV, HIV), cytostatic treatment, autoimmunity disorders

- Immature lymphocytes proliferate in the bone marrow → > 30% lymphoblasts in bone marrow and blood
- Proliferation of precursor B cells or T cells
- In children > 80% cancers of B cell precursors
- In adults – cancers of B cell precursors ≈ cancers of T cell precursors

Etiology

- viruses (HTLV-1, EBV, HIV), treatment with cytostatic drugs, autoimmunity
- Chromosomes: hyperploidy (> 50), aneuploidy (Down sy.), translocations - Philadelphia ch. (9 and 22) and other translocations (12 and 21)

19

Acute lymphoblastic leukemia

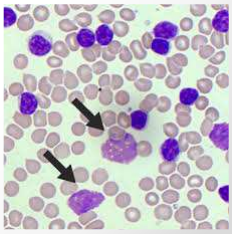
- Clinical signs
  - Anemia, palor, tiredness, infections, more intensive bleeding
  - Lymphonodes enlarged (more lymphatic groups at same time), weight loss often
  - Frequent infiltration of organs – spleen, liver, lymphatic nodes, meninges, testes (solitary lymphomas tend to infiltrate bone marrow preferably)

- Prognosis
  - Children better than adults

20

Chronic lymphocytic leukemia (CLL)

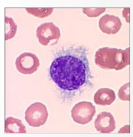
- The most frequent from all
- Manifestation in age over 50, M > W
- 70-95 % arises from B-ly
- Prolymphocytes in lymph nodes, high number of mitoses
- In blood small Ly, small amount of cytoplasm, fragile „smudge“ cells. Ly in bone marrow and other tissues
- Special immunophenotype
- Low number of chromosomal abnormalities



21

Chronic lymphocytic leukemia

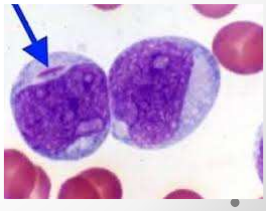
- Leukocytosis may reach up to 10-200x10^9/l (often asymptomatic)
  - Bone marrow affected – mild anemia and thrombocytopenia
  - Lymph node enlargement - ↑ incidence of infection , pain, paralysis from enlarged lymph nodes causing pressure
  - Decrease of functinal B-ly – decrease of Ig levels in blood
  - Up to 20 % suffer from autoimmune disorders – Ab against Ery, Tr
- Other disorders belonging to CLL
  - „Hairy cell“ leukemia
    - 2% of all adult leukemias, males > 40 years old
    - B lymphocytes that infiltrate the bone marrow and liver, cells have a "hairy" appearance
    - Splenomegaly, pancytopenia, infection, vasculitis
  - T-cells – prolymphocytic leukemia, skin lymphomas, Sezary sy.
  - Combined – signs of T-ly and NK-cells



22

Acute myelogenous leukemia (AML)

- Proliferation of myeloid tissue and an abnormal increase in the number of granulocytes, myelocytes, and myeloblasts in the circulating blood
- One fourth of all leukemias
  - Mostly in adults > 65 y.
  - 85% of the acute leukemias in adults
  - Atypical immature myeloid cells forms in bone marrow + peripheral blood + some organs
  - Auer rods - acid pH → crystalline structures derived from primary granules of myeloid cells.



Etiology:

- Translocation (chromosomes 15 and 17)
- Radiation
- Alkylating chemotherapy

23

Acute myelogenous leukemia

- Congenital predispositions – one allele mutated („loss of heterozygocity")
  - Down sy., familiár monosomy of Ch 7, neurofibromatosis type I, Fanconi anemia
- Genome changes – partial monosomies (Ch 5, Ch 7), translocations [t(8,21), t(15,17)]
  - Transcription factors – differentiation and functional maturation affected

Clinical signs

- Erythropoesis cessation – normochromic normocytic anemia
- Lower amount of functional Leu (granulocytes, monocytes) – susceptibility to infections
  - Bacterial, fungal disorders of skin, mucoses and lungs
- Thrombocytopenia – bleeding manifestations
- DIC risk increased – blasts presence in blood
- Splenomegaly, hepatomegaly, lymphadenopathy – infiltration by pathological clone

24

FAB (fra.-am.-brit.) classification of AML

Type	Name	%
M0	Minimally differentiated leukemia	2-3
M1	Myeloblastic leukemia without maturation	20
M2	Myeloblastic leukemia with maturation	25-30
M3	Promyelocytic leukemia (PML)	8-15
M4	Myelomonocytic leukemia (AMML)	20-25
M5	Monocytic leukemia (ACML)	20-25
M6	Erythroleukemia (m. di Guglielm)	5
M7	Megakaryoblastic leukemia	1-2

25

Acute promyelocytic leukemia (PML)

- Variation of AML
- Arises from promyelocytes

Etiology:

- Translocation (chromosomes 15 and 17)
- Creation of fusion gene PML/RARA
- Disruption of normal cell division
-

26

Chronic myelogenous leukemia (CML)

- Excessive development of mature neoplastic granulocytes in the bone marrow
  - Move into the peripheral blood in massive numbers
  - Ultimately infiltrate the liver and spleen
- 15-20 % leukemias
- Philadelphia chromosome in 90 %
- Uncontrolled proliferation of cells, inhibition of apoptosis
- Bone marrow is 100 % cellular (n: 50%)
- Leu in peripheral blood up to $100x10^9/l$
- ↑ granulocytes - ↓ antibacterial functions – recurrent infections
- Thrombocytosis
- Extramedullar hematopoesis

27

Chronic myelogeous leukemia

- Clinical signs
  - Slow nonspecific onset - fatigue, anemia, weight loss
  - Infections, pain of joints and bones, weight loss, hepatosplenomegaly, multiple blasts in peripheral blood
- Course
  - 1) Chronic phase – no signs, blasts <5 % (peripheral blood and bone marrow)
  - 2) Accelerated phase – blasts 5-30 %
  - 3) Blastic (acute) phase – blasts >30 %, symptomatology manifested
  - Duration – 4-6 yrs, often progresses to AML
- Therapy: Inhibition of BCR-ABL kinase
- Bone marrow transplantation

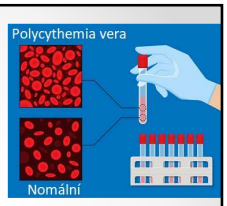
28

Myeloproliferative diseases

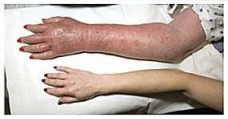
- Myeloid precurors line disorders
- Increased proliferative activity, increased resistance to apoptosis, lower hemopoetic stromal adhesion, incomplete maturation of functions
  - Myelodysplastic sy.
  - Acute myeloid (myeloblastic) leukemia
  - Chronic myeloid leukemia
  - Polycytemia vera rubra
  - Essential (primary) thrombocytemia
  - Myelofibrosis
  - Mastocytosis

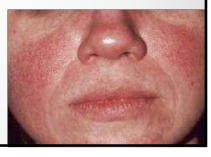
29

Polycythemia vera



- Pathological clone is more sensitive to erythropoetin (inhibition of apoptosis on CFU-E receptor)
- Erythropoetin level is low
- Increase of Leu and Tr, but less intensive
- Definitely matured Ery
- Hypervolemia, increased hematocrit, hyperviscous blood, more intensive bleeding after injury (epistaxis, GIT)
- Increased risk of thrombosis, increased heart work, prone to cyanosis
- Fairly benign disease
  - Possible transition to AML (adverse effect of cytostatic treatment?) or to myelofibrosis with hepatosplenomegaly (extramedular hemopoesis activated)





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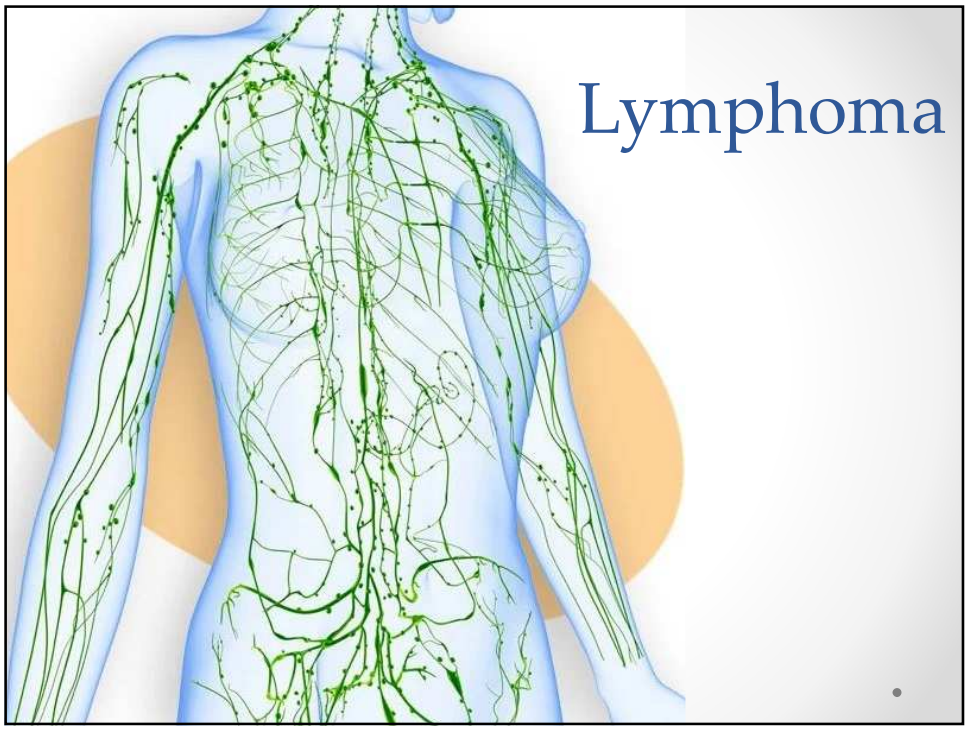
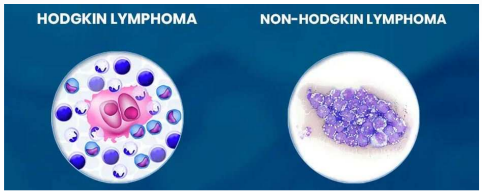


31

Lymphomas



Hodgkin

- Presence of Reed-Strenberg cells – abnormal mature B cells
- Spread is contiguous and predictable
- Extranodal involvement is uncommon
- Age: Young adults or old adults
- Better prognosis
- Highly curable

Non-Hodgkin

- Reed-Srenberg cells are absent
- Heterogenous – arise from B, T or NK cells; precursors or mature
- Spread is non-contiguous and unpredictable
- Extranodal involvement is common – GIT, skin, bone marrow, CNS
- Age: incidence increases with age
- Strong association with immunodeficiency, autoimmune diseases and chronic infections (EBV)
- Some forms are agressive - dificult to cure

32

Hodgkin lymphoma

33

Definition and classification

Definition
- 1% of all tumors
- 30% of malignant lymphomas
- Incidences: 1st maximum: 25-30 years, 2nd maximum: > 50 years
- Lymphoma type with typical presence of Reed–Sternberg cells.
- It can start in any type o lymphoid tissue – the most often in lymph nodes mainly in upper part of body – neck, axila, chest.
- It spreads through lymph vessels to other parts of lymphoid tissue.
- Later it can invade bloodstream and spread to other parts of body – liver, bones...

Classification
- Classic Hodgkin disease (95 %)
  - Nodular sclerosis Hodgkin disease
    - The most common
    - All ages mainly teens and young adults
  - Mixed cellulariry Hodgkin disease
    - Older people
  - Lymphocyte-rich Hodgkin disease
  - Lymphocyte-depleted Hodgkin disease
- Nodular lymphocyte predominant Hodgkin disease (5 %)
    - Popcorn cells (variants of Reed–Sternberg cells)
    - More in men

34

Causes and clinical signs

Causes

- Epstein–Barr virus (EBV)
- HIV
- family history

Clinical signs

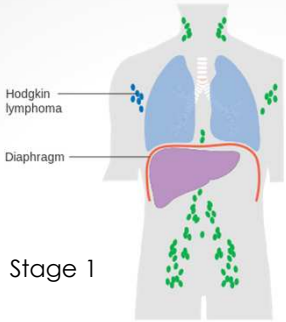
- The most typical
  - Enlarged painless lymph nodes
- Typical
  - Fever, night sweating, weight loss
- Possible
  - Itching skin, fatigue, loss of apetite, cough, chest pain

Diagnosis

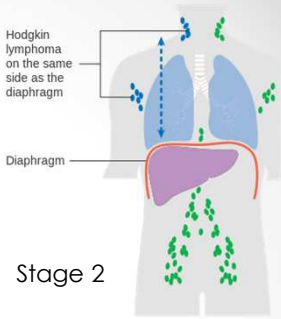
- multinucleated Reed–Sternberg cells in lymph nodes.

35

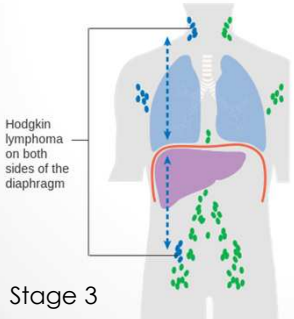
Staging



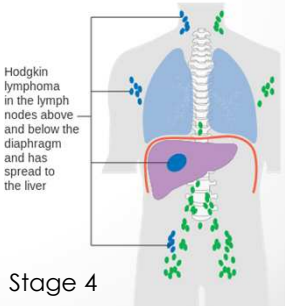
Stage 1



Stage 2



Stage 3

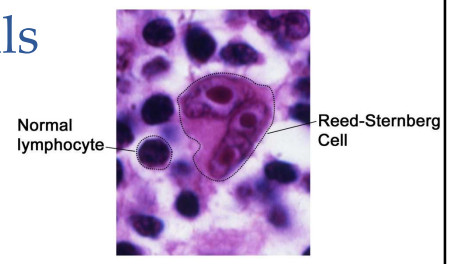


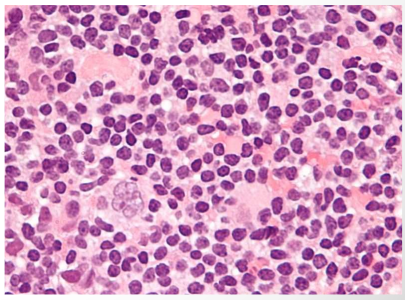
Stage 4

36

Reed-Sternberg cells

- size between 20 - 50 microns
- derived from B lymphocytes
- CD30 and CD15 positive
- amphofilic, finely granular/homogenous cytoplasm
- two mirror-image nuclei ("owl eyes") each with an eosinophilic nucleolus and a thick nuclear membrane (chromatin is distributed on the inner surface of the nuclear membrane, generating a halo image around the nucleolus)





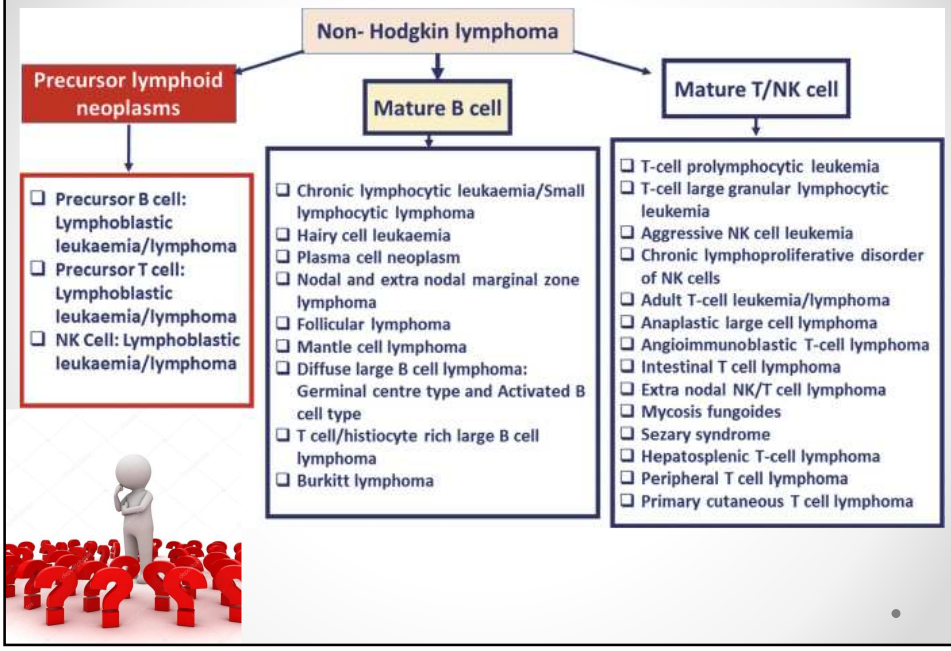
Popcorn cells

37

Non-Hodgkin lymphoma

38

Classification according to WHO



39

Causes and clinical signs

Causes (?)

- Epstein – Barr virus
- HTLV – human T-cell Lymphotropic virus
- HIV
- Posttransplantation (immunosupression?)
- Helicobacter – MALT lymphoma
- Translocations (bcl-2 oncogene)
- Immunodeficiency, autoimmune dis., chronic infections in patient history

Clinical signs

- Enlarged lymph nodes
- Swollen abdomen and feeling of fullness
- Chest pain or pressure, shortness of breath and chough
- Fever
- Night sweating
- Weight loss, fatigue
- Anemia

Diagnosis

- Peripheral blood, biopsy, antigens
- Chromosome and gene analysis

40

MALT lymphoma

- Mucosa-associated lymphoid tissue (MALT) lymphoma
- About 20-30% of all stomach malignancies
- Men > women
- At the age of about 60 years
- It affects the stomach (gastric MALT), but it can also affect others - lungs, skin, salivary glands... (non-gastric MALT)

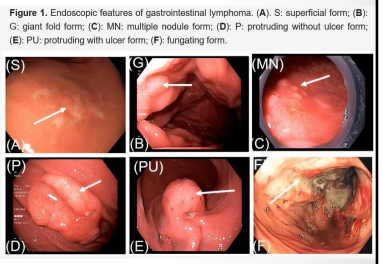


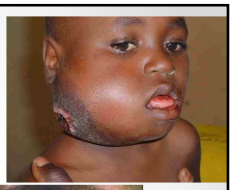
Figure 1. Endoscopic features of gastrointestinal lymphoma. (**A**). S: superficial form; (**B**): G: giant fold form; (**C**): MN: multiple nodule form; (**D**): P: protruding without ulcer form; (**E**): PU: protruding with ulcer form; (**F**): fungating form.

Causes
- Chronic inflammation
- Helicobacter pylori
- Autoimmune diseases

Signs
- loss of appetite, pain in the epigastrium, nausea, pyrosis
- gradual weight loss, weakness
- bleeding into the GIT - in about 20% of patients
- rarely - night sweats, febrility

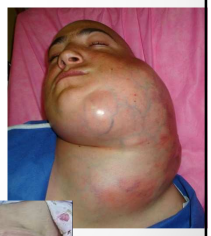
41

Burkitt lymphoma

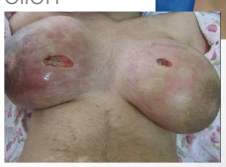


- About half of childhood malignant lymphomas
- Aggressive fast growth
- Mainly equatorial Africa

Causes (?)
- Epstein – Barr virus
- disorder of regulation of cell division and excessive proliferation of mature B-lymphocytes (memory cells).
- Typical translocation t(8;14) - present in up to 80% of cases,
- others - t(8;22) and t(2;8)

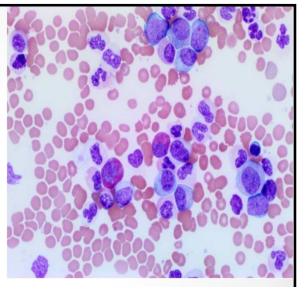


Signs
- Mainly affected - facial bones, jaw
- Rarely - other organs – breasts, ovaries
- Sometimes abdominal lymphadenopathy - swollen abdomen, pain



42

43



Leukocytosis

- increase in the white blood cell count

Causes:

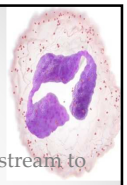
- primary disorder of bone marrow production
  - congenital
  - acquired malignant disorder
- secondary response to a disease process, drug, or toxin

Leukopenia

- much frequent – one or more populations affected, imbalance in the white cell subpopulations
- rare - decrease in the absolute total count

44

Neutrophilia



Congenital forms of neutrophilia

- Leucocyte adhesion deficiency
  - defect of integrins of leucocytes → phagocytes do not migrate from the bloodstream to sites of infection
  - Signs - recurrent cutaneous abscesses, periodontal infections, gingivitis
- Chronic idiopathic neutrophilia
  - No clinical signs
- Hereditary neutrophilia
  - Signs - splenomegaly

Secondary neutrophilia

- Acute bacterial infection
- Chronic inflammatory processes
- Neutrophilia in patients with osteomyelitis, empyema, septicaemia, and tuberculosis
- Non-infectious causes - carcinoma (lung, stomach, breast), Hodgkin's disease, juvenile rheumatoid arthritis...
- Stress neutrophilia - within minutes of exercise or emotional or physical stress, after surgery, seizures, or epinephrine injection
- Drugs—Steroids - stimulate the release of neutrophils from the bone
- Marrow stimulation—haemolytic anaemias or immune thrombocytopenia result in chronic bone-marrow stimulation
- Asplenia—functional or pathological asplenia, after surgical removal of the spleen, or in various congenital and acquired diseases

45

Neutropenia

- Leads to high risk of infection

Marrow failure

- aplastic anaemia, Fanconi's anaemia, myelodysplasia, acute leukaemia.

Primary inherited neutropenias

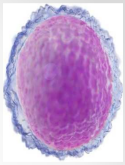
- Congenital agranulocytosis (Kostmann's syndrome)
  - frequent and life-threatening infections
- Schwachman-Diamond-Oski syndrome
  - triad of neutropenia, skeletal abnormalities, and exocrine pancreatic insufficiency
- Chediak-Higashi syndrome
  - oculocutaneous albinism, progressive neurological abnormalities
- Dyskeratosis congenita
  - abnormal skin pigmentation, nail dystrophy, and mucosal leucoplakia

Secondary neutropenias

- Drugs
  - phenothiazines, non-steroidal anti-inflammatory agents, gold salts, ibuprofen...
- Viral infections
  - HIV, varicella, measles, rubella, infectious mononucleosis, influenza, hepatitis A and B...
- Bacterial infections
- Autoimmune neutropenia
  - SLE, rheumatoid arthritis, autoimmune thrombocytopenic purpura, autoimmune haemolytic anaemia
- Lymphoproliferative disease
- Other causes
  - deficiencies of vitamin B12, folate, copper

46

Lymphocytosis



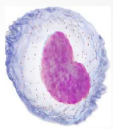
- Viral infections
  - Infectious mononucleosis
    - Epstein-Barr virus
    - characteristic large atypical lymphocytes
- Bacterial infections
  - Bordetella pertussis infection
- Drug-induced immunological reactions
  - atypical lymphocytes that are large, irregular, and deeply basophilic

Lymphopenia

- Severe combined immunodeficiency
  - deficiency of both T and B lymphocytes
- A deficiency of adenosine deaminase
  - accumulation of the toxic metabolites of purine metabolism
- Acute infections
  - HIV infection - reduction in CD4-positive T lymphocytes is one of the earliest immunological consequences of HIV infection

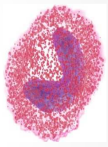
47

Monocytosis



- Chronic infectious or inflammatory disorders
- Several leukaemic disorders
  - Chronic myelomonocytic leukaemia
  - Juvenile myelomonocytic leukaemia - children younger than 4 years

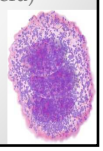
Eosinophilia



- Mainly secondary
  - inflammatory, allergic, or atopic disorder
  - parasitic infections
  - several malignant disorders, including Hodgkin's and non-Hodgkin

Basophilia

- Acute hypersensitivity reactions
- Chronic infections and inflammatory disorders (tuberculosis, rheumatoid arthritis, ulcerative colitis)
- Viral infections (influenza, varicella)
- Chronic myeloproliferative disorders (chronic myeloid leukaemia, polycythaemia vera)
- Mast-cell leukaemia
  - rare
  - the presence of large numbers of mast cells in the peripheral blood, associated with leucocytosis and granulocytosis
  - these patients generally survive for less than 6 months



48