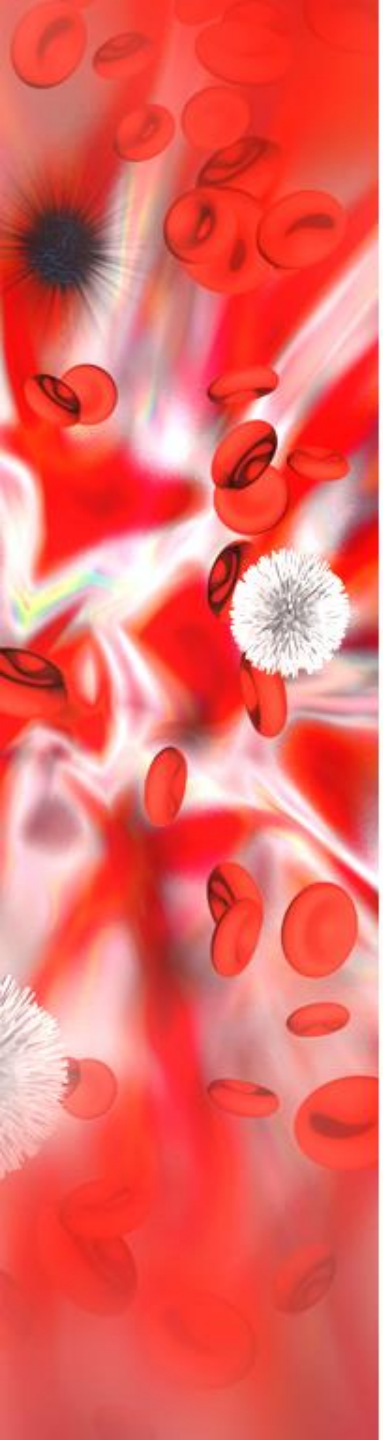
Lecture 11: Lymphoproliferative disorders

[What is Hodgkin's lymphoma]
[Understanding multiple myeloma]
[What is multiple myeloma?]
[Chronic Lymphocytic Leukemia]
[Follicular Lymphoma Overview]



INTRODUCTION

- The difference between the lymphoma and leukemia :
  - Lymphoma: Malignant mass of lymphoid cells.
  - Leukemia: circulating cancer either blasts or mature cells.
- lymphoma actually is lymphocytosis.
- Lymphoma is represent 30% of malignant cancer in KSA
- Lymphoproliferative disorders doesn't include only lymphoma!
- Autoimmune disease is caused by B- Cell lymphocyte.

Definition:

- Lymphoproliferative disorders:

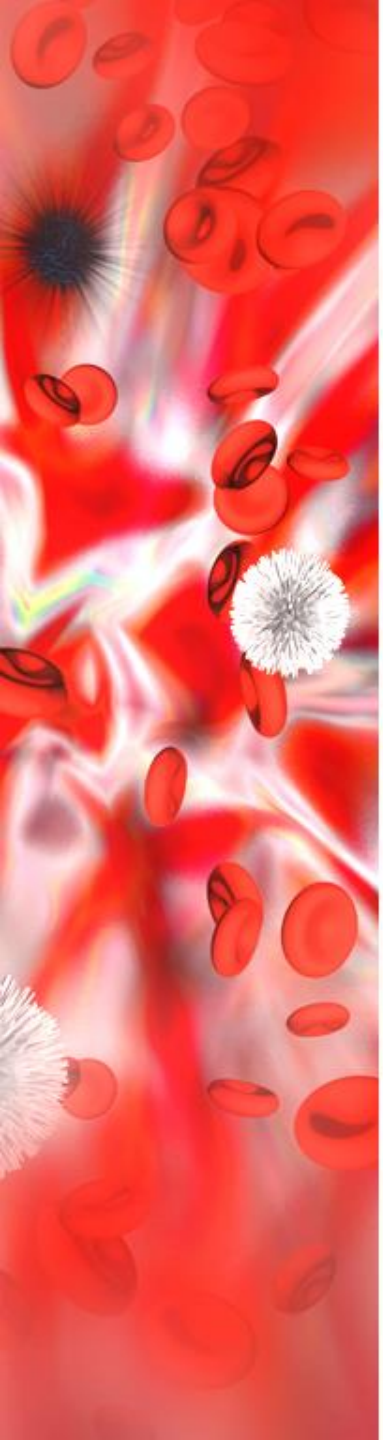
Several clinical conditions in which lymphocytes are produced in excessive quantities (Lymphocytosis)

- Lymphoma:

Malignant lymphoid mass involving the lymphoid tissues (± other tissues e.g : skin ,GIT ,CNS …)

- Lymphoid leukemia:

Malignant proliferation of lymphoid cells in Bone marrow and peripheral blood (± other tissues e.g : lymph nods ,spleen , skin ,GIT ,CNS …)

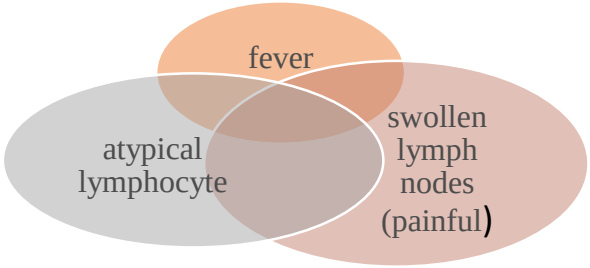


Lymphocytosis:

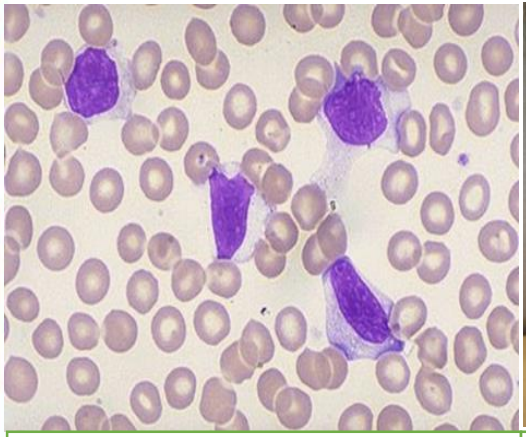
1- Viral infection :	Infectious mononucleosis ,cytomegalovirus* ,rubella, hepatitis, adenoviruses, varicella….
4-bacterial infection:	(Pertussis ,brucellosis …)
3-Immune	SLE , Allergic drug reactions
4- Other conditions	splenectomy, dermatitis ,hyperthyroidism metastatic carcinoma….)
5- Chronic lymphocytic leukemia (CLL)	
6- Other lymphomas: Mantle cell lymphoma ,Hodgkin lymphoma…	

*cytomegalovirus :
Newborns infected with CMV in the womb (congenital CMV), babies who become infected during birth or shortly after birth (perinatal CMV) — such as through breast-feeding — and people with weakened immune systems are more at risk of developing signs and symptoms than are healthy adults.

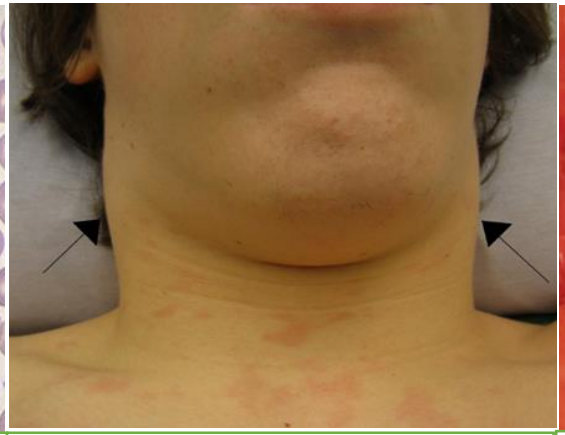
Infectious mononucleosis



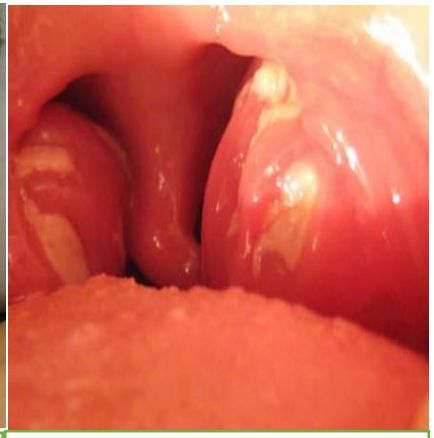
- An acute, infectious disease, caused by **Epstein-Barr virus**
- EBV is herpes virus transmitted through **saliva** cause IM and implicated in the development of **Burkitt's lymphoma and Hodgkin's disease**.
- it can take up to a month before symptoms begin.



Atypical lymphocyte

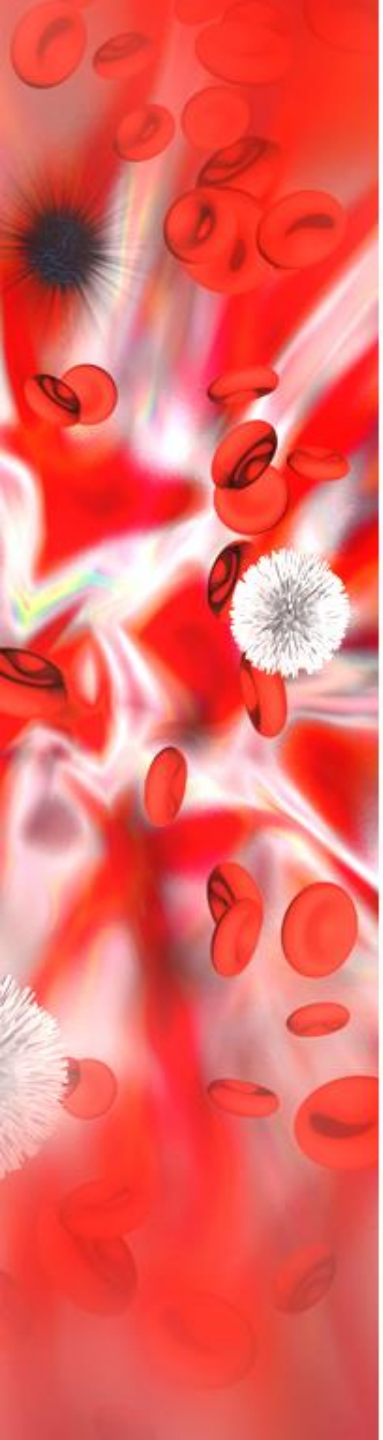


Enlarged lymph node
e.g. tonsillitis, pharyngitis



Exudative pus

However, one of the best way to get Hodgkin lymphoma and burkitt's lymphoma is to fight this virus
Because it goes in B- cells in transformation of the genetics.



- Lab investigation:

Virus specific antibodies	
IgM	early and last for few month
IgG	Develops later and persists for life
Heterophile antibodies (old tests)	
Antibodies produced due to infection and react to antigen in animal RBCs.	
Paul-Bunnell test	**Sheep RBCs**
Monospot test	**Horse RBCs**

- Treatment:

Supportive, Rest, Analgesia

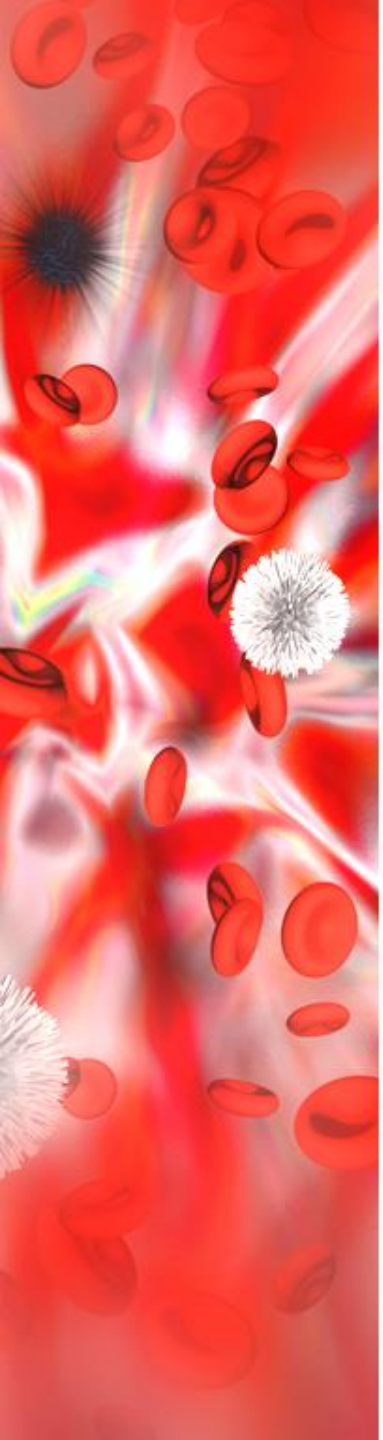
Steroid or Acyclovir in severe cases or at complication

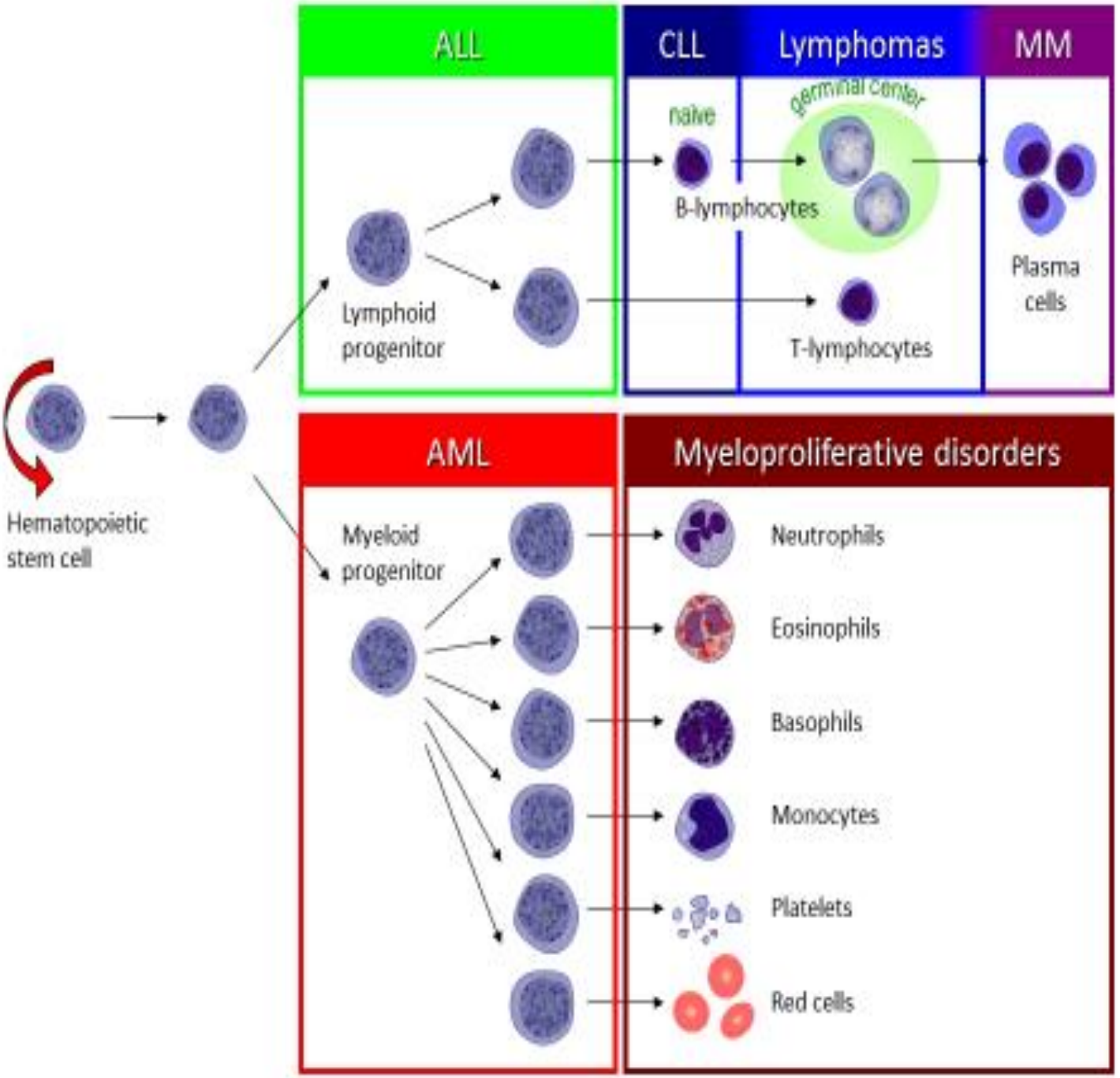
- Complication:

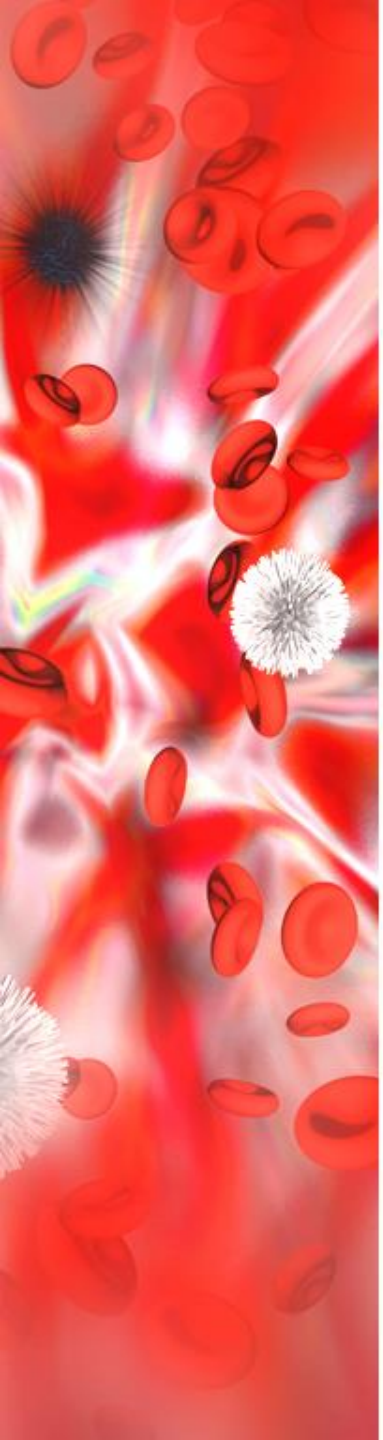
hepatitis

encephalitis

splenic rupture




ALL
CLL
Lymphomas
MM
naive
germinal center
B-lymphocytes
Plasma cells
Lymphoid progenitor
T-lymphocytes
Hematopoietic stem cell
AML
Myeloproliferative disorders
Myeloid progenitor
Neutrophils
Eosinophils
Basophils
Monocytes
Platelets
Red cells



Malignant Lymphoproliferative disorders

1- Immature: ALL

2- Mature:

A. Lymphoma

- **Non Hodgkin lymphoma:**
  - **B- cell neoplasm 90%**

    Burkitt lymphoma ,Diffuse large B lymphoma ,Follicular lymphoma , Multiple myeloma
  - **T- cell neoplasm 10%**

    Adult T leukemia lymphoma, Sezary syndrome*, Large anaplastic* T lymphoma
- **Hodgkin lymphoma**

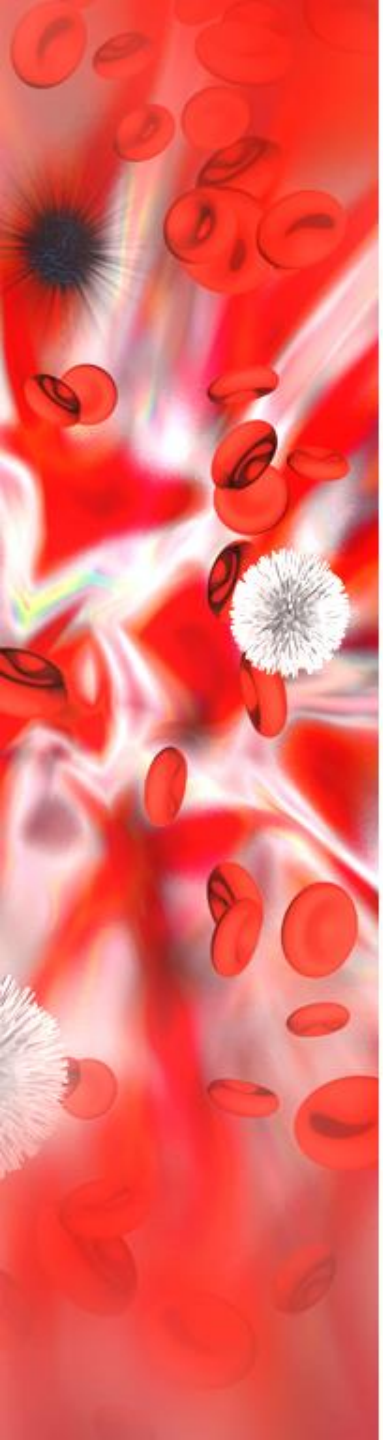
B. Lymphoid leukemia

- **CLL, Hairy cell leukemia*, T- prolymphocytic leukemia ,Leukemic phase of lymphoma**

*Sezary syndrome: proliferation of T-cell with CD4 in peripheral blood and erythroderma in the skin

*Large anaplastic T lymphoma characteristically in pediatrics

*Hairy cell leukemia "B-Cell"



Chronic lymphoid Leukemia

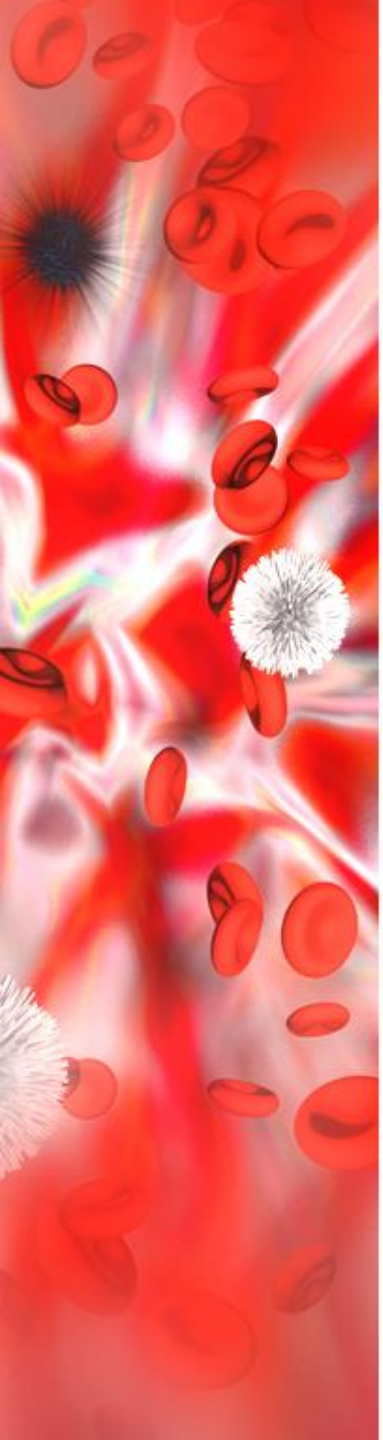
Malignant neoplasim characterized by an increased number of small, mature lymphocytes in the blood (>5,000) and bone marrow (± spleen and lymph node)
The most common adult leukemia (~25% of adult leukemias)
The median age is ~55 to 65 years. (rare < 40 years).
1.5 to 2 times more common in men than women.

Features of CLL
- 40% of patients are asymptomatic at diagnosis.
- Moderate lymphadenopathy and splenomegaly
- Predisposition to infection
- Autoimmune phenomena (autoimmune hemolytic anemia)
- Transformation to large cell lymphoma (Richter's syndrome)

Charactersitcs

IMPORTANT

- **Small mature-appearing lymphocytes**
- **Condensed ("soccer ball") nuclear chromatin**
- **Numerous "smudge cells"**

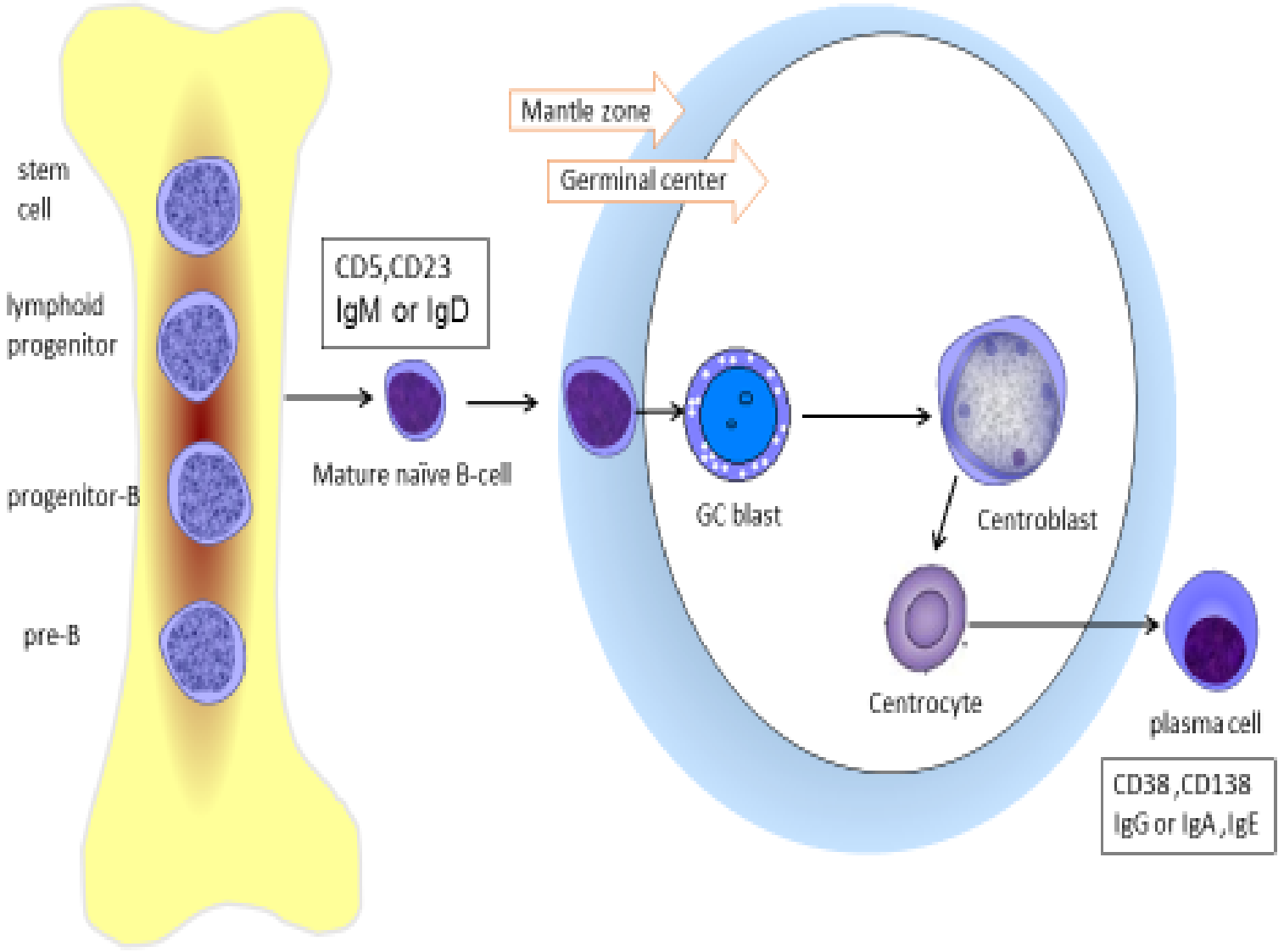


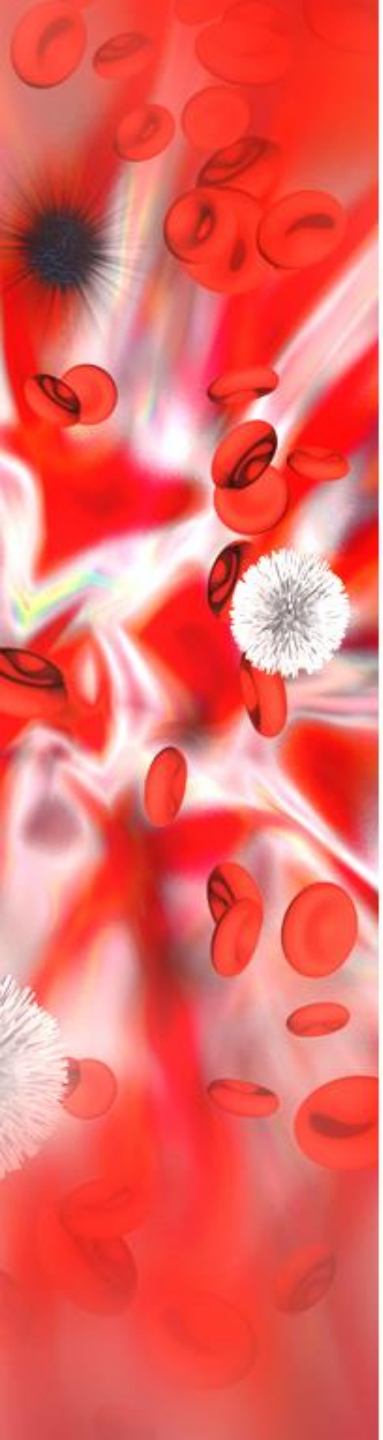
CD34 &TDT | Surface immunoglobin

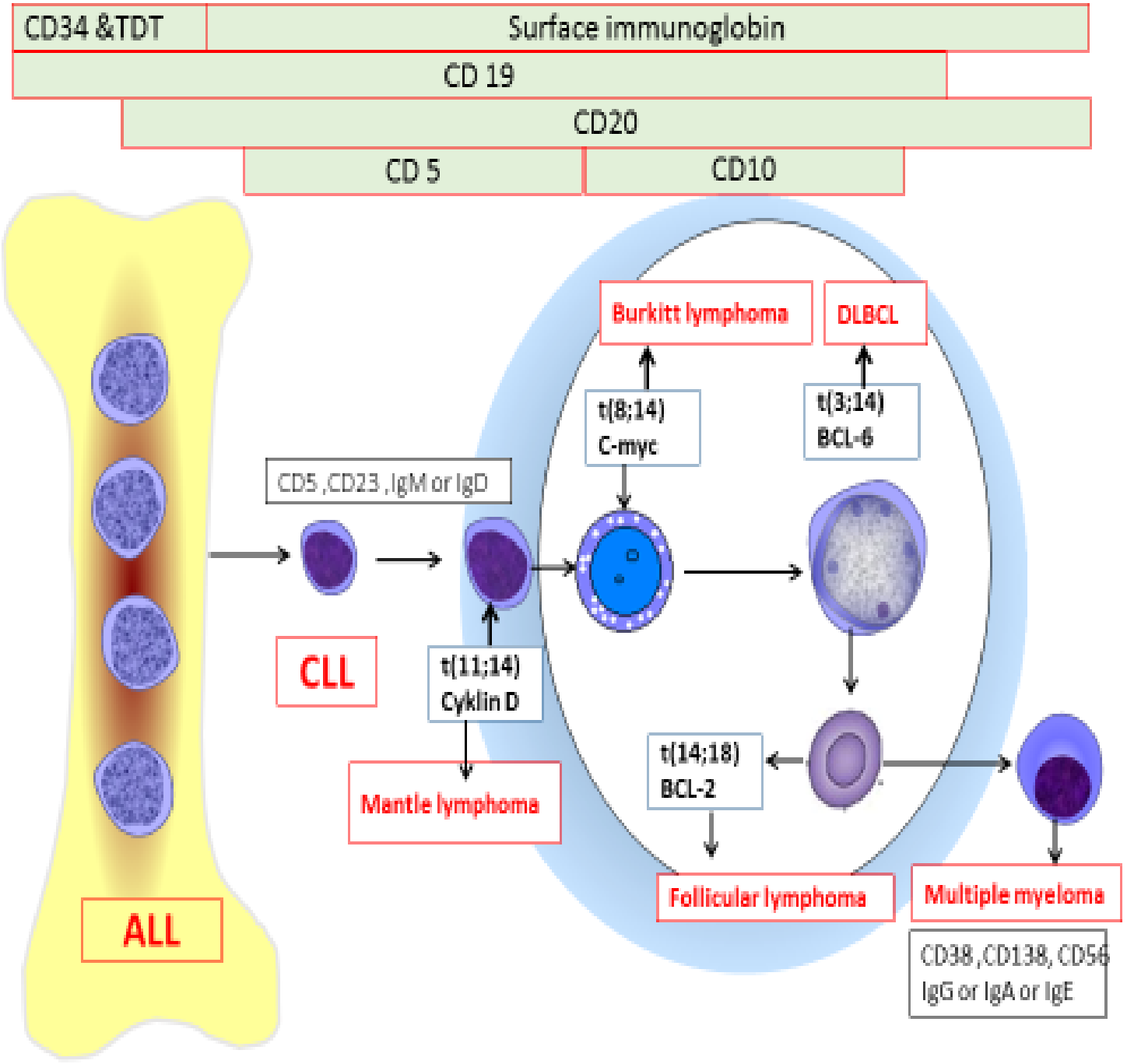
CD 19

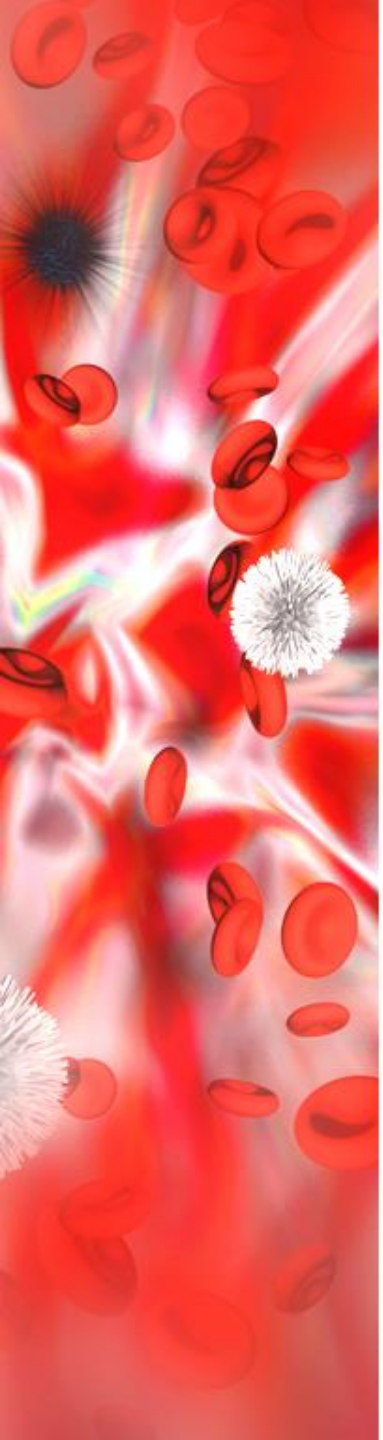
CD20

CD 5 | CD10






CD34 &TDT
Surface immunoglobin
CD 19
CD20
CD 5
CD10
ALL
CD5 ,CD23 ,IgM or IgD
CLL
t(11;14)
Cyklin D
Mantle lymphoma
t(8;14)
C-myc
Burkitt lymphoma
t(3;14)
BCL-6
DLBCL
t(14;18)
BCL-2
Follicular lymphoma
Multiple myeloma
CD38 ,CD138, CD56
IgG or IgA or IgE



Explanation of previous figure:

- Bone marrow:
- Stem cell > Lymphoid progenitor > Myloid > Progenitor-B > pre-B
- At that stage it will be **CD34 & TDT** "majority"
- Once the cell express surface **immunoglobin** it means it is mature cells!
- Mature naïve B-cell is positive Surface immunoglbin, **CD19, CD20, and CD5**. And negative is **CD10.**

and express IgM, and IgD (it is like MD doctor postgraduate :)

➢ When "**mature naïve B-cell**" enter the germ center it will do:

1- class switching from IgM and IgD to (IgG, IgA, and IgE)

2- Somatic hypermutation: which recognize a few antigen

* the cells in the germinal center is represent 5% of T-lymphocyte

Burkitt's lymphoma:

- **High-grade non-Hodgkin's B-cell lymphoma.**
- Rapidly growing and highly aggressive with extremely short doubling time (24 hrs)

Types

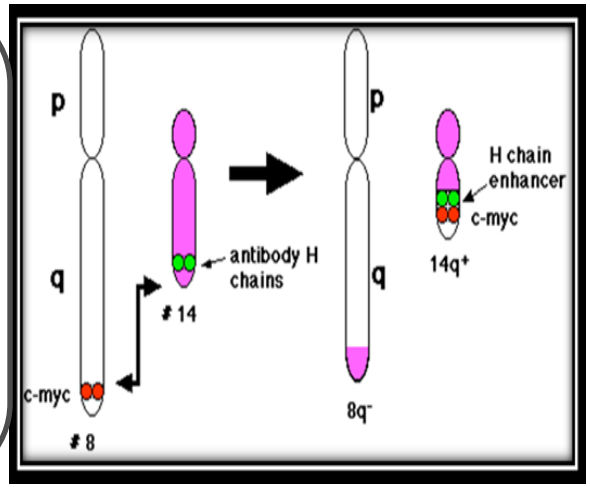
Endemic*:* chronic malaria and EBV In equatorial Africa particularly affects the jaw, other facial bone and breast

Sporadic: occurs throughout the world and affects GIT.

Immunodeficiency-associated: HIV infection or the use of immunosuppressive drugs.

• Genetics of BL:

- **Highly associated with t(8;14):**
- **Translocation of the c-MYC proto-oncogene at chromosome 8 to immunoglobulin gene at chromosome 14**
- The c-MYC is nuclear transcription factor.
- Burkitt's lymphoma is the **<u>fastest growing tumor</u>** in humans.

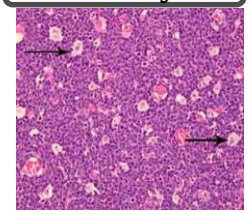


• Morphology:

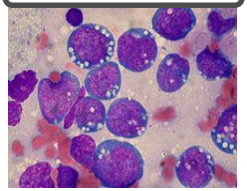
Diffuse infiltration with "starry sky"
(Macrophages engulfing the apoptotic cells)

Homogenous medium size cells with round nuclei and deeply basophilic and vacuolated cytoplasm

Biobsy



BMA



Cure rate: 90% at early phase, 70% at advance disease

Follicular lymphoma

IMPORTANT!!

- Follicular Lymphoma is malignant proliferation of germinal center B cells centrocyte which has at least a partially follicular pattern.
- Due to overexpression o f Bcl2 caused by t(14;18) .
- Most common type of “indolent” lymphoma (25%). BUT incurable Median survival is around 10 years.

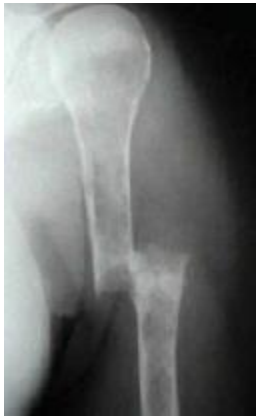
Clinical Presentation	
100%	Lymphadenopathy
80%	Splenomegaly
60%	Bone Marrow involvement
40%	Blood involvement

Diagnosis	
	Immunophenotyping
+	CD10,CD20 and Bcl2
-	CD5 (in most cases)

MANGEMEENT:

Low grade Follicular Lymphoma: Watch and wait	in transformation: **Chemothearpy**	Aggressive transformation (DLBCL): **Aggressive Chemotherapy(± SCT)**

Multiple Myeloma



Malignant B neoplasm characterized by a triad of abnormalities:

- Accumulation of plasma cells* in the bone marrow
- Lytic Bone lesions
- Production of a monoclonal immunoglobulin (Ig) or Ig fragments
- Patient present with bone pain, multiple fractures, hypercalcemia
- One of the Most common malignancy in Saudi Arabia

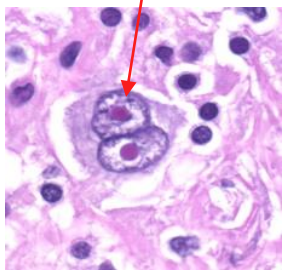
Classical Hodgkin Lymphoma:

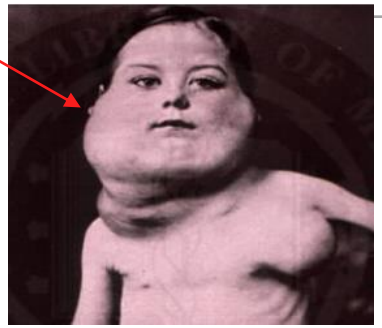
Characteristics

1- Presence of few large binucleated cells (Reed-Sternberg) surrounded by reactive cells (lymphocytes, plasma cells ,eosinophils)

2- Involving cervical lymph nodes in young adults (most often)*

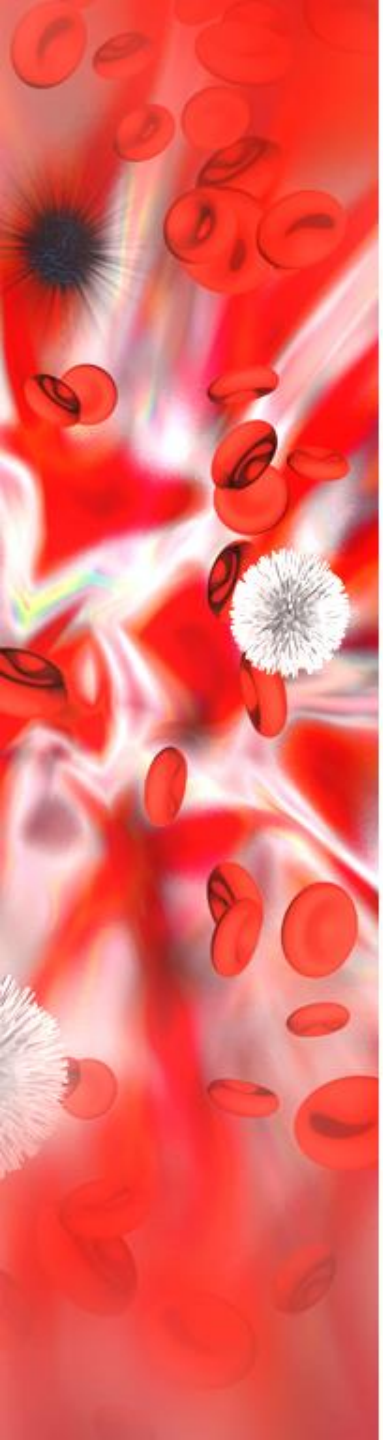
Diagnosis
CD 30
CD 15





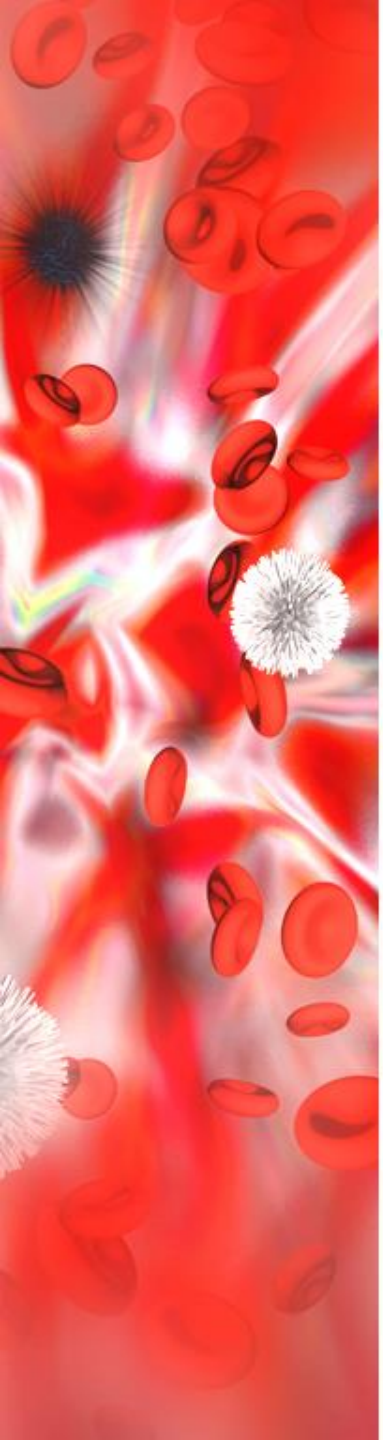
*Plasma cell will activate osteoclast (which resorbs bone tissue) and inhibit osteoblast (synthesize bone), that will lead to osteolytic lesion and vertebrae fracture

*Classical presentation: young patient, bilateral lymphadenopathy



Summary from essential hematology for Hodgkin lymphoma

- Lymphomas are a group of diseases caused by malignant lymphocytes that accumulate in lymph nodes and cause lymphadenopathy.
- The major subdivision of lymphomas is into Hodgkin lymphoma and non-Hodgkin lymphoma and this is based on the presence of Reed–Sternberg cells in Hodgkin lymphoma.
- Reed–Sternberg cells are neoplastic B cells but most cells in the lymph node are reactive inflammatory cells.
- The usual clinical presentation is with painless asymmetrical lymphadenopathy – most commonly in the neck.
- Constitutional symptoms of fever, weight loss and sweating are prominent in patients with widespread disease.
- Blood tests may show anaemia, neutrophilia and raised erythrocyte sedimentation rate (ESR) or lactic dehydrogenase (LDH).
- Diagnosis is made by histological examination of an excised lymph node and there are four subtypes of disease.
- Staging of the disease is important for determining treatment and prognosis. History, examination, blood tests, CT and PET scan are typically used.
- Treatment is with radiotherapy, chemotherapy or a combination of both. The choice depends on the stage and grade of the disease.
- The response to treatment can be monitored by CT and PET scans. Disease relapse can be treated with chemotherapy, sometimes with stem cell transplantation.
- The prognosis is excellent and over 85% of patients can expect to be cured. Late side effects of treatment are a concern.



Summary from essential hematology for Non-Hodgkin lymphoma

- Non-Hodgkin lymphomas are a large group of clonal lymphoid tumours. Approximately 85% are of B-cell origin and 15% derive from T or NK cells.
- Their clinical presentation and natural history are more variable than Hodgkin lymphoma and can vary from very indolent disease through to rapidly progressive subtypes that need urgent treatment.
- For many years clinicians have divided lymphomas into low-grade and high-grade disease. This is useful as low-grade disorders are typically slowly progressive, respond well to chemotherapy but are very difficult to cure, whereas high-grade lymphomas are aggressive and need urgent treatment but are more often curable.
- Investigation is with lymph node biopsy, blood tests and radiology. Immunohistochemistry of the lymph node is valuable and cytogenetic analysis is performed in many cases.
- Clinical staging is performed as for Hodgkin lymphoma.
- Some of the more common subtypes include:

  Small lymphocytic lymphoma is the lymphoma equivalent of chronic lymphocytic leukaemia.

  Lymphoplasmacytic lymphoma usually produces an IgM paraprotein, when it is also known as Waldenström's macroglobulinaemia, and often leads to anaemia and hyperviscosity.

  Marginal zone lymphomas arise from marginal zone B cells of lymphoid follicles and can occur in many organs, usually as a result of chronic antigenic stimulation.

  Follicular lymphoma represents 25% of all NHL and is associated with the t(14; 18) translocation. Treatment usually achieves disease remission but the only curative option is allogeneic stem cell transplantation.

  Mantle cell lymphoma is associated with increased expression of the cyclin D1 gene and has clinical features of an 'intermediate grade' lymphoma.

  Diffuse large B-cell lymphoma is a common subtype and is an aggressive disease which needs urgent treatment. It shares features with acute leukaemia and the majority of cases are cured.

  Burkitt lymphoma is one of the most highly proliferative subtypes of any tumour. Endemic cases in Africa are associated with EBV infection. Treatment is with aggressive chemotherapy regimens.

  T-cell lymphomas are less common but include *mycosis fungoides*, *peripheral T-cell lymphomas* and *anaplastic large cell lymphoma.*
- Treatments for NHL are based on a variety of chemotherapy regimens. Anti-CD20 antibodies are used in most cases of B-cell lymphomas and have markedly improved the outlook.

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