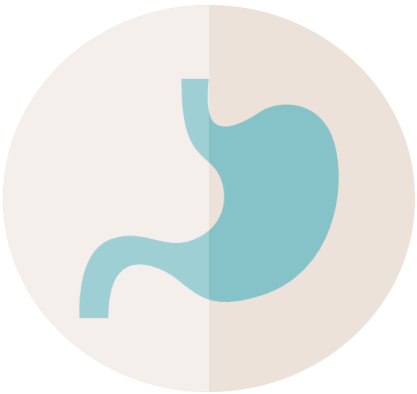


Lymphoproliferative disorders

Objectives:

- To understand the general features of lymphoproliferative disorders (LPD)
- To understand some benign causes of LPD such as infectious mononucleosis
- To understand the general classification of malignant LPD
- To understand the clinicopathological features of chronic lymphoid leukemia
- To understand the general features of the most common (LPD) (Burkitt lymphoma, Follicular
- lymphoma, multiple myeloma and Hodgkin lymphoma).

Important.

Extra.

Notes

"Success is the result of perfection, hard work, learning from failure, loyalty, and persistence. Colin"

Powell

References:

436 girls & boys' slides

435 teamwork slides

Editing file

Do you have any suggestions? Please contact us!

@haematology436 E-mail: Haematology436@gmail.com

or simply use this form

Definitions

Lymphoma (20min)

Lymphoproliferative disorders: Several clinical conditions in which lymphocytes are produced in excessive quantities (**Lymphocytosis**) increase in lymphocytes that are **not** normal

Lymphoma: Malignant lymphoid mass involving the lymphoid tissues. (± other tissues e.g: skin, GIT, CNS ..) The main deference between Lymphoma & Leukemia is that the Lymphoma proliferate primarily in Lymphoid Tissue and cause Mass , While Leukemia proliferate mainly in BM& Peripheral blood

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

BCL is an anti-apoptotic (prevent apoptosis)

Lymphocytosis (causes)

1- Viral infection: ***Infectious mononucleosis***, *cytomegalovirus, rubella, hepatitis, adenoviruses, varicella*

The most common cause of lymphocytosis is viral infection

2- Some* bacterial infection: (*Pertussis, brucellosis)***

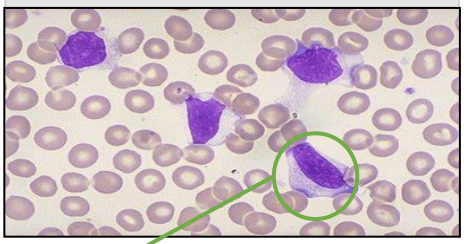
* Usually bacterial infections give PMN

3- Immune : SLE, Allergic drug reactions

4- Other conditions:, *splenectomy, dermatitis, hyperthyroidism metastatic carcinoma*)

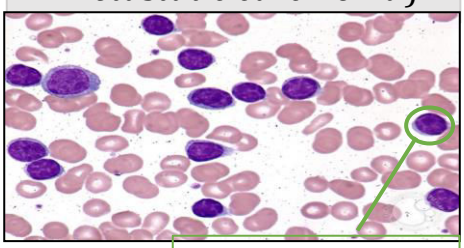
5- Chronic lymphocytic leukemia (CLL)

6- Other lymphomas: ***Mantle cell lymphoma* , *Hodgkin lymphoma***

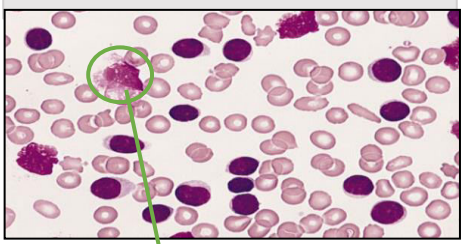


Reactive lymphocyte

NO blasts!



Mature lymphocyte

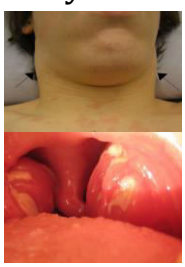


Smear cell

Infectious mononucleosis (May predispose the patient to Lymphoma if it chronic)

An acute, infectious disease, caused by Epstein-Barr virus(EBV) characterized by:

- Fever
- Swollen lymph nodes (painful) 'lymphadenopathy'
- Sore throat
- **Atypical lymphocyte** مميز

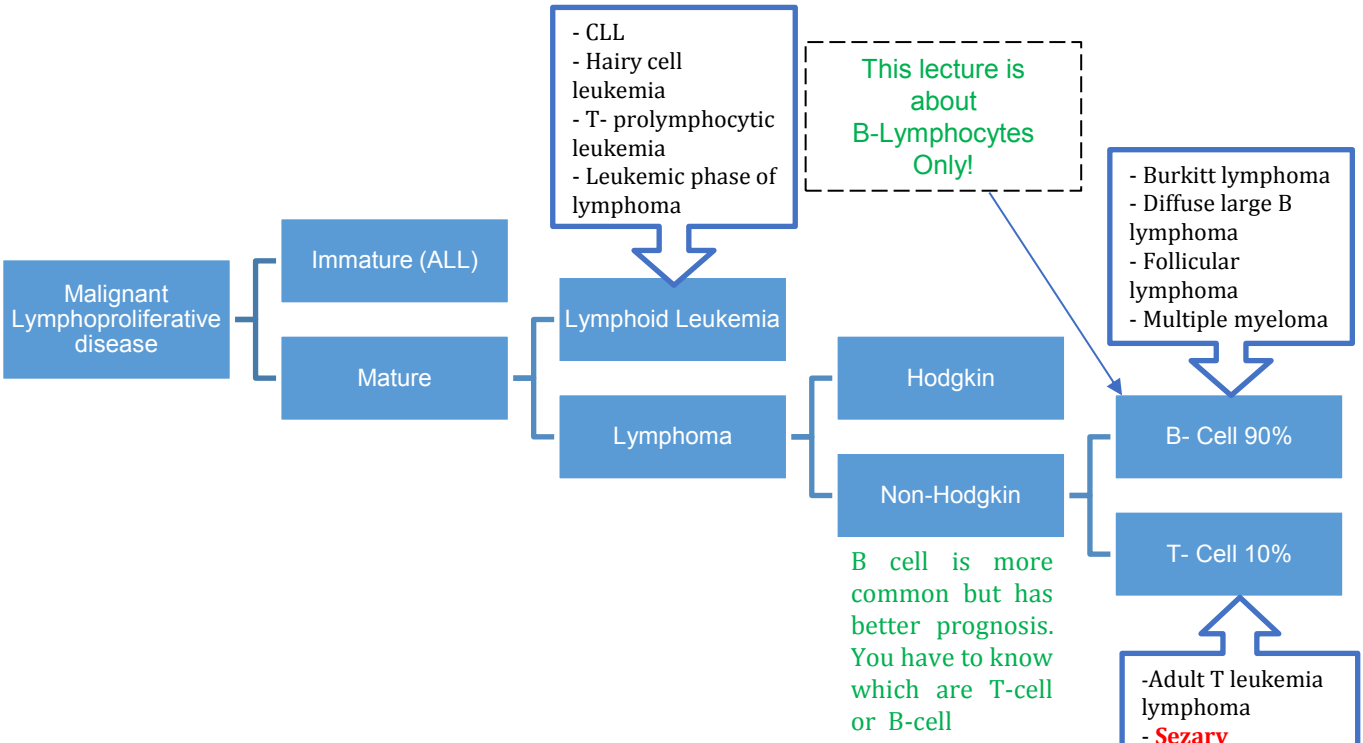


Affect young people (usually) most common cause of lymphocytosis in children

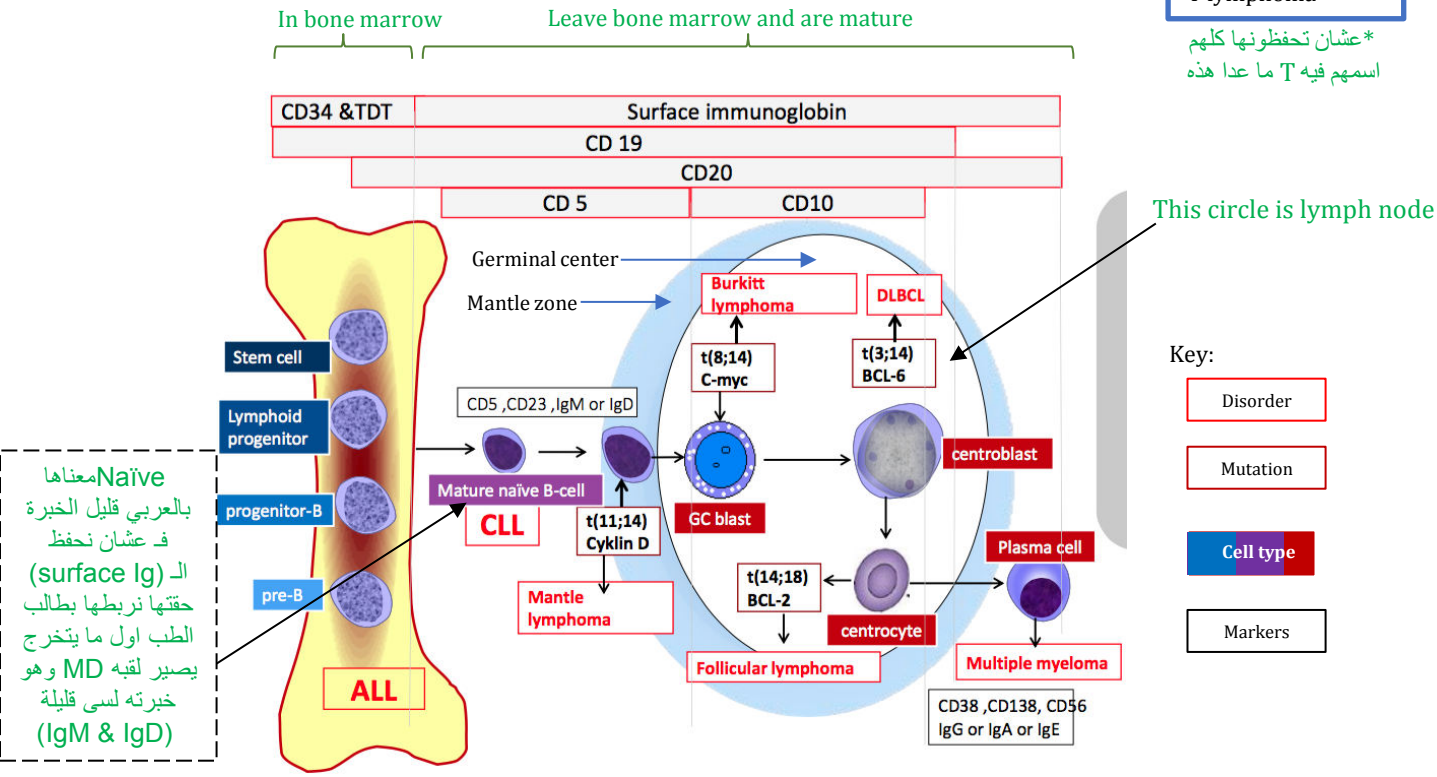
Clinically, IM presents like ALL. But when we do blood smear we will find atypical lymphocytes and NO blasts and this will rule out ALL.

In a hurry? Skip to the table (slide 7) مستعجل\ة؟ اقفزاي إلى الجدول

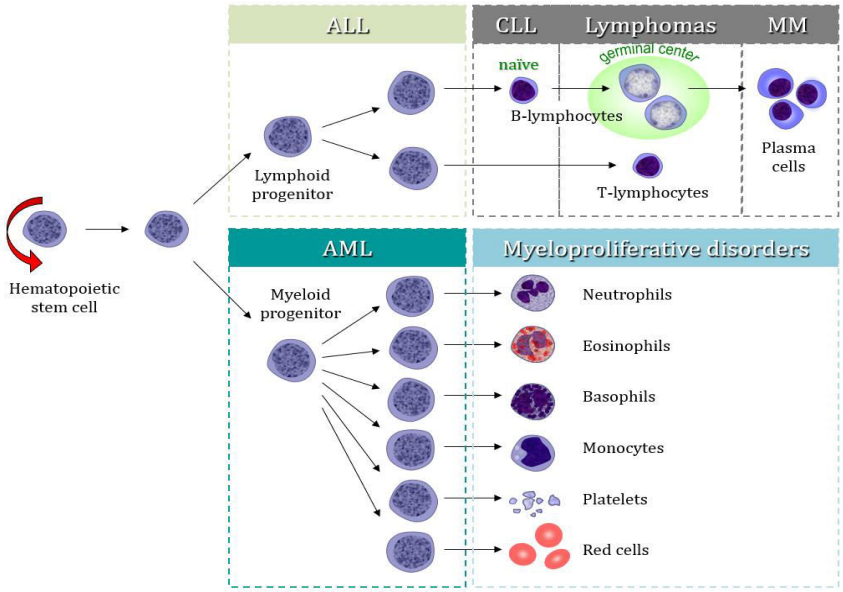
Malignant lymphoproliferative disorders



Journey of B-lymphocytes & mutations that cause disorders:-



Throughout the maturation where ever the disease occurs (at which stage) there will be specific findings
For the mutations notice that they all have the number 14 so just memorise the other number.

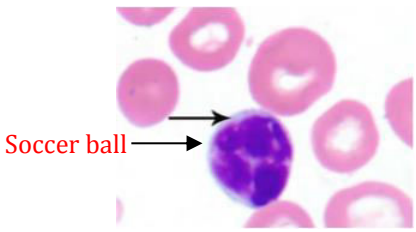


Chronic lymphocytic leukemia

- Malignant neoplasm characterized by an increased number <u>of **small, mature lymphocytes**</u> **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.

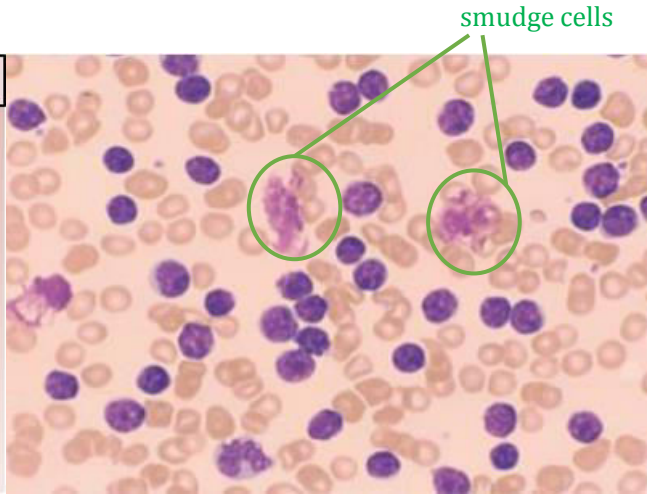
Features:

- 40% of patients are asymptomatic at diagnosis.
- Moderate lymphadenopathy and splenomegaly
- Lymphocytosis (>5,000): (Most important)
  - Small mature-appearing lymphocytes
  - Condensed ("soccer ball") nuclear chromatin
  - Numerous "smudge cells"
- Predisposition to infection
- Autoimmune phenomena (autoimmune hemolytic anemia)
- Transformation to **large cell lymphoma** (Richter's syndrome)



CLL Staging

Rai Staging		Prognosis
Stage 0:	Lymphocytosis only (blood and marrow)	Low risk
Stage I:	Lymphocytosis plus enlarged nodes	Watch &wait
Stage II:	Lymphocytosis plus enlarged spleen and/or liver, ± nodes	Intermediate
Stage III:	Lymphocytosis plus anemia (Hgb <11 g/dL), ± above	± chemo
Stage IV:	Lymphocytosis plus thrombocytopenia (<100 × 10^9/L) ± above	High risk FCR



Burkitt's Lymphoma

High-grade **non-Hodgkin's B-cell lymphoma** which is rapidly growing (**fastest growing tumor** in humans) and highly aggressive with extremely short doubling time (24 hrs) but it has excellent response if we act quickly (see the picture)

Types:-

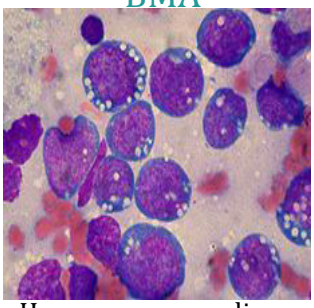
1-**Endemic**: associated with chronic malaria and EBV In equatorial Africa . It particularly affects the jaw, other facial bone and breast.

2-**Sporadic**: occurs throughout the world and affects GIT.

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

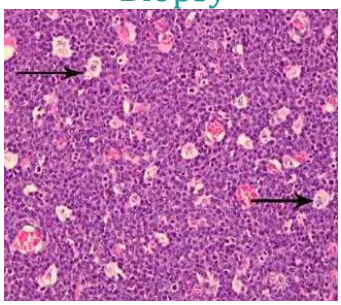
Morphology

BMA



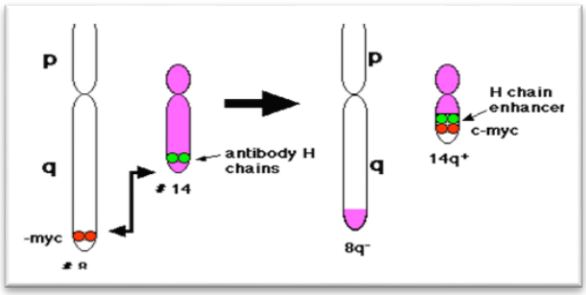
Homogenous medium size cells with round nuclei and deeply basophilic and **vacuolated** cytoplasm

Biopsy



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

Genetics



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 .

Follicular Lymphoma

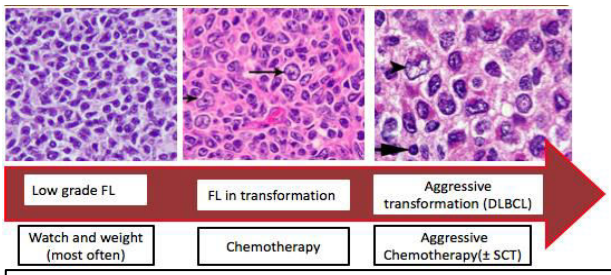
- A malignant proliferation of germinal center B cells centrocyte which has at least a partially follicular pattern.
- Due to overexpression o f Bcl2 (anti apoptotic gene become + عشان كذا اللمفوسايت يصير لها تجمع وما تموت) caused by t(14;18) .
  - Most common type of "indolent" lymphoma (25%).
  - Indolent but incurable (some exceptions)

May take long time to present but when it does it is incurable (تطبخ على نار هادية)

Presented as:

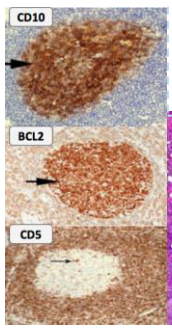
- Lymphadenopathy (100%)
- splenomegaly (80%)
- BM involvement (60%)
- blood involvement (40%).

Follicular Lymphoma Management

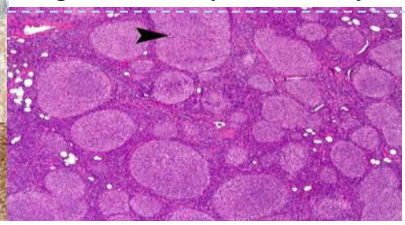


Median survival is around 10 years.
Transformation to aggressive lymphoma (DLBCL) can occur

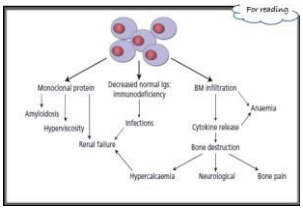
Diagnosis



Immunophenotyping:
Positive for CD10, CD20 and Bcl2
Negative for CD5 (in most cases)



Multiple Myeloma

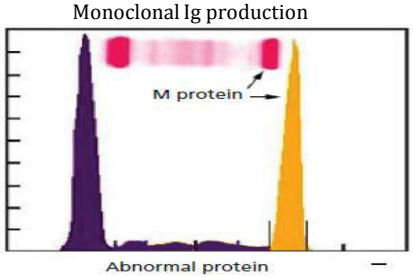


Pathogenesis

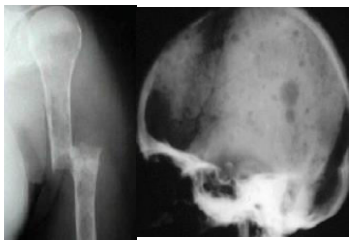
Malignant B neoplasm characterized by a **triad** of abnormalities:

1. Accumulation of plasma cells in the bone marrow
2. Lytic Bone lesions (can cause bone Pain & Fracture)
3. Production of a monoclonal immunoglobulin (Ig) or Ig fragments

Monoclonal Ig production

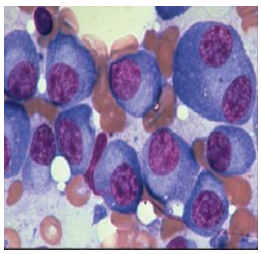


Bone Lesions



شكل العظم متأكل او يكون فيه
Fracture in bones

Accumulation



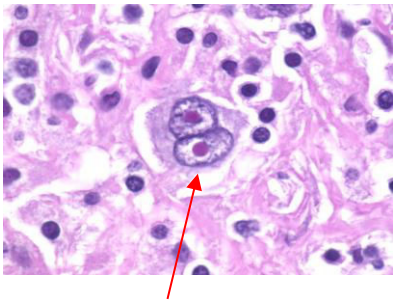
Dark basophilic cytoplasm & nucleus is at the side

Hodgkin Lymphoma

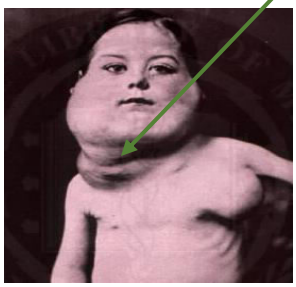
Indolent (Idle) malignant lymphoma
characterized by:

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

2- Involving cervical lymph nodes in young adults (most often) They become very huge!

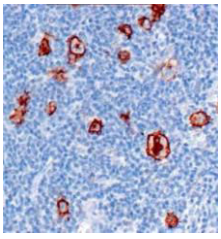


Reed-Sternberg

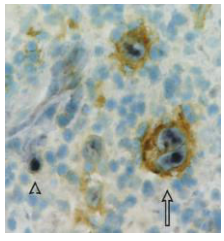


Lymph node Involvement

Diagnosis



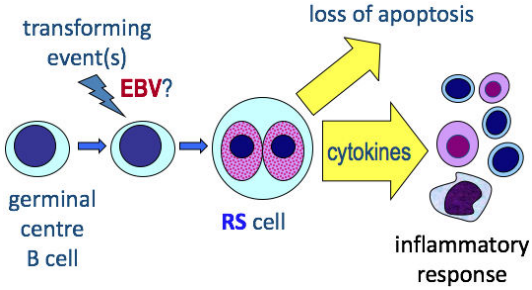
CD 30



CD 15

These markers should be positive.

Possible Pathogenisis

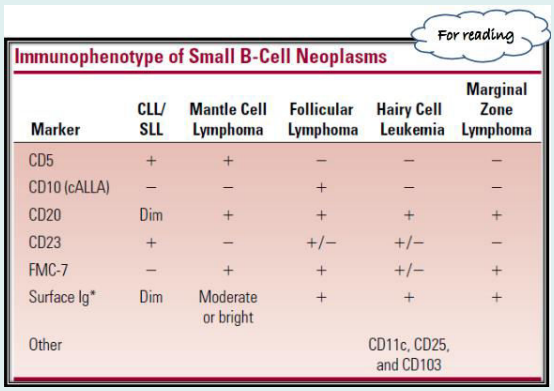


Germinal center B cell with EBV leads to dinucleate (RS cell) which in response lead to loss of apoptosis (accumulation) & recruit cytokines

Summary

Malignant Lymphoproliferative Disorders

Types	Mature						
	Lymphoid leukemia	Lymphoma					
	CLL	Non Hodgkin lymphoma B- cell neoplasm					Hodgkin
		Burrkit's	Follicular	DLBCL	Multiple Myeloma	Mantle Cell	
Markers	CD19, CD20 CD23, **CD5**	CD19, CD20 CD10			CD20, CD138 CD56	CD5 CD19 CD20	CD15 CD30
Mutations	Mature naïve B-cell IgM & IgD	t(8;14) C-myc GC blast	t(14;18) BCL-2 Centrocytes	t(3;14) BCL-6 Centro-blasts	Plasma cells	t(11;14) Cyklin D	
Features	**Diagnosis**: **Lymphocytosis (>5,000):** • Small mature-appearing lymphocytes • Condensed ("**soccer ball**") nuclear chromatin • Numerous "smudge cells" -Moderate lymphadenopathy and splenomegaly	rapidly growing and highly aggressive with extremely short doubling time (24 hrs) **Morphology**: 1- **BMA**: Homogenous medium size cells with round nuclei and deeply basophilic and vacuolated cytoplasm 2- **Biopsy**: Diffuse infiltration with **"starry sky"** (Macrophages engulfing the apoptotic cells)	- a partially follicular pattern Presented as: • Lympha-denopathy (100%) • Spleno-megaly (80%) • BM involve-ment (60%) • Blood involve-ment (40%)		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		Indolent (Idle) malignant lymphoma characterized by: **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)
Notes	Most common adult leukemia Male > Female **Complications**: • Predisposition to infection • Autoimmune phenomena (autoimmune hemolytic anemia) • Transformation to large cell lymphoma (Richter's syndrome)	**Types**: **1-Endemic**: associated with chronic malaria and EBV In equatorial Africa. affects the jaw, other facial bone and breast. **2-Sporadic**: affects GIT. **3-Immunodeficiency-associated**: associated with HIV infection or immunosuppressive drugs **Cure rate:** 90% at early phase 70% at advance disease	Most common type of "indolent" lymphoma, but incurable (some exceptions). Transformation to aggressive lymphoma (DLBCL) can occur				



MCQs:

1- Which of the following can cause Infectious Mononucleosis?
a- Autoimmune diseases b- Malaria
c- E.Coli d- Epstein-Barr Virus

2- Ahmad is 35-Years old went to his family physician suffering from severe pain in his bones, After investigations his physician advised him to see Hematologist, the Hematologist told Ahmad that he has type of B-cells lymphoma, What is the most likely diagnosis in Ahmad's condition?
a- CLL b- Multiple myeloma
c- Burkitt Lymphoma d-Hodgkin Lymphoma

3- Khaled 25-Years old come to you to make general check-up, in CBC you find that his Lymphocyte number is more than 5000 (normal=1500-2700), in blood film you found Soccer ball appearance & Smudge cells, what is most likely diagnosis in this case?
a- CLL b- Multiple myeloma
c- Burkitt Lymphoma d-Hodgkin Lymphoma

4- Which type of lymphoma is featured by presence of Binucleated cells (Reed-Sternberg) & involves cervical lymph nodes mainly?
a- CLL b- Multiple myeloma
c- Burkitt Lymphoma d-Hodgkin Lymphoma

5- t(8;14) C-MYC Mutation is associated with which one of the following?
a- CLL b- Multiple myeloma
c- Burkitt Lymphoma d-Hodgkin Lymphoma

1- d
2- b
3- a
4- d
5- c

GOOD LUCK!

Team members:

Khalid Al-Eisa

Abdulkarim Al-Harbi

Jawaher Abanumy

Team Leaders:

Abdulaziz Al-Hussainy

Safa Al-Osaimi