MED439
KING SAUD UNIVERSITY

Lymphoproliferative Disorder

Objectives:

- To understand the general features of lymphoproliferative disorders
- 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 lymphoma (Burkitt lymphoma, Follicular lymphoma, multiple myeloma and Hodgkin lymphoma)

Dr's notes
Important
Extra notes
** Only in girls slide
** Only in boys slide

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Introduction

Lymphoproliferative disorders

- General term including several clinical conditions in which lymphocytes are produced in excessive quantities (↑Lymphocytes = lymphocytosis).
- **Etiology:**
  - Autoimmune
  - Infection
  - Malignancy

1. **Viral infection: Infectious mononucleosis** (most important cause)**,** Cytomegalovirus, Rubella, Hepatitis, Adenoviruses, Varicella and coronavirus. "Benign lymphocytosis". Most common cause of lymphocytosis.
2. **Bacterial infection:** Pertussis, Brucellosis."Benign lymphocytosis"
3. **Immune:** Systemic lupus erythematosus, Allergic drug reactions. "Benign lymphocytosis"
4. **Other conditions**: Splenectomy, Dermatitis ,Hyperthyroidism metastatic carcinoma."Benign lymphocytosis"
5. **Lymphoid leukemia**: Chronic lymphocytic leukemia (CLL)."Malignant lymphocytosis"
6. **Lymphomas**: Mantle cell lymphoma, Hodgkin lymphoma. "Malignant lymphocytosis"

Lymphoma

- Malignant lymphoid **mass** involving the **lymphoid tissues** like lymph nodes, spleen and thymus (± other tissues e.g: skin ,GIT ,CNS ...). Here we are not talking about proliferation in the bone marrow or in the peripheral blood, here the patient will come with a **mass**

Lymphoid leukemia

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

Lymphoma Vs. Leukemia

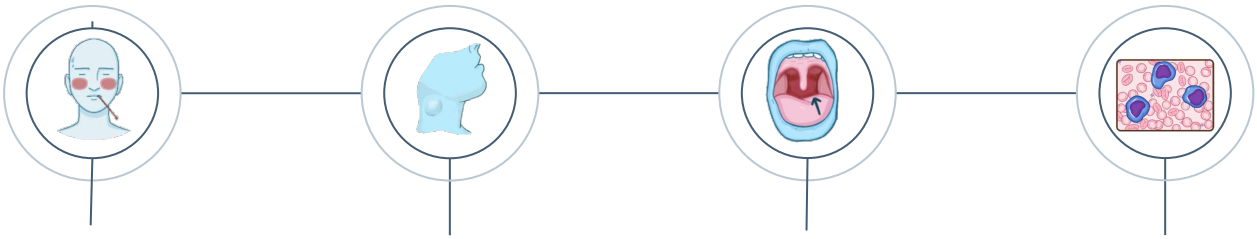
Lymphoma: proliferate primarily in lymphoid tissue and cause a mass

Leukemia: proliferate mainly in bone marrow & peripheral blood

Infectious Mononucleosis (IM)

Osmosis

- Known as "kissing disease" because it spreads by saliva.
- EBV is herpes virus transmitted through saliva cause IM and the virus is implicated in the development of Burkitt's lymphoma and Hodgkin's disease.
- Infectious mononucleosis is a major differential diagnosis of lymphoma.
- After the virus enters the body it can take up to a month before symptoms begin.
- **Infectious mononucleosis is an acute, infectious disease ★ caused by Epstein-Barr virus and it affect young people (usually) characterized by:**



Fever

Swollen lymph nodes (painful)

The infected B cells spread through the lymph tissue causes them to swell up.
You **should** worry when the mass is painless.
Painless masses indicate malignancy.

Sore throat

The epithelial cells infected which will cause inflammation of the throat
""Pharyngitis"
We will see some abscess on the tonsils

Atypical lymphocyte

#436: 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.

Lab investigation

01

Virus specific antibodies:

- IgM : Develops early and last for few month
- IgG: Develops later and persists for life.

Final diagnosis is made through:

- PCR, serology, IgM, IgE

02

Heterophile antibodies (old tests)
Antibodies produced due to infection and react to antigen in animal RBCs.

- Paul-Bunnell test: Sheep RBCs agglutinate in the presence of heterophile antibodies
- Monospot test: Relies on the agglutination of the horse RBCs by heterophile antibodies in patient's serum

Management

- Self limiting disease (4-6 weeks).
- Unusual complication such hepatitis ,encephalitis and splenic rupture may occur.

Treatment

- Supportive
- Rest
- Analgesia
- Steroid or Acyclovir in severe cases or at complication

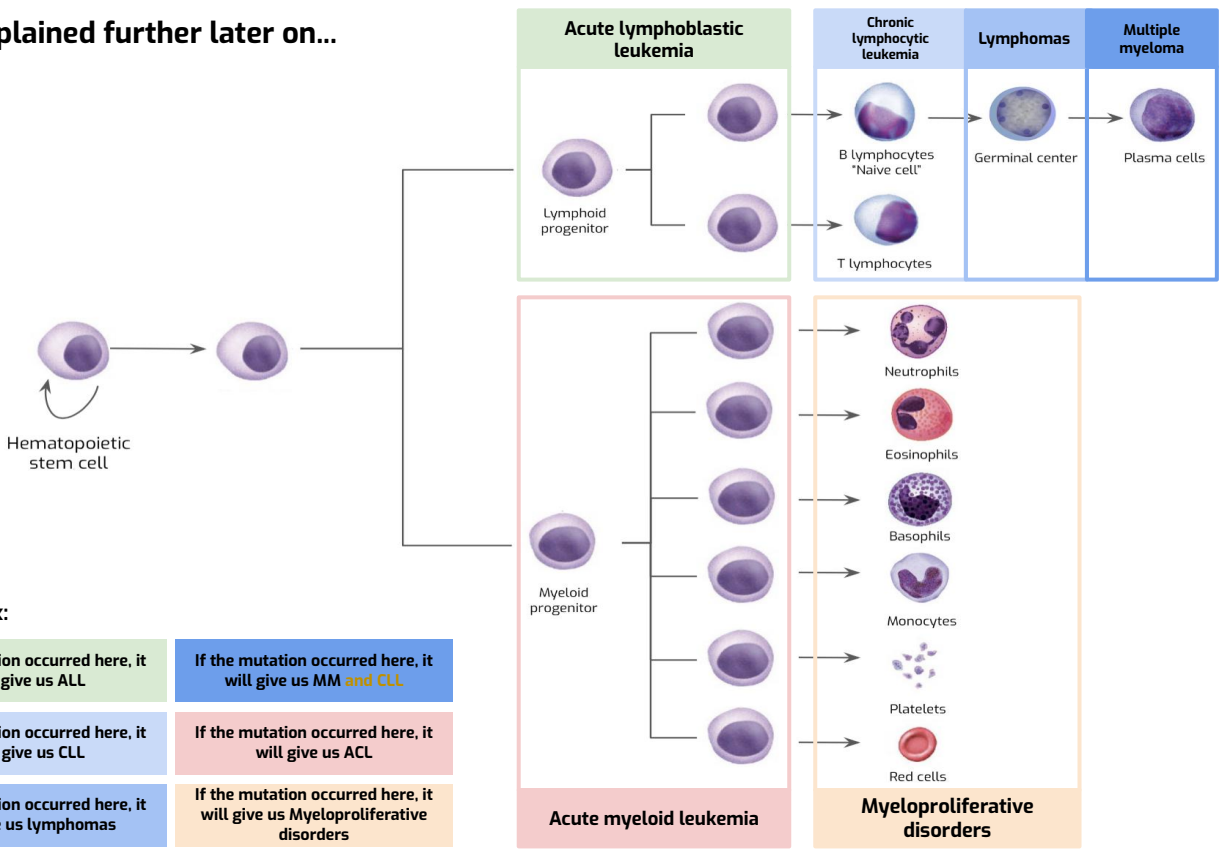
Malignant Lymphoproliferative Disorder

Make sure you read the examples

Malignant Lymphoproliferative Disorders

- **Immature**
  - **Acute lymphoblastic leukemia**
    - Markers for **immature B cells** (Lymphoblasts): CD34 and TDT+
- **Mature**
  - **Lymphoma**
    - The mass primarily located in the lymph node and spleen then it can metastasize.
    - **Non Hodgkin lymphoma**
      - **90% B-cell neoplasm**
        - B cell is more common and has better prognosis than T cell
        - Burkitt lymphoma
        - Diffuse large B lymphoma
        - Follicular lymphoma
        - Multiple myeloma
      - **10% T-cell neoplasm**
        - We worry about it because it's very aggressive
        - Adult T leukemia lymphoma
        - Sezary syndrome
        - Large anaplastic T lymphoma
    - **Hodgkin lymphoma**
  - **Lymphoid leukemia**
    - Cells are seen in bone marrow and peripheral blood
    - **Chronic lymphocytic leukemia**
    - Hairy cell leukemia
    - T- prolymphocytic leukemia
    - Leukemia phase of lymphoma

Will be explained further later on...

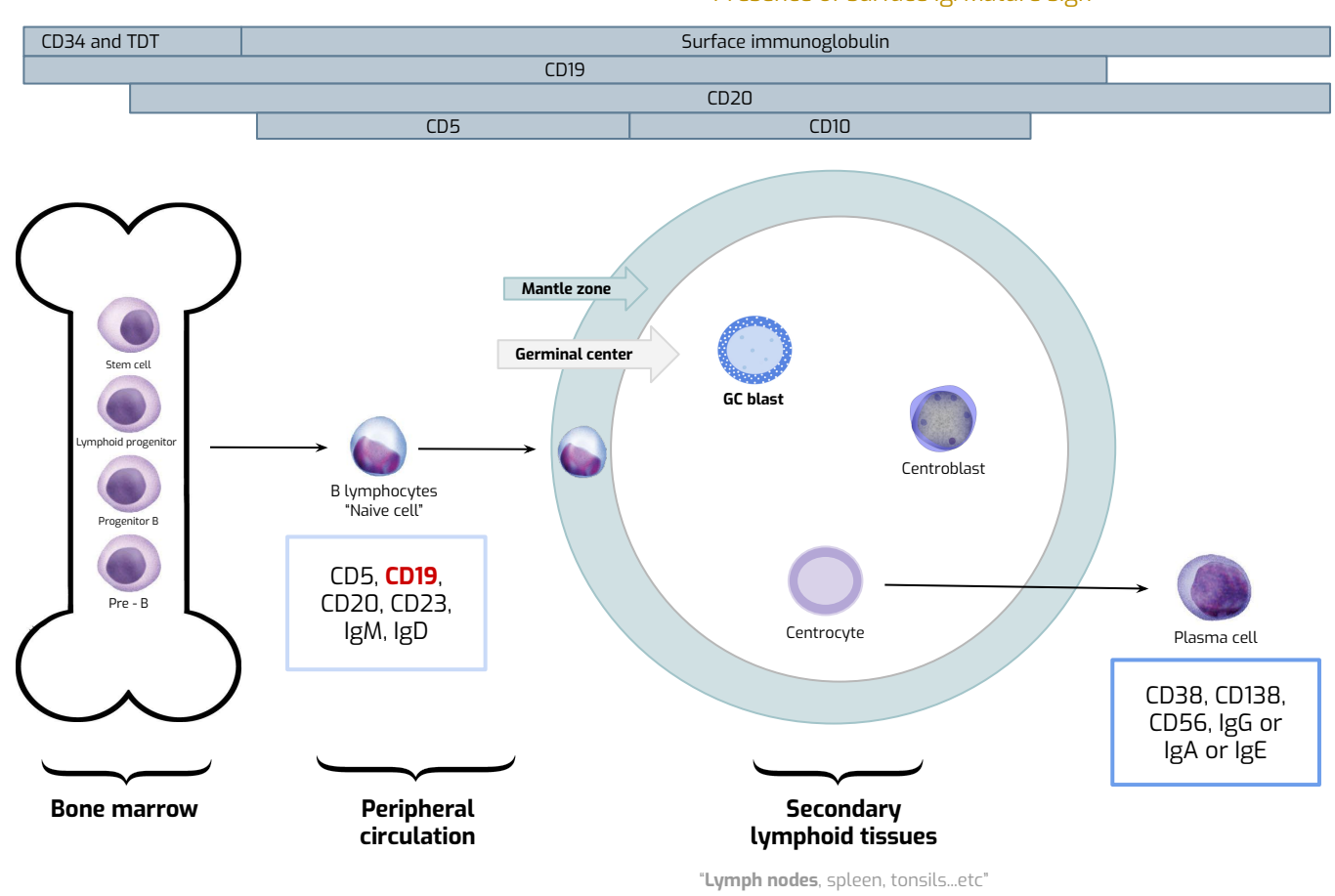


Color index:

If the mutation occurred here, it will give us ALL	If the mutation occurred here, it will give us MM and CLL
If the mutation occurred here, it will give us CLL	If the mutation occurred here, it will give us ACL
If the mutation occurred here, it will give us lymphomas	If the mutation occurred here, it will give us Myeloproliferative disorders

Malignant Lymphoproliferative Disorder, Contd...

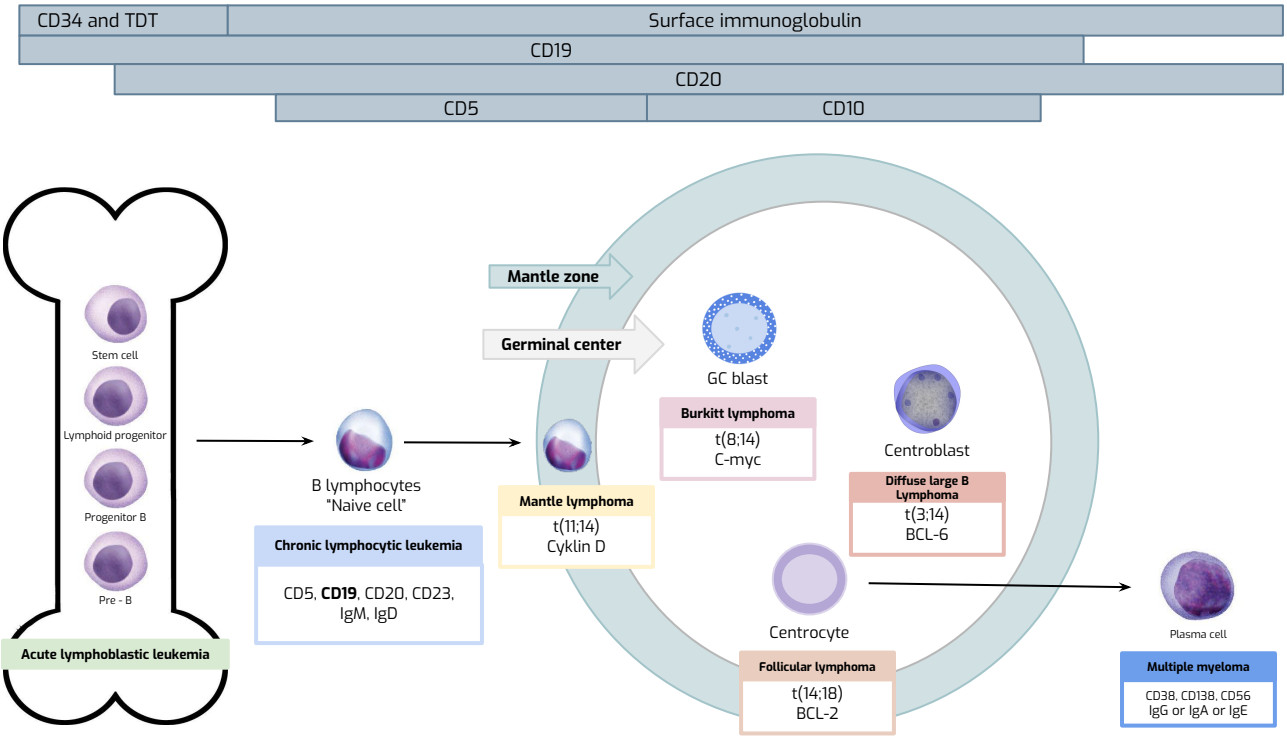
B Cell Development Stages



The following explains normal physiology of B cell development

- **CD34+ is a stem cell marker.**
- **All B cells are CD19+ except for plasma cells. T Cells are CD3+.**
- As you can see in the pic we have the stem cells in the bone marrow, once the cell gets mature it will go outside the bone marrow and go to the peripheral circulation, in order to call the cell "mature" it has to have IgM and IgD "MD like med student" but it's naïve "ماعندها خبرة زي طبيب الامتياز" which is recognized by CD5+, CD20+, CD19+, IgM and IgD. Whereas IgG, IgA and IgE is highly specialized Igs " يعني خبيرة تكون على الخلايا الخبيره زي الاستشاري"
- Now the naïve mature cell will enter the mantle zone which is also recognized by CD5+, CD20+, **CD19+**, IgM and IgG. The cell will go to the germinal center which responsible for proliferation of B cells "المصنع حقنا" or the residency program we could say because it will teach the B-cells to increase its affinity to recognize more antigens and to do class switch which means we want to add to it IgG, IgA and IgE" now the naïve cell will be converted to GC blast (germinal center blast), but it's mature because it is TDT and CD34 **negative**.
- Then it will converted to centroblast then centrocyte " عندها خبرة زي الاستشاري" and finally it will be converted to plasma cell which can produce any type of Igs and we call it terminally differentiated ".

Malignant Lymphoproliferative Disorder, Contd...



The following explains pathology of B cell development:

- **Mantle zone mutation** t(11;14), there's translocation of cyklin D from Ch.11 to Ch.14 which will lead to **overexpression** of cyklin D giving us mantle cell lymphoma.
- **GC blast mutation** will give us burkitt's lymphoma which is c-myc t(8;14). C-myc is transcription factor, which means the mutation is **inside the nucleus** making it a very aggressive disorder.
- **Centrocyte mutation** it will give us follicular lymphoma which is BCL-2 t(14;18). **BCL-2** is anti-apoptotic marker "الروح", Cells with BCL-2 do not die. Normally once the B cell enters the germinal center the BCL-2 should be **switched off**, but the mutation here will **activate the BCL-2 again** so any cell will be produced here it won't die which will lead to accumulation of cells.

Male Dr: make sure you know the markers. Especially for CLL. **Remember** the morphology of **GC Blast**

Disease	Mature Malignant Lymphoproliferative Disorders					
	Lymphoid leukemia	Lymphoma				Multiple Myeloma
	CLL	Mantle	Burkitt's	DLBCL	Follicular	
Cell affected	Mature naïve B-cell	Mantle zone	Germinal center blast	Centroblast	Centrocyte	Plasma cells
Markers	**CD5, CD19, CD20, CD23, IgM & IgD**	**CD5**,CD19 CD20	**CD10**, CD19, CD20	-	**CD10**, CD19, CD20	CD38, CD138, CD56, IgG, IgA, IgE
Mutations	-	t(**11**;14) Cyklin D	**t(8;14)** C-myc	t(3;14) BCL-6	**t(14;18)** **BCL-2**	-

Chronic Lymphocytic Leukemia (CLL)

Pathoma (Skip to 1:11) Osmosis (Skip to 5:33)

- It is a malignant neoplasm characterized by an **increased** number of small, mature **lymphocytes** in the **blood** (>5,000) and bone marrow (± spleen and lymph node). "It's Neoplastic proliferation of naïve B-Cells"
- The most common adult leukemia (~25% of adult leukemias) in western countries whereas in our region the most common is Multiple myeloma.
- The median age is ~55 to 65 years (rare < 40 years).
- 1.5 to 2 times more common in men than women.

Presentation

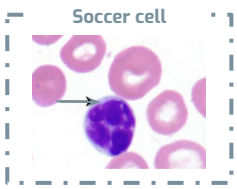
- 40% of patients are **asymptomatic** at diagnosis. Moderate lymphadenopathy and splenomegaly

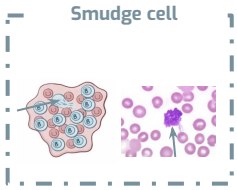
Complications

- **Predisposition to infection** Most of the patient die because of it
- **Autoimmune phenomena** (autoimmune hemolytic anemia). The cells attack its own RBCs and kill them off.
- Transformation to large B-cell lymphoma (Richter's syndrome). The patient will present with enlarged lymph nodes "**lymphadenopathy**"

Lab Findings

- Lymphocytosis (>5,000):
  - ❏ Small mature-appearing lymphocytes.
  - ❏ Condensed ("**Soccer ball**") nuclear chromatin.
  - ❏ Numerous ("**Smudge cells**") "B-cells broken into smear".





CLL Staging

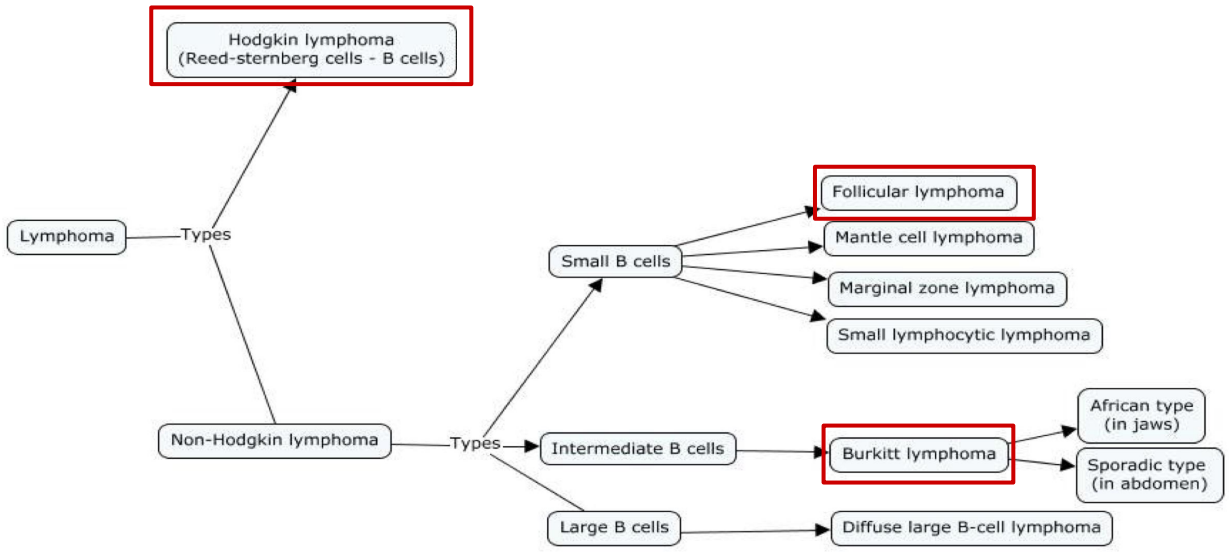
Male dr: we should now the staging because we behave according to it
Female dr: I don't care about staging as much as features

Rai Staging		Prognosis
Stage 0	lymphocytosis only (blood and marrow)	Low risk (Watch and Wait)
Stage I	lymphocytosis plus enlarged nodes	
Stage II	lymphocytosis plus enlarged spleen and/or liver, ± nodes	Intermediate (± Chemotherapy)
Stage III	lymphocytosis **plus anemia(H gb<11 g/dL)**,± above	
Stage VI	lymphocytosis **thrombocytopenia** (<10 x 10^9),± above	High risk (FCR)

Overview of Lymphomas

From Pathoma

What is a lymphoma? Neoplastic proliferation of lymphoid cells that makes a mass; may arise in lymph node or extranodal tissue. The ones highlighted in red are to be discussed in this lecture.



Distinguish Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL):

	Hodgkin lymphoma	Non-Hodgkin lymphoma
Frequency	40%	60%
Malignant cells	Reed-Sternberg cells (owl eye cells) - B cells induce inflammation and fibrosis	Lymphoid cells - many subtypes - most are B cell than T cells
Mass composition	Inflammatory cells and fibrosis (reactive cells)	Lymphoid cells
Clinical	- Painless lymphadenopathy - B symptoms - Bimodal: classically seen in young adult and >55 yrs	- Painless lymphadenopathy - Classically seen in late adults
Spread	Contiguous (touching); rarely extranodal	Diffuse; often extranodal
Staging	Guides therapy Radiation mainstray treatment	Limited importance
Leukemic phase	Doesn't occur	occurs
Prognosis	Much better prognosis than non-Hodgkins	
Association	EBV	HIV and autoimmune diseases

Burkitt's Lymphoma (BL)

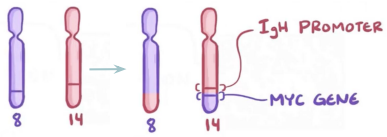
Osmosis
(Skip to 5:40)

It is a high-grade non-Hodgkin's B-cell lymphoma which is **rapidly growing and highly aggressive** with extremely short doubling time (24 hrs),
#436: has excellent response if we act quickly.

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

Genetics of BL

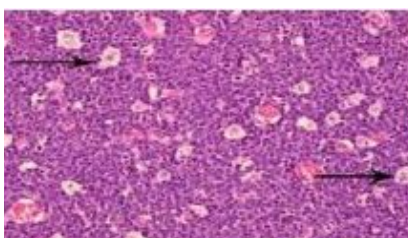


- Highly associated with **t(8;14)**: Translocation of the c-MYC proto-oncogene (Nuclear transcription factor) at chromosome 8 to immunoglobulin gene at chromosome 14.
- c-MYC is a nuclear transcription factor located inside the nucleus.
- Burkitt's lymphoma is the fastest growing tumor in humans.

Clinical picture & Morphology

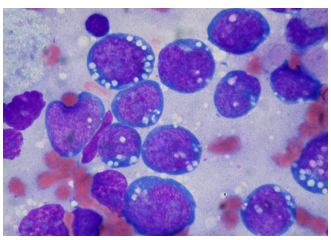
*Bone marrow Appearance

Biopsy

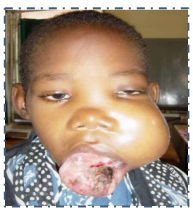


Diffuse infiltration with "**starry sky**" (Macrophages engulfing the apoptotic cells) benign

BMA*



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



After 25 days of intensive chemotherapy

Cure rate

- **90% at early phase**
- **70% at advance disease**

Follicular Lymphoma (FL)

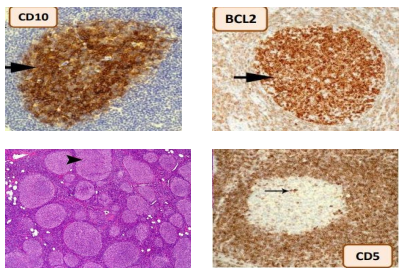
Osmosis
(Skip to 4:57)

- It is a malignant proliferation of germinal center B cells **centrocyte** which has at least a partially follicular pattern.
- Most common type of **indolent** lymphoma (25%). Indolent lymphomas are **slow-growing**.
- Indolent but incurable (some exceptions).
- **Due to overexpression o f BCL-2 caused by t(14;18).** BCL-2 is an antiapoptotic gene, any cell expressing this marker will not die. In FL, no proliferation nor apoptosis occurs due to overexpression of BCL-2 which causes accumulation of the malignant cells.
- Presented as:
  - Lymphadenopathy (100%)
  - Splenomegaly (80%)
  - BM involvement (60%)
  - Blood involvement (40%)

#436: May take a long time to present but when it does it is **incurable**
(تطبخ على نار هادية)

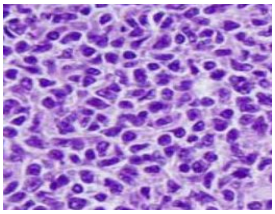
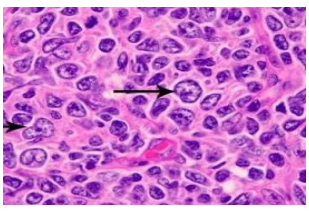
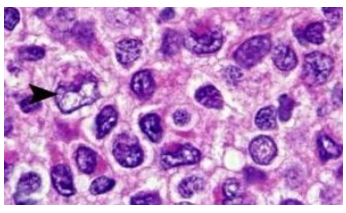
Diagnosis

- Using immunophenotyping, follicular lymphoma tests **positive** for the following markers:
  - **CD10, CD20, and BCL-2**
- And tests **negative** for **CD5** (in most cases).
- The malignant cells accumulate only in the germ center.



Management

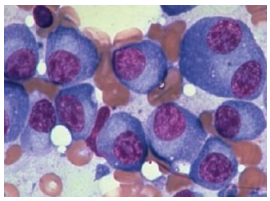
- Median survival is around 10 years.
- Transformation to aggressive lymphoma (DLBCL) can occur.
- Following table shows stages of FL from low grade to higher grade.

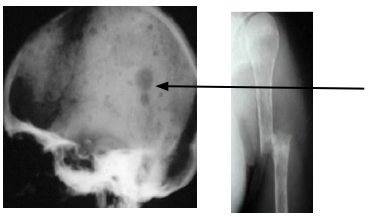
Stage	Low grade FL	FL in transformation	Aggressive transformation (DLBCL)
Morphology			
Treatment	Watch and wait (most often)	Chemotherapy	Aggressive Chemotherapy(± SCT)

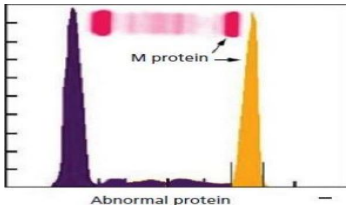
Multiple Myeloma

It is a malignant B neoplasm characterized by a triad of abnormalities:

- Accumulation of plasma cells in the bone marrow
- ★ **Lytic Bone lesions**
  "cancerous plasma cells building up in your bone marrow"
- Production of a monoclonal immunoglobulin (Ig) or Ig fragments





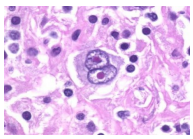


The presentation of multiple myeloma is weird, patient may present with only back pain. So, if you have patient >50 year old with back pain with no trauma, you should consider multiple myeloma.

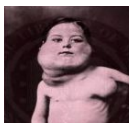
Hodgkin lymphoma

- It is an indolent (slow growing) malignant lymphoma characterized by:

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



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

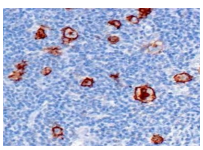


أبرز مشكلة فيه ان العلاج يحتاج لمدة طويلة، فما تضمن ان المريض يواظب عليه

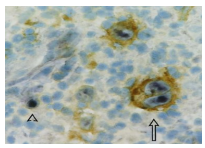
Diagnosis

- Using immunophenotyping, **Hodgkin lymphoma** tests **positive** for the following markers:
  - **CD15, CD30**

CD 30



CD 15

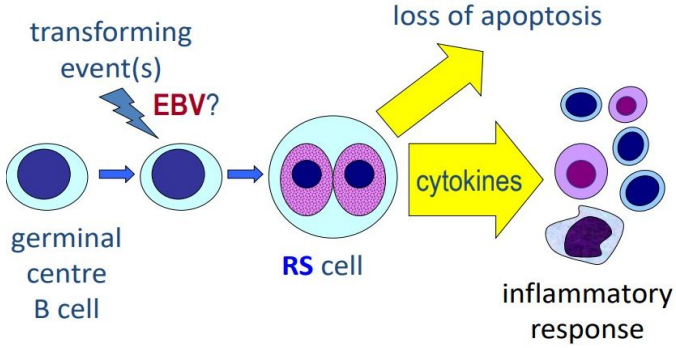


A possible model of pathogenesis

Germinal center B cell with EBV leads to binucleate (RS cell) which in response lead to:

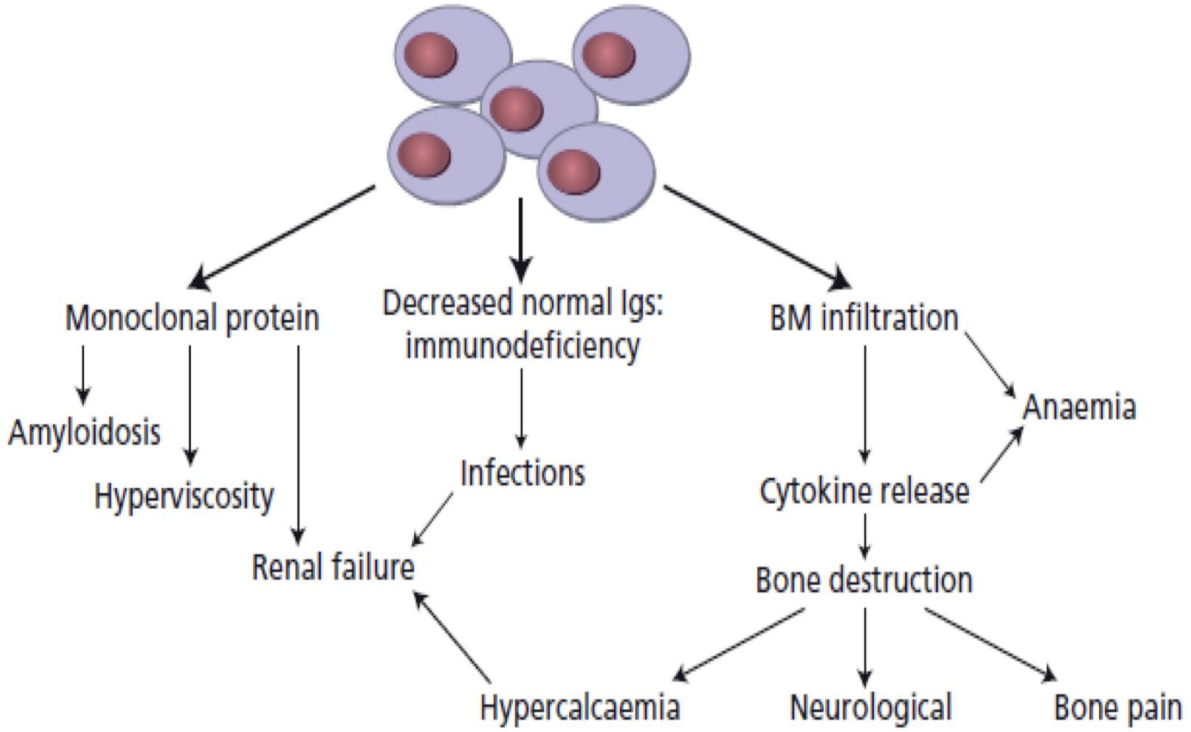
1. loss of apoptosis (accumulation)
2. Release of cytokines which attracts inflammatory cells and cause fibrosis

EBV is one of the most common viruses that associates with the establishment of lymphomas in general (including Hodgkin)



For Reading

Pathogenesis of Multiple Myeloma



Immunophenotype of Small B-Cell Neoplasms

Marker	CLL/ SLL	Mantle Cell Lymphoma	Follicular Lymphoma	Hairy Cell Leukemia	Marginal Zone Lymphoma
CD5	+	+	–	–	–
CD10 (cALLA)	–	–	+	–	–
CD20	Dim	+	+	+	+
CD23	+	–	+/–	+/–	–
FMC-7	–	+	+	+/–	+
Surface Ig*	Dim	Moderate or bright	+	+	+
Other				CD11c, CD25, and CD103	

Summary

Lymphoproliferative disorders are characterized by lymphocytosis caused by either: **malignancy**, autoimmune, infection.

Infectious Mononucleosis	• Its an acute, infectious disease caused by ★**Epstein-Barr virus** and it affect young people (usually) characterized by: Fever, Swollen lymph nodes (painful), Sore throat, ★**Atypical lymphocyte.** It's the major differential diagnosis of lymphomas.

IMP markers: Stem cell = CD 34, B cells = CD19 except for plasma cells, T Cells = CD3

	General	Markers	Mutation
Chronic Lymphocytic Leukemia	• Malignant neoplasm characterized by an increased number of **small**, mature lymphocytes in the blood **(>5,000)** and bone marrow • Most common adult leukemia • Asymptomatic or Moderate lymphadenopathy and splenomegaly Lab findings: • Small mature-appearing lymphocytes • **Condensed "soccer ball" nuclear chromatin** • Numerous smudge cells • Autoimmune phenomena	**CD5, CD19, CD20, CD23, IgM & IgD**	-
Mantle Lymphoma		**CD5,CD19,CD20**	t(11;14) **Cyklin D**
Burkitt's lymphoma	• Rapidly growing and highly aggressive with extremely short doubling time (24 hrs), It is the **fastest growing tumor in humans** Burkitt's > بركض> fastest growing tumor • Morphology: Diffuse infiltration with **"starry sky"**	**CD10,CD19,CD20** (no CD 5)	**t(8;14)** **c-myc**
Follicular lymphoma	• Malignant proliferation of germinal center B cells • Presents with **lymphadenopathy** (100%) and splenomegaly (80%)	**positive** for: **CD10, CD20, and BCL-2** **negative** for **CD5** (in most cases).	**Due to over expression of BCL-2 caused by t(14;18)**
Multiple Myeloma	• Malignant B neoplasm. Characterized by a **triad** of abnormalities: 1. Accumulation of plasma cells in the bone marrow 2. Production of a **monoclonal immunoglobulin** (Ig) or Ig fragments 3. **Lytic Bone lesions** (osteoclast over stimulation and bone destruction)	**CD38, CD138, CD56, IgG, IgA, IgE**	-
Classical Hodgkin	• Indolent malignant lymphoma • presence of few large binucleated cells (**Reed-Sternberg**) surrounded by reactive cells (lymphocytes, plasma cells ,eosinophils) • Involving cervical lymph nodes in young adults (most often)	**positive** for CD15,CD30 and BCL-2	-

Quiz

Q1) One of the most important feature of CLL:							
A	Less than 5,000 lymphocytes	B	More than 5,000 lymphocytes	C	Less than 10,000 lymphocytes	D	More than 5,000 neutrophils
Q2) Burkitt's lymphoma cytogenetic abnormality (mutation)?							
A	t(8;16)	B	t(5;18)	C	t(8;14)	D	t(8;21)
Q3) one of the most important feature of multiple myeloma:							
A	Splenomegaly	B	Smudge cells	C	Lytic bone lesions	D	Large cells lymphoma
Q4) which of the following diseases is associated with lymphocytosis?							
A	EBV	B	HIV	C	TB	D	HBV
Q5) 12 years old male presented to ER with enlarged lymph nodes involving the cervical nodes, present of Reed–Sternberg cells under the microscope. What's the diagnosis?							
A	Multiple myeloma	B	Hodgkin's lymphoma	C	Follicular lymphoma	D	Burkitt's lymphoma
Q6) Which of these cells is associated with Follicular lymphoma?							
A	GC cell	B	Centrocyte	C	Plasma cell	D	Centroblast
Q7) 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	Multiple myeloma	B	Hodgkin's lymphoma	C	Burkitt's lymphoma	D	CLL
Q8) 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 most likely the diagnosis in Ahmad's condition?							
A	Multiple myeloma	B	Hodgkin's lymphoma	C	Burkitt's lymphoma	D	CLL
Q9) Which of the following can cause Infectious Mononucleosis?							
A	EBV	B	E. Coli	C	Malaria	D	HBV

Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
B	C	C	A	B	B	D	A	A

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