Lymphoproliferative disorder

GNT Block

COLOR INDEX:

- Main text
- Dr. Notes
- Male's text
- Femal's text
- Important
- Extra

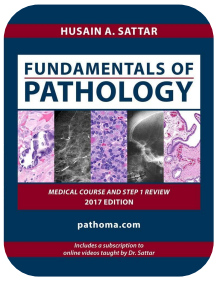
Editing file:

Objectives

*No objectives were found in both male and female slides

Click HERE for summarised Podcast & written TEXT! ZERO TO FINALS

Click on PATHOMA for a revision and more info!



Our YouTube's playlist for this lecture!

This lecture was given by: Dr. Mansour Aljabry and Prof. Fatma Al Qahtani

Introduction

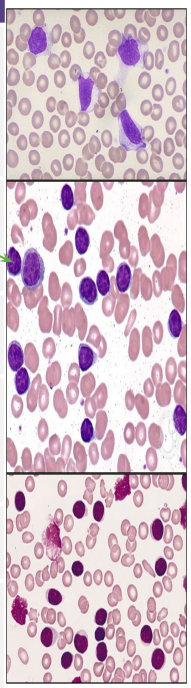
Lymphoproliferative disorders

Increase lymphocyte level and lymph node problems.

Several clinical conditions in which lymphocytes are produced in excessive quantities (**Lymphocytosis**) (increase lymphocyte level and lymph node problems)

Etiology of lymphocytosis		
infection	**Viral infection**	Infectious mononucleosis common ,cytomegalovirus ,rubella, hepatitis, adenoviruses, varicella
	bacterial infection	Pertussis ,brucellosis
Autoimmune	**SLE** , Allergic drug reactions	
Other conditions	splenectomy, dermatitis ,hyperthyroidism metastatic carcinoma	
Malignant	**Chronic lymphocytic leukemia (CLL)**	
	Other lymphomas: Mantle cell lymphoma ,Hodgkin lymphoma	

Small not atypical



All are causing large benign lymphocytosis, except for CLL and lymphomas they cause malignant lymphocytosis with smudge cell appearance.

Lymphoma

All lymphoid tissues

Malignant ALL lymphomas are malignant. lymphoid **mass** involving the **lymphoid tissues** (±infiltration to other tissues e.g : skin ,GIT ,CNS …) ex. axillary and cervical lymph nodes (Lymphadenopathy), spleen (splenomegaly),

Lymphoid leukemia

If BM and Peripheral blood aren't involved, so we still in lymphoma

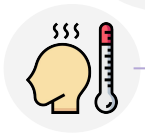
Malignant **proliferation** of lymphoid cells in **Bone marrow and peripheral blood** (± other tissues e.g : lymph nodes ,spleen , skin ,GIT ,CNS …)

Lymphocytosis →increased synthesis and number of lymphocytes (seen in many conditions including lymphomas and lymphoid leukemia).
Lymphoma→ lymphoid tissue enlargement (malignant mass).
Lymphoid Leukemia→ proliferation of malignant lymphoid cells mainly in BM and blood (not a mass).

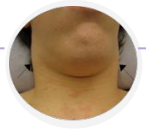
Infectious mononucleosis (IM)

IM or kissing disease

An **acute**, infectious disease affect young people (usually) caused by **Epstein-Barr virus** (**EBV**). characterized by:

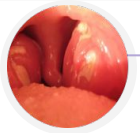


Fever



Painful swollen lymph nodes

Painful swollen lymph nodes are most likely infectious related, painless swollen lymph nodes are associated with malignancy



Sore throat

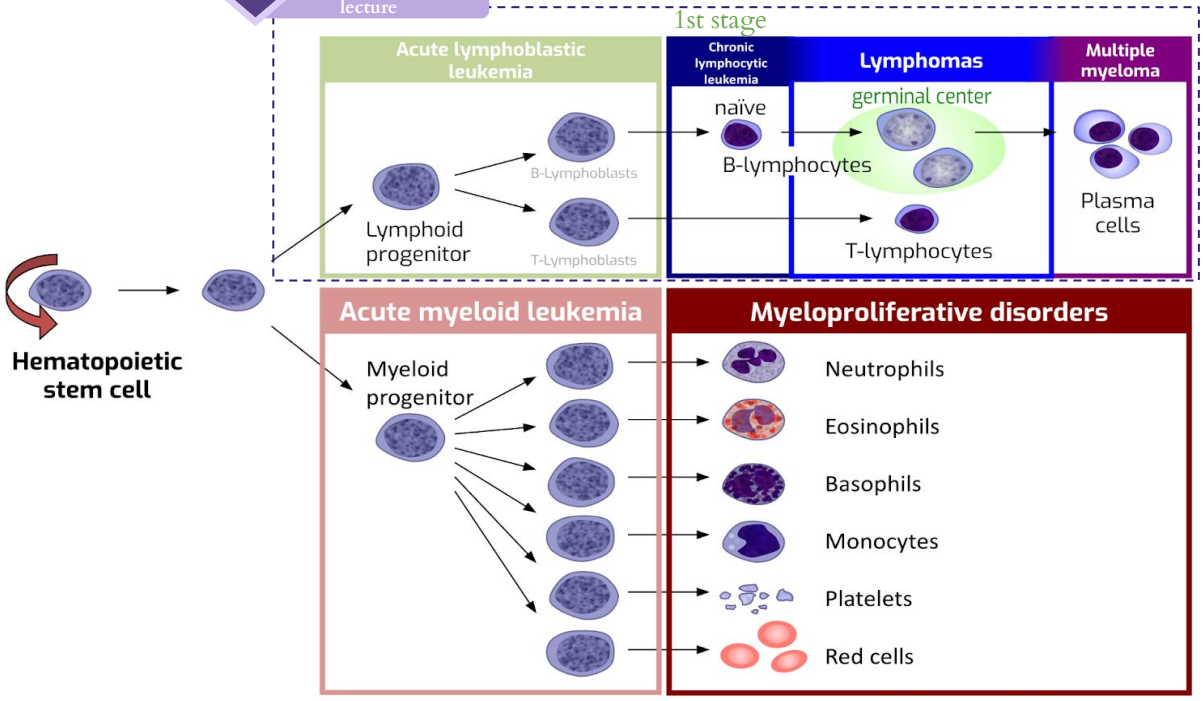
pharyngitis and tonsillar abscess
Enlarged and infected

Atypical lymphocytes (lymphocytosis)

- Infectious mononucleosis is transmitted through saliva (kissing disease).
- IM is a major **differential diagnosis** of lymphomas especially hodgkin lymphoma, and a **predisposing factor** of lymphomas as burkitt and hodgkin lymphoma.
- Diagnosed by: PCR, serology (IgM, IgE).

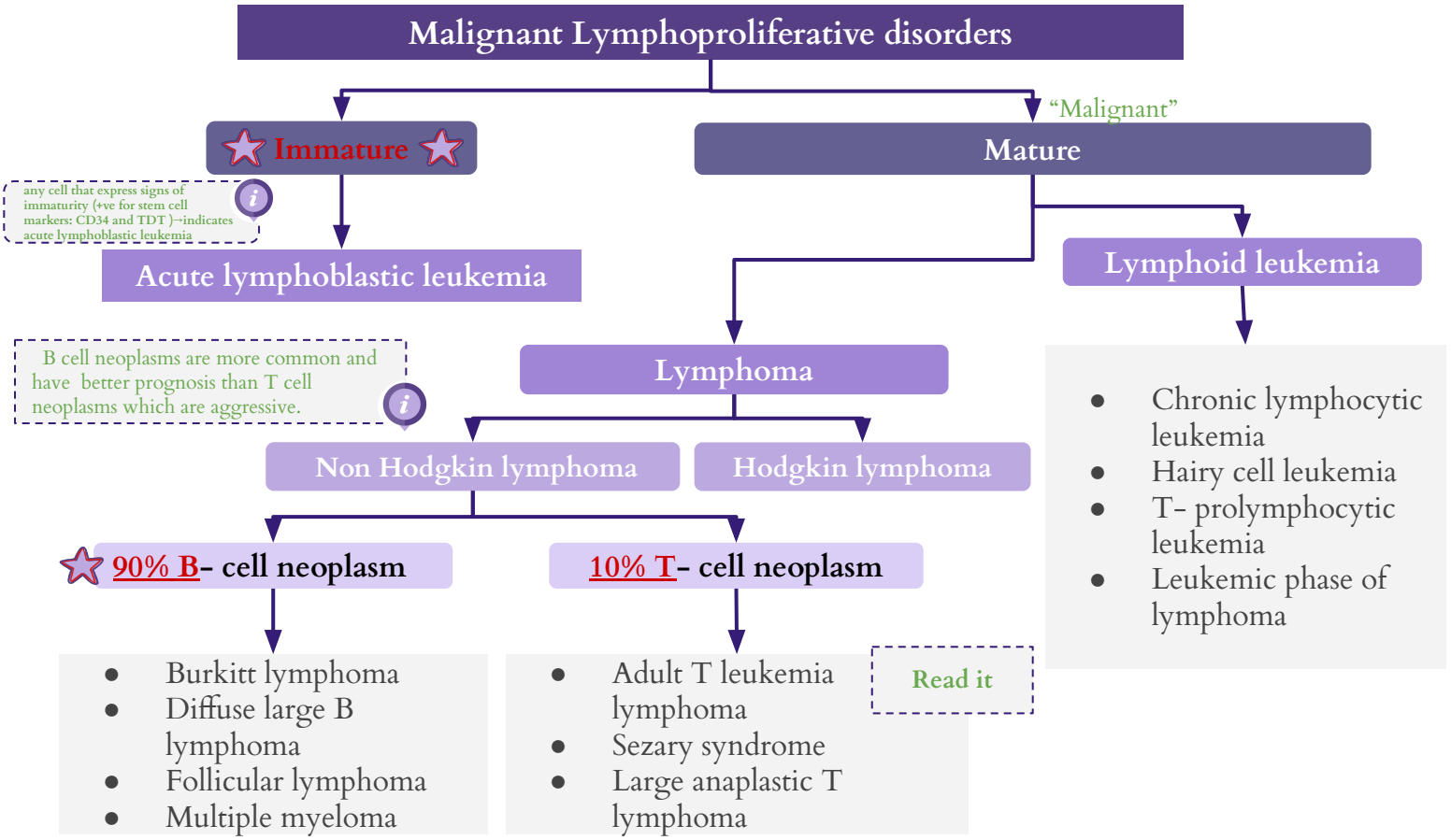
Malignant Lymphoproliferative Disorders

Discussed in this lecture



- Mutation of any of the cells inside the boxes will result in their respective disorder involved, ex. Mutation of the immature lymphoid progenitor cell or lymphoblasts will cause acute lymphoblastic leukemia
- if the mutation occurred after the maturation it will result in chronic lymphocytic leukemia and lymphomas

Malignant Lymphoproliferative Disorders



Dr's Notes and from next slides

	Hodgkin lymphoma	Non-Hodgkin lymphoma
Prevalence	40% Usually seen in young adults	60% more common and prevalent
Malignant cells	Reed-Sternberg cells (owl eye cells) surrounded by reactive cells	Most are B cell than T cells
Clinical findings	**Painless** lymphadenopathy	
Association	EBV	EBV, HIV and autoimmune diseases
Prognosis	Hodgkin lymphoma has better prognosis than non-Hodgkins in general	
EXTRA Leukemic phase	Doesn't occur	occurs

Malignant Lymphoproliferative Disorders cont..

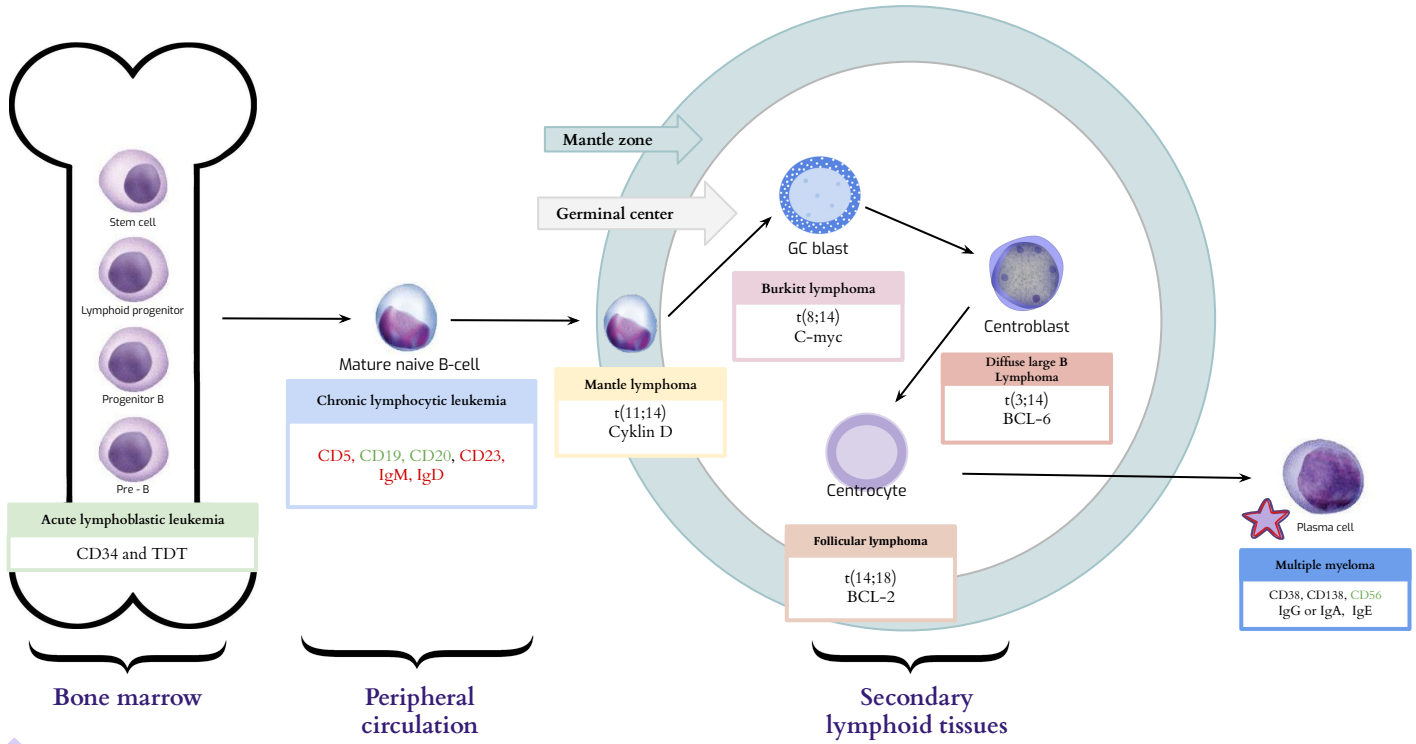
CD34+ is a stem cell marker | Presence of surface Ig: Mature sign | Mature cells: TDT and CD34 negative. | All B cells are CD19+ except plasma cells.

CD34 and TDT | Surface immunoglobulin

CD19

CD20

CD5 | CD10



CLICK here for 441 notes

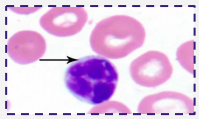
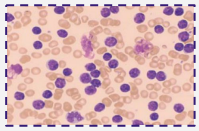
normal physiology of B cell development:
-in order to call B cell "mature naïve" it has to have IgM + IgD "like M.D. degree for intern"
naive → غير متخصصة كفاية , IgM + IgD → M.D. طبيب امتياز شهادته
-the germinal center is responsible for proliferation of B cells (مصنع) to increase B-cells ability to recognize more antigens for class switching i.e. adding IgG, IgA and IgE to it
-IgG, IgA and IgE are highly specialized Igs found in plasma cells "متخصصة، كالاستشاري"

Male dr: markers are important Female dr: mantle and burkitt's lymphoma mutations are important

Mature Malignant Lymphoproliferative Disorders						
Disease	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			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	-

mantle cell lymphoma : there's translocation of cyklin D from Ch.11 to Ch14 [t(11;14)] ,leading to overexpression of cyklin D.

Chronic lymphocytic leukemia (CLL)

Chronic lymphocytic leukemia (CLL)	
Overview	• 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" ظهر السلحفاة  Soccer cell  Smudge cells

Male dr: staging is important because we behave according to it. Female dr: it's easy so understand it, everything is important :)

	CLL 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 IV High Risk	lymphocytosis **thrombocytopenia** (<10 x 10^9), ± above	High risk (FCR)

Burkitt's lymphoma (BL)

Burkitt's lymphoma

Overview

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).

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

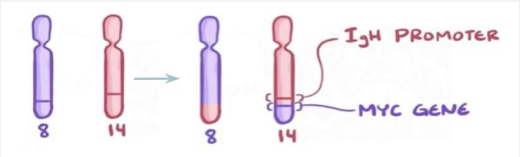
Immunodeficiency-associated: Associated with HIV infection or the use of immunosuppressive drugs.

Genetics of BL

Highly associated with t(8;14):

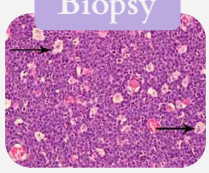
- Translocation of the **c-MYC** proto-oncogene at chromosome **8** to immunoglobulin gene at chromosome **14.**
- c-MYC is a nuclear transcription factor (It normally controls cell growth & division but in this case, after translocation it will play a role in excessive cell proliferation)

Burkitt's lymphoma is the fastest growing tumor in humans.



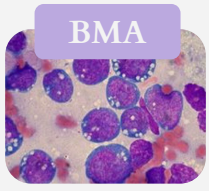
Morphology

Biopsy



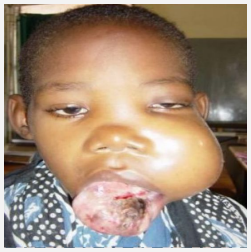
Diffuse infiltration with **"starry sky"** whitish color
(Macrophages engulfing the apoptotic cells)

BMA



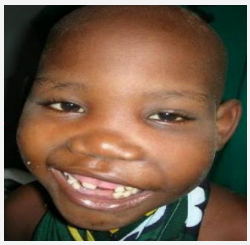
Homogenous medium sized cells with round nuclei and deeply basophilic and vacuolated cytoplasm
Bone marrow aspiration

Clinical picture



It's fast growing but has good response to chemotherapy

After **25 days** of intensive chemotherapy



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

في الearly phase نسبة التعافي تقريبا 100%
EARLY PHASE اهم شيء

Follicular Lymphoma (FL)

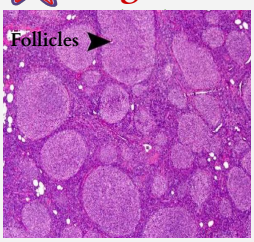
Follicular Lymphoma (FL)

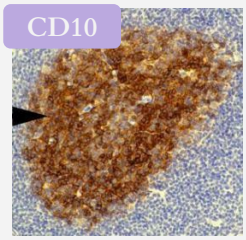
Overview

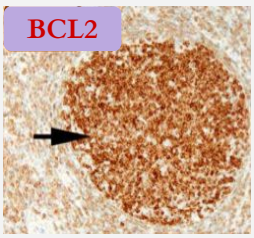
- It is a malignant proliferation of **germinal center B cells centrocyte** which has at least a partially **follicular pattern.**
- **Most common type of indolent lymphoma (25%).** Indolent lymphomas are slow-growing, تاخذ وقت طويل، May take a long time to present, but when it does it is incurable (تطبخ على نار هادئة)
- Indolent but incurable (some exceptions).
- Due to **overexpression** of **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%)**

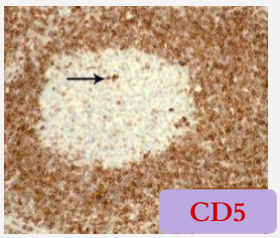
Diagnosis

- Using immunophenotyping, follicular lymphoma tests
- Positive for the following markers:
  CD10, CD20, and **BCL-2**
- **Negative for CD5** in most cases. The malignant cells accumulate only in the germinal center (which is



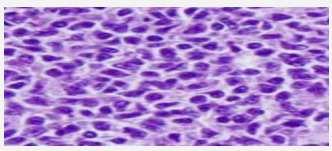
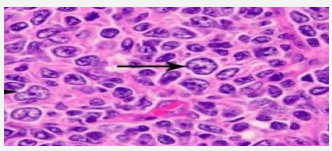
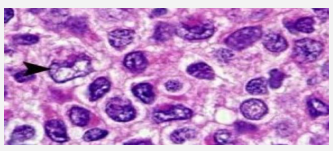






Management

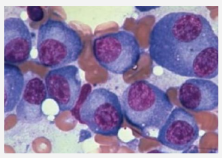
- Median survival is around 10 years.
- Transformation to aggressive lymphoma (DLBCL) can occur.

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

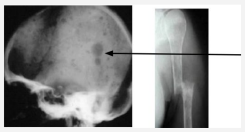
Multiple Myeloma

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

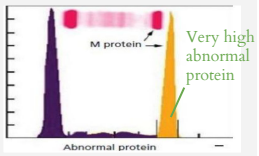
1. **Accumulation of plasma cells in the bone marrow**



2. **Lytic Bone lesions**
(areas where bone has been destroyed, leaving a hole in the bone)



3. **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.

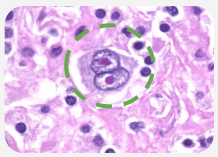
Hodgkin lymphoma

The biggest issue with hodgkin lymphoma, is the prolonged treatment course so the patient most likely won't stick to it :(

Thomas Hodgkin
(1798-1866)

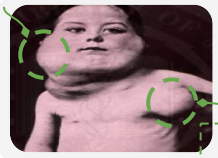
It is an indolent **malignant** lymphoma characterized by:

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



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

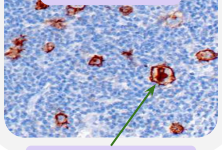
Cervical

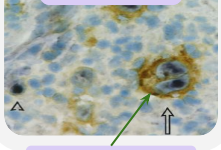


Axillary

Diagnosis:

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

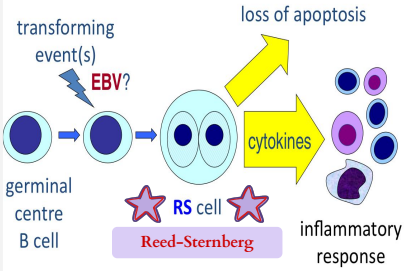




A possible model of pathogenesis:

EBV infection leads to the transformation of Germinal center B cell to **Reed-Sternberg (RS cell)** which in response lead to:
1. Loss of apoptosis (accumulation).
2. Release of cytokines which attracts inflammatory cells and cause fibrosis.

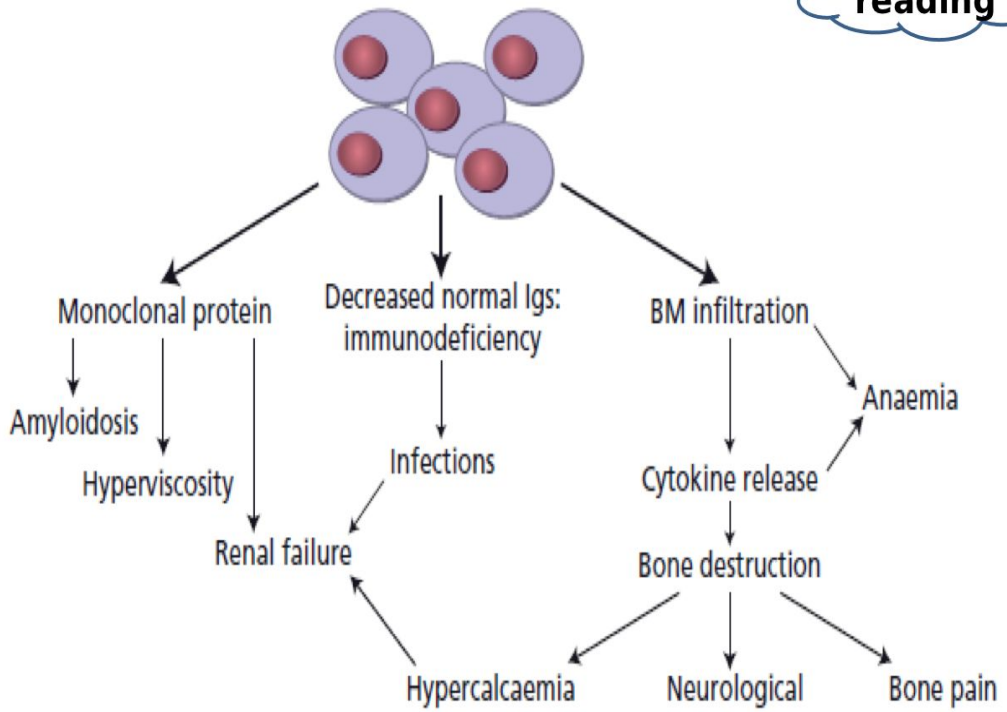
EBV is one of the most common viruses that is associated with the establishment of lymphomas in general (including Hodgkin)



For Reading

Pathogenesis of MM

For reading



For reading

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

Special thanks to team 441

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 = CD34, 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	• High grade **non**-Hodgkin's B-cell 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	-

Members board

Team Leaders:

Aleen AlKulyah **Remaz Almahmoud** **Sultan albaqami**

Team Members:

- Milaf alotaibi
- Reuf Alahmari
- Deema almadi
- huda bin jadaan
- Elaf moatabi
- Aseel Alsaif
- Razan alsoteehi
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