7/11

Lymphoproliferative Disorders

432 ***Hematology*** *Team*

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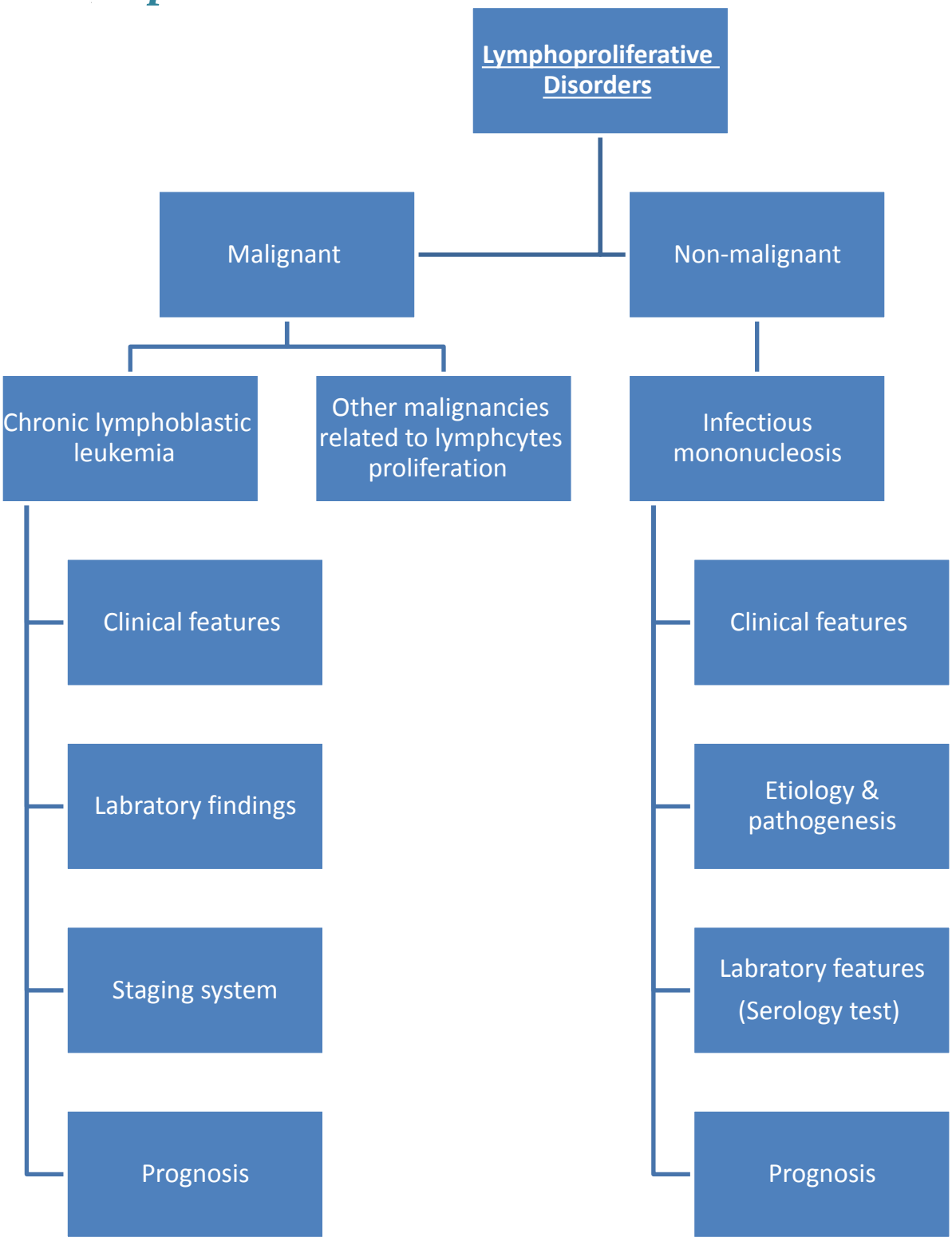
Color Index: Female notes are in Green. Male notes are in Blue. Red is important. Orange is explanation.

Lymphoproliferative Disorders

Mind Map:



Lymphoproliferative Disorders

Diseases characterized by increased lymphocyte mass or "lymphocytosis".

LYMPHOCYTOSIS: Lymphocyte count exceeding $4x10^9$/ (4000/ul).

The normal count is usually higher in childhood reaching up to $8.5/10^9$/L.

Cause of Lymphocytosis:

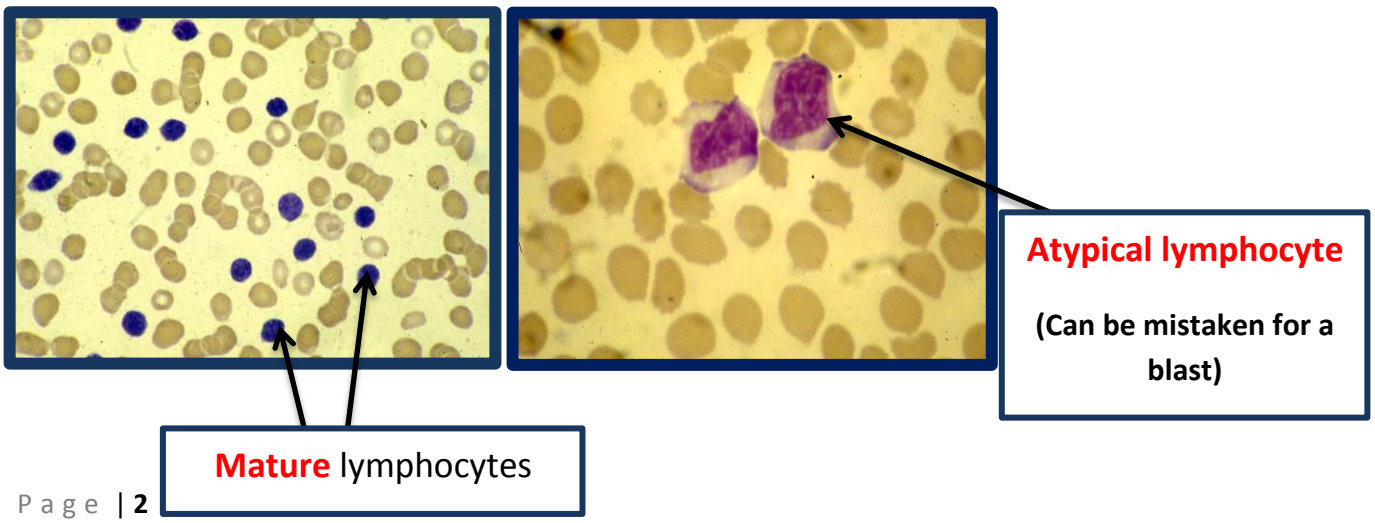
1. **Benign:** 1. Acute infections: usually viral e.g. infectious mononucleosis, mumps, rubella Bacterial e.g. pertussis.
   2. Chronic infections: e.g. tuberculosis, syphilis.
2. **Malignant:** **e.g. chronic lymphocytic leukaemia (CLL)**

NOTE: **Lymphocytes in *children* are *normally* high, because they frequently get infected; if lymphocytes are high, first thing we have to do is ask about the age.**

Non- malignant Causes:

1- **Viral infections:** infectious lymphocytosis; infectious mononucleosis; cytomegalovirus infection; occasionally: rubella, hepatitis, adenoviruses, varicella, HIV, human herpes virus-6, mumps, chickenpox, dengue
2- **Bacterial infections**: pertussis; occasionally: healing tuberculosis, brucellosis, secondary and congenital syphilis, cat scratch fever, typhoid fever, diphtheria
3- **Protozoal infections:** toxoplasmosis; occasionally: malaria
4- **Other conditions:** serum sickness; allergic drug reactions; splenectomy; dermatitis herpetiformis; metastatic melanoma; hyperthyroidism; congenital adrenal hyperplasia.

NOTE: **The MOST common cause of lymphocytosis is infectious mononucleosis**



INFECTIOUS MONONUCLEOSIS

- Incubation period 5 – 8 weeks.
- More common in females
- Usually in young patients 15-25 years.
- Fever
- Pharyngitis, follicular tonsillitis (sore throat).
- Lymphadenopathy (Enlarged lymph nodes): usually cervical, but can be generalized.
- Splenomegaly: in about 50%.
- Hepatomegaly.
- Rash.
- Bleeding: in severe cases.
- Tachycardia and ECG abnormalities.
- CNS symptoms e.g. convulsions, rare.
- Eye symptoms: photophobia, conjunctivitis.
- Acute abdomen: acute abdominal pain due to involvement of mesenteric lymph nodes.

Clinical Features

INFECTIOUS MONONUCLEOSIS

1. Leukocytosis with lymphocytosis: WBC usually 10-20,000/µl with lymphocytes forming >50%. Atypical lymphocytes are seen.)
2. Anemia: Can be due to cold autoimmune hemolytic anemia.
3. Thrombocytopenia: Autoimmune.
4. Liver enzymes: ↑ due to hepatitis.
5. Serological tests (Antibodies) – Discussed in the next page-: Types of antibodies seen in infectious mononucleosis are:
   - A. EB virus specific.
   - B. Heterophile
   - C. Autoimmune.

Laboratory findings

Etiology

Epstein-Barr (EB) virus

(Herpes group)

Pathogenesis

1. EB virus enters into epithelial cells of oropharynx or into B lymphocytes or Waldeyer's ring
2. B lymphocytes proliferation
3. T lymphocytes proliferation and the lymphocytes will appear in the peripheral blood as atypical lymphocytes
4. T lymphocytes are of the cytotoxic type. They will attack the B lymphocytes causing severe pharyngitis.
5. Involvement of other lymphoid tissues.
6. Viremia.

NOTE: 1- The presentation can be so severe that it could be mistaken for acute leukemia.

2- The serological test is very important in diagnosing.

Serology Tests

A. Virus specific antibodies: (Best test)

1. IgM: Develop early in the disease and lasts for few months.
2. IgG :
   a) One type against capsid antigen (VCA). Appears early in the acute phase and used to diagnose new infections.
   b) Against nuclear antigen (EBNA). Develops after the acute phase and persists for life. Usually indicates old infection.

B. Heterophile Antibodies:

Antibodies that are produced as a result of the infection but react with an antigen different from the causative agent.

Paul Bunnel Test:

* To detect antibodies that can agglutinate sheep red cells.
* Can also be positive in other disease e.g. serum sickness or leukemia (Forsemann antibody). To differentiate it from IM (Infectious mono). Guinea pig kidney cells are used. Forsemann antibodies react with the kidney cells. IM antibodies do not.

Monospot Test:

* Replaced the Paul Bunnel test.
* Serum mixed with guinea pig kidney cells and then with horse RBCs.

(Both Paul Bunnel and Monospot tests are old tests and are not used anymore)

C. Autoimmune Antibodies: (Antibodies against RBCs and platelets)

1. Autoimmune cold hemolytic anemia.
2. Immune thrombocytopenia.

Differential Diagnosis:

A similar clinical syndrome and atypical lymphocytes can be seen in other disease e.g. toxoplasmosis and cytomegalo-virus. However, these can be differentiated by serology. (IM) is + while these disease are negative.

Course and Prognosis of IM:

* Most patients recover in 4 – 6 weeks.
* Unusual complications are hepatitis, encephalitis, hepatic failure, glottic edema and splenic rupture.

Malignant Lymphocytosis

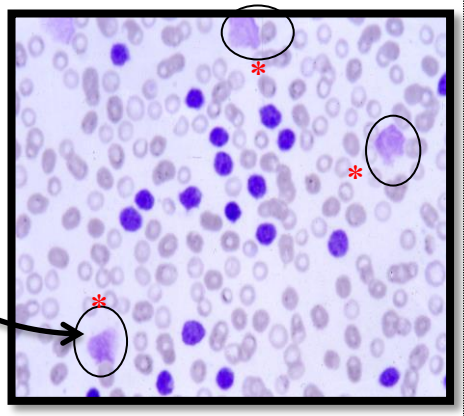
Chronic Lymphocytic Leukaemia (CLL)

Neoplastic proliferation of mature lymphocytes usually B lymphocytes.
Usually seen in the elderly (Never see child with CLL). More common in the west and more common in males. Accounts for about 25% of all leukaemias.

Clinical Features of CLL:

1. Accidental: about 25% of cases are diagnosed on routine blood exams. (Silent, CBC requested for other condition).
2. Pallor: Due to anemia. (Infiltration of bone marrow will affect other cell: erythrocyte, thrombocyte).
3. Lymphadenopathy.
4. Splenomegaly.
5. Hepatomegaly.
6. Bruising and purpura: due to thrombocytopenia. (Infiltration of bone marrow will affect other cell: erythrocyte, thrombocyte).
7. Herpes Zoster and simplex infection. (Depressed immunity)
8. Pruritis.
9. Skin infiltration.
10. Depressed immunity, both cellular and humoral.

Laboratory Features of CLL:



1. Lymphocytosis: > 5,000/µl is required for diagnosis.
The lymphocytes are mature, small round lymphocytes.
Another feature seen on peripheral blood are smudge (smear) cells.* (Remaining broken cell)
2. **Anemia:** can be due to:
    a. Warm autoimmune hemolytic anemia seen in (seen in 10% of cases).
    b. Bone marrow failure (indicates poor prognosis).
3. **Thrombocytopenia:** can be due to:
    a. Autoimmune (seen in 5% of cases).
    b. Bone marrow failure (indicates poor prognosis).
4. **Bone Marrow and Lymph Node:** Infiltration by mature lymphocytes.
5. **Immunoglobulins:**
    * Monoclonal band on serum protein electrophoresis.
    * ↓ Immunoglobulin levels.
6. **Uric Acid:** ↑

Classification of the chronic lymphoid leukaemias and leukaemia/lymphoma syndrome:

B-cell	T-cell
Chronic lymphoid leukaemias *	
B-cell chronic lymphocytic * **Leukaemia (B-CLL,CLL)** **B-cell prolymphocytic leukaemia (B-PLL) with >55% prolymphocytes** * **Hairy cell leukaemia (HCL) (Classic and Varient form)** * **Plasma cell leukaemia** *	Large granular lymphocytic leukaemia T-cell prolymphocytic leukaemia (T-PLL) *
Leukaemia/Lymphoma syndromes	
Splenic lymphoma with villous lymphocyte * **Follicular lymphoma** * **Mantle cell lymphoma** * **Lymphoplasmacytic lymphoma*** **Large cell lymphoma**	Sézary syndrome Adult T-cell leukaemia/lymphoma Large cell lymphoma

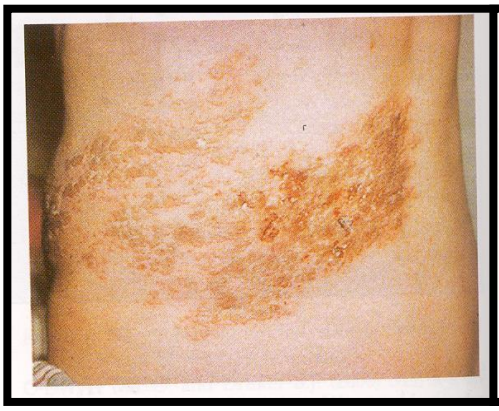
Immunophenotype of the chronic B-cell leukaemias/lymphomas: (use flow cytometry)

Important table

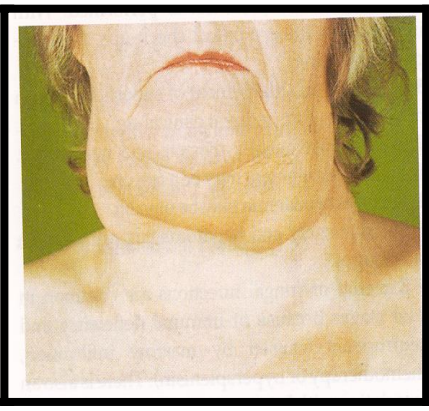
	CLL	PLL	HCL	FL	MCL
Sig	Weak	++	++	++	+
CD5	+	-	-	-	+
CD22/FMC7	-	+	+	+	+
CD79b	-	++	-/+	++	++
CD19+	+	+	+	+	+

NOTE

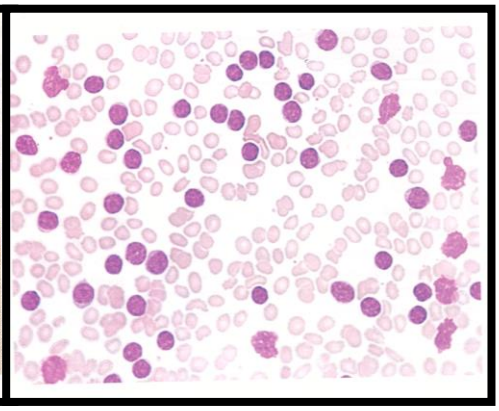
CLL: chronic lymphocytic leukaemia
PLL: prolymphocytic leukaemia
HCL: hairy cell leukaemia
FL: follicular lymphoma
MCL: mantle cell lymphoma
Sig: surface immunoglobulin
NB. CD103 is positive only in HCL. And (CD19+) in all cases



Herpes Zoster



Enlarge lymph node



Mature lymphocyte with smear cell

STAGING SYSTEM

1. RAI SYSTEM: Five stage: o, I, II, III, IV.

0: Lymphocytosis

I: Lymphocytosis + Lymphadenopathy

II: Lymphocytosis + Splenomegaly +/or Hepatomegaly.

III: Lymphocytosis + anemia (not autoimmune). ± Lymphadenopathy. (Advance stage)

IV: Lymphocytosis + Thrombocytopenia (not autoimmune). ± Lymphadenopathy. (Advance stage)

2. International System: three stage: A, B, C

A. Lymphocytosis + < 3 areas of nodal involvement (nodal includes liver, spleen and lymph nodes).

B. 3 or more nodal areas involvement.

C. Anemia +/or thrombocytopenia

Course and Prognosis:

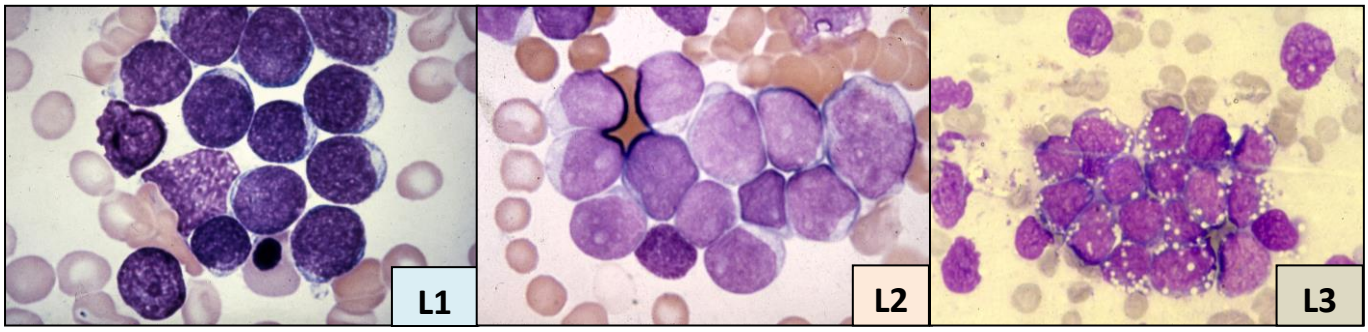
1. **Stage O or A may remain stable for many years and they may not require treatment.**
2. **Advances stages (III.IV.C) may terminate in marrow failure with consequent infection, or in a high grade type of lymphoma (Rechter's syndrome). IF we not treat the patient will end up with Rechter's syndrome**

Prognosis:

Related to:

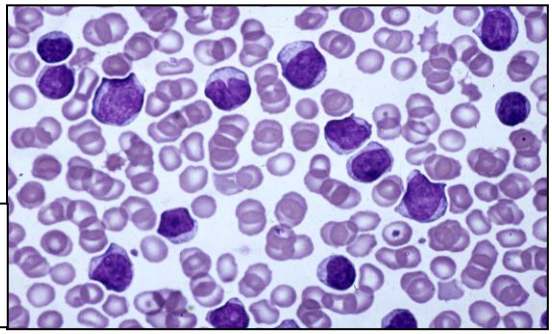
1. Stage
2. Age: worse if >70 years.
3. WBC: Worse if > 50,000.
4. Pattern of bone marrow involvement: diffuse involvement.IN advanced stage

Acute lymphoblastic leukemia



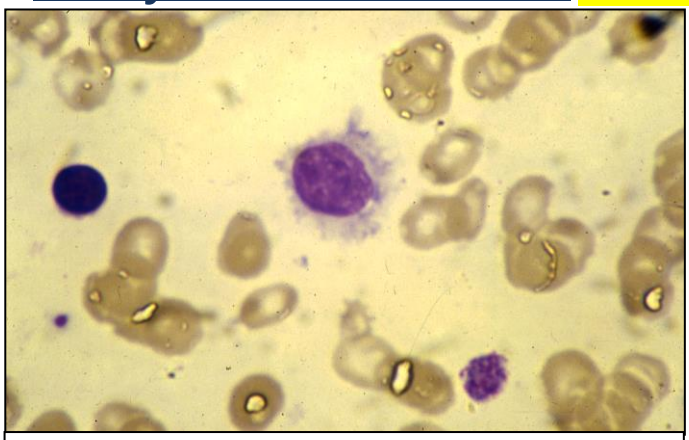
Pro-lymphocytic Leukaemia

Not blast and before maturation

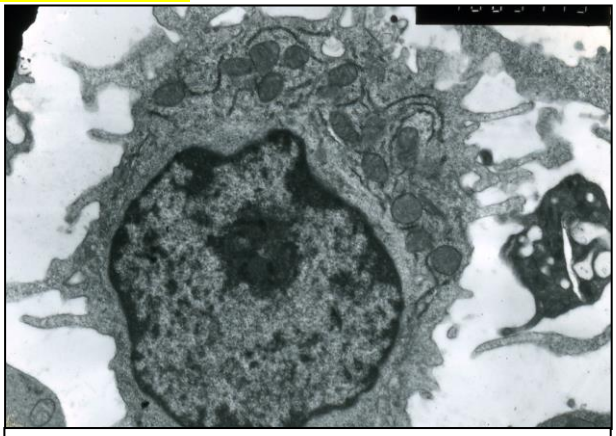


Large cell contain cytoplasm, nuclear no smear cell

Hairy Cell Leukaemia **Massive splenomegaly**



Disconnected cytoplasm look like hair

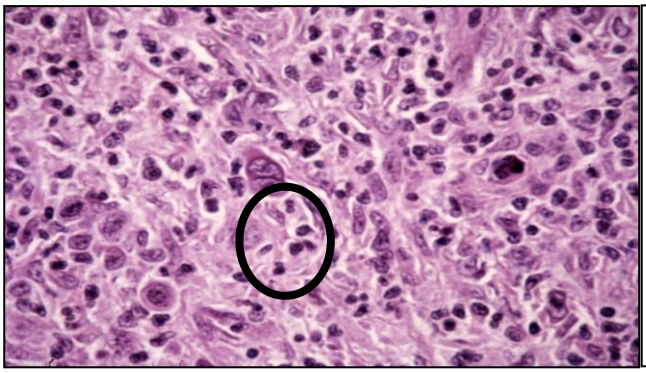


Electron microscope: hair projection

Lymphoma

1- **Hodgkin's Lymphoma**
2- **Non-Hodgkin's Lymphoma**

NOTE: Hodgkin's Lymphoma contain Reed - Sternberg, while Non-Hodgkin's Lymphoma not

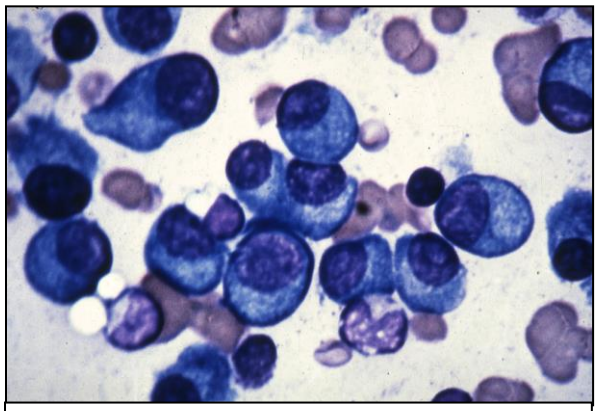


Section of lymph node shows large, multinucleated cell which is Reed – Sternberg contain: CD 15+CD 30 positive

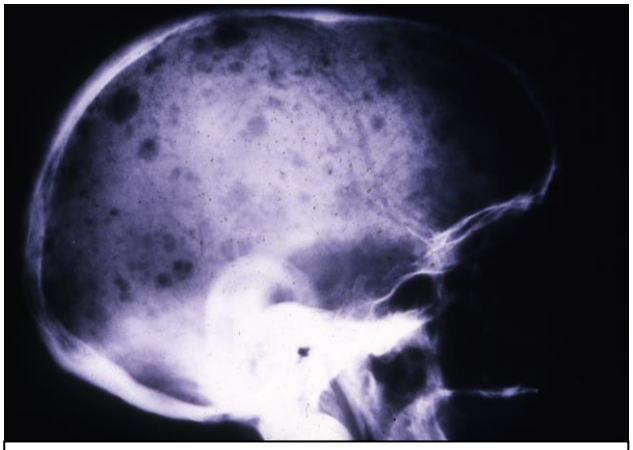
It may mononucleated

Multiple Myeloma

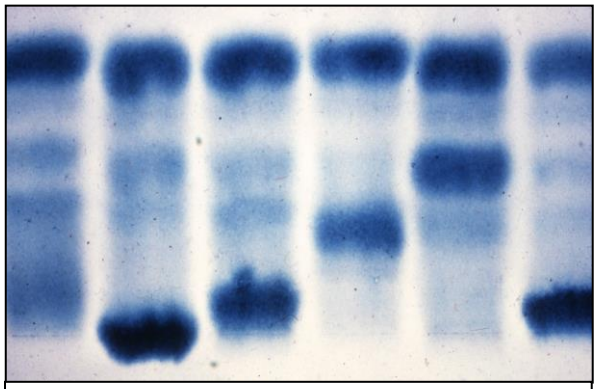
- Disease of plasma cell of bone marrow
- normally 3%
- more than 3% multiple myeloma
- hypercalcaemia
- abnormal production of immunoglobulin



Plasma cell: dark cell, peripheral nuclei



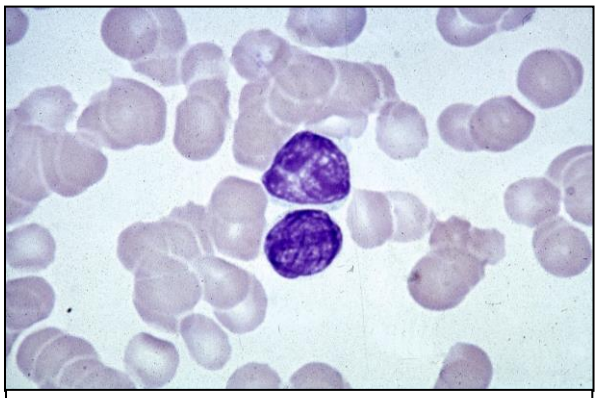
Punched out lesion the plasma cell will eat bone cause this lesion



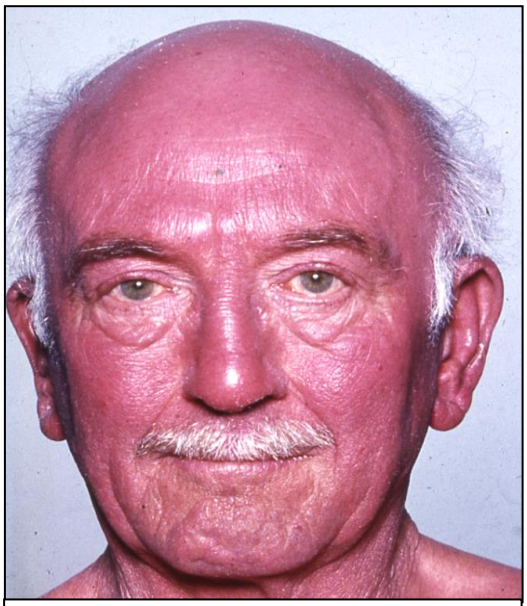
Serum immunoglobulin study

Sezary syndrome

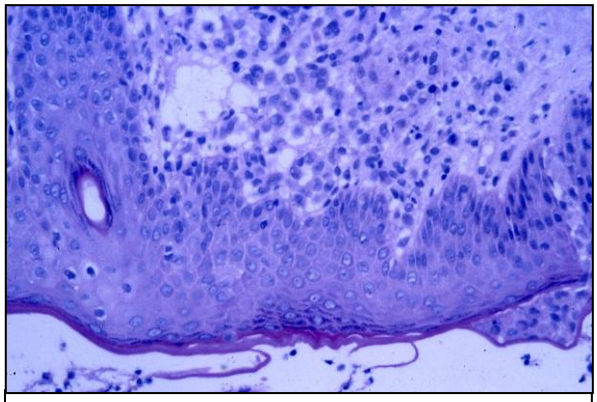
- T cell cutaneous lymphoma
- Malignant T-lymphocyte



Small, mature lymphocyte deep clivtting nuclei lymphocytosis mainly CD4



Red skin (erythroderm)
Red man syndrome



Skin: lymphocytosis infiltration

Summary

Chronic Lymphocytic Leukaemia (CLL) involve mature lymphocytes usually B lymphocytes. Usually seen in the elderly

Mean clinical feature of CLL are: anemia, Lymphadenopathy. Splenomegaly. Hepatomegaly, Herpes Zoster and simplex infection.

Mean Laboratory Features of CLL: lymphocytosis the lymphocytes are mature, small round lymphocyte on peripheral blood are smudge (smear) cells, ↓ Immunoglobulin levels, Uric Acid ↑

All cases of lymphoma positive to CD19

CD103 is positive only in HCL.

Questions

1/ what is the most common cause of Lymphocytosis?

A. **infectious lymphocytosis**
B. **infectious mononucleosis**
C. **cytomegalovirus**
D. **Rubella Virus**

2/ what is the most important finding in **infectious mononucleosis**?

A. **Atypical lymphocytes**
B. **Anemia**
C. **Antibodies against Capsid gene**
D. **Antibodies against nuclear antigen**

3/ what will we see in blood film of CLL?

Mature lymphocyte, smear cell

4/ which infection mainly seen with CLL?

Herpes Zoster infection

5/ which marker involve in all case of lymphoma?

CD19

6/ what is the mean feature of Hodgkin's Lymphoma?

Reed - Sternberg contain: CD 15+CD 30 positive

7/ which syndrome will involve in advance stage of lymphoma?

Rechter's syndrome

Answers:

- 1- B
- 2- A

اللهم إني استودعك ما قرأت و ما حفظت و ما تعلمت فرده عليَ عند حاجتي إليه انك على كل شيء قدير

If there is any mistake or feedback please contact us on: 432PathologyTeam@gmail.com

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*Good Luck ^_^*