LYMPHOPROLIFERATIVE DISORDERS

Disease characterized by increased lymphocyte mass or "lymphocytosis".

***LYMPHOCYTOSIS:***

lymphocyte count exceeding 4 x109/L, (4000 /μL). The normal count is usually higher in childhood.

***Cause:v***

1. **Benign:** 
   * 1. **Acute infections:** Usually viral e.g. infectious mononucleosis, mumps, rubella in bacterial e.g. pertussis.
     2. **Chronic infections:** e.g. tuberculosis, syphilis.
2. **Malignant:** e.g. chronic lymphocytic leukemia.

# INFECTIOUS MONONUCLEOSIS

### Etiology:

Infection with Epstein – Barr (EB) virus, (from the herpes group of viruses)

## Pathogenesis:

1. EB virus enters into epithelial cells of oropharynx or into B lymphocytes of Waldeyers' ring.
2. B-lymphocytes proliferation.
3. T-lymphocytes proliferation and T-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 cause
5. Involvement of other lymphoid tissues.
6. Viremia.

## Clinical Features:

* Incubation period 5 - 8 weeks.
* More common in females.
* Usually in young patients 15 - 25 years.

***Features:***

1. Fever.
2. Pharyngitis, follicular tonsillitis (sore throat).
3. Lymphadenopathy: usually cervical, but can be generalized.
4. Splenomegaly: in about 50%.
5. Hepatomegaly (10-20% of cases)
6. Rash.
7. Bleeding: in severe cases, due to thrombocytopenia.
8. Tachycardia and ECG abnormalities.
9. CNS symptoms e.g. convulsion, rare.

10. Eye symptoms: photophobia, conjunctivitis.

11. Acute abdomen: acute abdominal pain due to involvement of mesenteric lymph nodes.

## Laboratory Finding:

1. **Leukocytosis with lymphocytosis:** WBC usually 10 - 20,000 /μL with lymphocytes forming >50 % (The normal lymphocyte count is 40,000/μL

Atypical lymphocytes are seen.

1. **Anemia:** can be due to cold autoimmune hemolytic anemia.
2. **Thrombocytopenia:** Autoimmune.
3. **Liver enzymes:** increasedue to hepatitis.
4. **Serological tests (antibodies):** Types of antibodies seen in infectious mononucleosis are:
   1. EB virus specific antibodies
   2. Heterophile (antibodies against non-human Antigens, sheep blood cells)
   3. Autoimmune.
5. **Virus specific antibodies:**
6. **IgM:** Develop early in the disease and lasts for few months**.**
7. **IgG :** 
   1. **One type against capsid antigen (VCA).** Appears early in the acute phase and used to diagnose new infections.
   2. **Against nuclear antigen (EBNA)**. Develops after the acute phase and persists for life. Usually indicated old infection.

1. **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: (4 hours manually)

To detect Antibodies that can agglutinate sheep red cells.

Can also be positive in other diseases 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: (5 minutes only !!)

Replaced the Paul Bunnel test.

Serum mixed with guinea pig kidney cells and then with horse RBCs.

***C. Autoimmune antibodies:***

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 cytomegalovirus. However, these can be differentiated by serology. (IM) is (+) while these diseases are (-).

## Course and Prognosis:

* Most patients recover in 4 - 6 weeks.
* Unusual complications are hepatitis, encephalitis, hepatic failure, glottic edema *(*انسداد القصبة*)* and splenic rupture.

# CHRONIC LYMPHOCYTIC LEUKEMIA

Neoplastic proliferation of mature lymphocytes usually B-lymphocytes. Usually seen in the elderly. More common in the west and more common in males. Account for about 25% of all leukemias.

== 10% T-cell. Rare in KSU & Asia

## Clinical features:

1. **Accidental:** about 25% of cases are diagnosed on routine blood exams. (asymptomaptic)
2. **Pallor:** Due to anemia.
3. Lymphadenopathy.
4. Splenomegaly.
5. Hepatomegaly.
6. **Bruising and purpura:** due tothrombocytopenia.
7. Herpes Zoster and simplex infection.
8. Pruritis.
9. Skin infiltration.
10. Depressed immunity, both cellular and humeral.
    1. Hypogammaglobulinemia (can’t produce Ig normally)

## Laboratory features:

1. **Lymphocytosis:** absolute count > 5,000/ul is required for diagnosis. the lymphocytes are mature, small round lymphocytes. Another feature seen on peripheral blood is smudge *"*مكسرة*"* (smear) cells.
2. **Anemia:** can be due to:

* Warm autoimmune hemolytic anemia (seen in 10% of cases).
* Bone marrow failure (indicates poor Prognosis).

1. **Thrombocytopenia:** can be due to:

* Autoimmune (seen in 5 % of cases).Bone Marrow failure (indicates poor prognosis).

1. **Bone marrow and Lymph node:** infiltration by mature lymphocytes.
2. **Immunoglobulins:**

* Monoclonal band on serum protein electrophoresis (indicating malignancy). Monoclonal means one type of light chain Ig
* Immunoglobulin levels.

1. **Uric Acid: increased** (hemolytic aanemia)

## Prognosis:

Related to:

* 1. Stage:
  2. Age: worse if > 70 years.
  3. WBC: worse if > 50 years.
  4. Pattern of bone marrow involvement: diffuse involvement.

*Staging Systems:* RAI system: 5 stages

* 0: Lymphocytosis 🡺 absolute lymphocyte count: 1.5 *×* 109
* I: Lymphocytosis + Lymphadenopathy
* II: Lymphocytosis + Splenomegaly +/- Hepatomegaly +/- Lymphedenopathy.
* IV: lymphocytosis + Anemia (not autoimmune) +/- Lymphadenopathy.
* IV: Lymphocytosis + thrombocytopenia (platelets < 100,000) (not autoimmune) +/– Lymphadenopathy

Lymphadenopathy occurs in 5 nodal areas

1. Cervical
2. Axillary
3. Groin
4. Liver
5. spleen

## International system:

* + easier
* **Stage A.** lymphocytosis + < 3 areas of nodal involvement (nodal includes liver, spleen and lymph nodes).
* **Stage B.** 3 or more nodal areas involvement.
* **Stage C.** Anemia + or thrombocytopenia

## Course and prognosis:

1. Stage O or may remin stable for many years and they may not require treatment.
2. Advances stages may terminate in marrow failure with consequent infection or in a high grade type of lymphoma ( Rechter's syndrome).

Immunophenotype of chronic B-cell leukemia 🡺 CD103