Pathology

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Lympho-Reticular System

Third and Fourth Lectures

Non-Hodgkin Lymphoma (NHL)

General Characters:

1. NHL arises from monoclonal proliferation of a single transformed malignant lymphoid cell.
2. NHL can be Nodal (2/3rd, 70%) and Extranodal (1/3rd, 30%) (BM, Thymus, GIT, Pharynx, Tonsils, Testes, Ovaries, Skin, and CNS).
3. B-cell NHL (80% of NHL) and T-cell NHL (20% of NHL).
4. NHL is more than HL (NHL is more than 2/3rd of all Lymphomas) .
5. Occurs in adults and children. Males are affected more than Females.
6. Localized or Generalized Painless LAP (Commonly Cervical LAP).
7. Hepato--splenomegaly.
8. Bone Marrow involvement.
9. Widely disseminated at time of presentation or diagnosis.
10. Systemic B-symptoms are present.

Etiology of NHL

- ✓ No a single cause
- ✓ Chromosomal Translocations
- ✓ Infection :
  - Virus: EBV, HTLV, and HIV.
  - Bacteria: *Helicobacter Pylori* ➔➔ Gastric Lymphoma.
- ✓ Immunology
  - Immunodeficiency

NHL-Classification (WHO 2008/Updated 2016-2017)

Depending on the following characters :

- Clinical features of the patients.
- Morphology of lymphoma by microscopical (histological) examination whether Follicular or Diffuse growth patterns, Small or Large sized lymphoid cell type.
- Cell of origin (B- cells or T- cells).
- Immunophenotyping by Immunohistochemistry.
- Genotyping (Chromosomal abnormalities, gene mutation, presence or absence of viral genome, such as EBV genome).

Immunophenotyping: By using of monoclonal antibodies which are called CD markers (CD means Cluster of Differentiation) against specific lymphocyte Antigens (Ag) to know the cell of origin whether B-cell or T- cell in origin.

Four main categories of NHL:

- ☒ Precursor (Immature) B- cell Neoplasms.
- ☒ Precursor (Immature) T- cell Neoplasms.
- ☒ Peripheral (Mature) B- cell Neoplasms.
- ☒ Peripheral (Mature) T- cell Neoplasms.

Pattern of growth in B- cell lymphomas can be either follicular or diffuse pattern.

NHL- Classification: (جدول للاطلاع فقط وليس للحفظ)

1. Precursor B-Cell Neoplasms

   Precursor B-cell lymphoblastic leukemia / lymphoma.

2. Peripheral B-cell Neoplasms :

   - Chronic lymphocytic leukemia / Small lymphocytic lymphoma.
   - B-cell prolymphocytic leukemia
   - Lymphoplasmacytic lymphoma
   - Splenic and nodal marginal zone lymphoma
   - Extranodal marginal zone lymphoma (MALT lymphoma)
   - Mantle cell lymphoma
   - Follicular lymphoma
   - Hairy cell leukemia
   - Plasmacytoma / Plasma Cell Myeloma
   - Diffuse large B-cell lymphoma
   - Burkitt lymphoma

3. Precursor T-cell Lymphoblastic Lymphoma / Leukemia

4. Peripheral T-Cell and NK-Cell Neoplasms :

   - T-cell prolymphocytic leukemia
   - Large granular lymphocytic leukemia
   - Mycosis fungoides / Sézary syndrome
   - Peripheral T-cell lymphoma, unspecified
   - Anaplastic large cell lymphoma
   - Angioimmunoblastic T-cell lymphoma
   - Enteropathy-associated T-cell lymphoma
   - Panniculitis-like T-cell lymphoma
   - Hepatosplenic T– cell lymphoma

- Adult T-cell leukemia / lymphoma
- NK / T-cell lymphoma (Nasal type)
- Aggressive NK-cell leukemia

NHL-Examples

1-Precursor (Immature) B- cell Neoplasms

1. Acute Lymphoblastic Leukemia, ALL (85 % of the cases).
2. Lymphoblastic Lymphomas (15 % of the cases).

Both: Consist of immature lymphocytes (lymphoblasts)

- ✓ Predominantly, affect children and adolescent, High grade and Aggressive Malignancy.
- ✓ Cure is possible with aggressive chemotherapy.
- ✓ Usually present as Leukemia / Lymphoma Picture.
- ✓ Extensive BM and peripheral blood involvement as ALL.
- ✓ Involvement of Extranodal Sites (Testes, CNS, Liver, and Spleen).

2-Precursor (Immature) T- cell Neoplasms

1. Lymphoblastic Lymphomas (85 % of the cases)
2. Acute Lymphoblastic Leukemia, ALL (15 % of the cases)

T- cell Lymphoblastic Lymphoma

- ✓ It mostly affects males, old children and adolescent.
- ✓ It constitutes 40% of all Childhood Lymphomas.
- ✓ Mediastinal Mass (Thymic Mass in 50 -70 % of cases) and LAP.
- ✓ Then it progresses to ALL (15% of ALL).

3-Peripheral (Mature) B-cell Lymphomas

Small Lymphocytic Lymphoma and CLL

- ☒ Low grade, Well differentiated, indolent slowly growing lymphoma.
- ☒ M/E : Diffuse growth pattern of small lymphocytes.
- ☒ Diagnosis as Lymphoma if absolute lymphocyte count in peripheral blood is less than < 5000 cell/μL. If it is more, Diagnosis as CLL.
- ☒ Most common lymphoma in adults and elderly.
- ☒ Generalized LAP and Hepato – splenomegaly.
- ☒ Bone Marrow involvement ➔➔ CLL.
- ☒ Liable to Infection because of Hypogammaglobulinemia.

Follicular Lymphoma

- ❖ Most common type in western countries (40% of NHL).
- ❖ IT is Not uncommon in Iraq.
- ❖ Chromosomal Translocation (14 : 18).
- ❖ M/E : Follicular growth pattern of small lymphoid cells have cleaved or irregular nuclei and mixed with large lymphoid cells.
- ❖ It is always nodal lymphoma, Not curable (indolent course).

Diffuse Large B-cell Lymphoma

- Most common in adult (50% of adult NHL) also occurs in children.
- Nodal or Extranodal lymphoma.
- M/E : Diffuse growth pattern of large lymphoid cells (B-cell).
- Without treatment, it is Aggressive Lymphoma and Rapidly Fatal.

In general : When lymphoma Diffuse X Follicular

- Large cells X Small cells
- More aggressive and poor prognosis

Burkitt Lymphoma (BL)

- ☒ High grade Peripheral B-cell lymphoma.
- ☒ It mostly affects the children (30% of NHL) and young adults.
- ☒ It mainly occurs in Extranodal Sites (rarely as Nodal Lymphoma).
- ☒ Two main types :
    1. Endemic (African) BL : Due to EBV infection

       Jaw mass (Mandible + Maxilla).
    2. Non-Endemic (Sporadic) BL: Involves Bowel (Ileum), Ovary, and Abdominal Lymph Nodes.
- ☒ Chromosomal Translocation (8 : 14).
- ☒ High - grade, very aggressive tumor and rapidly growing with good response to chemotherapy.
- ☒ M/E : Diffuse growth pattern of uniform malignant lymphoid B- cells with a characteristic Starry-Sky appearance of the tumor.

4- Peripheral (Mature) T-cell Lymphomas

Mycosis Fungoides and Sézary syndrome

Mycosis Fungoides (MF)	Sézary Syndrome
Most common Primary Peripheral T-cell lymphoma of the skin. Low- grade T-cell Lymphoma	More aggressive variant of MF Skin Lesion + Lymphadenopathy (LAP) and Leukemia
Occurs in elderly patient with Itchy Erythematous skin lesion "Skin rash"	Diffuse skin Erythema (Erythroderma) Tumor cells (Sézary cells) in Peripheral Blood " a Leukemic phase " of MF Prognosis is Poor.

Clinical Differences between HL and NHL

HL	NHL
Localized to single LN group	Involve multiple LN groups
Spread by contiguity (regular)	Non- contiguous spread (irregular)
Mesenteric LN and Waldeyer ring are rarely involved	Mesenteric LN and Waldeyer ring are commonly involved
Rare Extranodal involvement	Common Extranodal involvement (Extranodal NHL 30%)
HL …75% cured	NHL …35% cured
Staging more important	Grading more important
Non-variable clinical course	More variable clinical course

Spleen

- ✓ Largest lymphoid tissue in the body (150-200 gm)
- ✓ Functions:
  - Phagocytosis
  - Production of IgM.
- ✓ It is Not essential organ – its removal in children ➔ ➔ increased risk of infection.

✓ Splenomegaly : Enlargement of the spleen from any cause.

✓ Hypersplenism : It is a clinical syndrome, characterized by triad of :

1. Splenomegaly
2. Pancytopenia (Anemia + Leukopenia + Thrombocytopenia)
3. Correction by Splenectomy.

Causes of Splenomegaly

(According to the Weight)

1. Massive Splenomegaly (weight > 1000 gm) :

- CML, CLL, Polycythemia rubra vera, Myelofibrosis, Lymphoma, and Hairy cell leukemia (primary tumor of the spleen).
- Malaria, Kala-azar, and Hydatid cyst.
- Gaucher Disease.

2. Moderates Splenomegaly (weight 500-1000 gm) :

- Congestive splenomegaly (Right-sided heart failure and Portal hypertension caused by Cirrhosis, Schistosomiasis, and Portal vein thrombosis).
- Acute leukemia, Spherocytosis, Sickle cell anemia, Thalassemia, and Autoimmune hemolytic anemia.
- Tuberculosis, Typhoid fever, Brucellosis, Syphilis, Bacterial endocarditis, and Chronic splenitis.
- Sarcoidosis and Amyloidosis.
- Langerhans Cell Histiocytosis and Niemann-Pick disease.
- Metastatic Carcinoma or Sarcoma.
- Idiopathic Splenomegaly.

3. Mild Splenomegaly (weight < 500 gm) :

- Acute splenitis.
- Acute splenic congestion.
- Infectious mononucleosis.
- Infection and septicemia.
- SLE.

Causes of splenomegaly

(According to the Etiology)

1. Infections :

- Protozoal: Malaria, Leishmaniasis and Kala-azar, Schistosomiasis, Toxoplasmosis, and Hydatid cyst.
- Bacterial: Tuberculosis, Secondary, syphilis , Brucellosis, Bacterial endocarditis, and Typhoid fever.
- Viral: Infectious mononucleosis and Cytomegalovirus.
- Fungal: Histoplasmosis.

2. Immunological Causes :

Sarcoidosis, SLE, Rheumatoid arthritis, Felty syndrome, and Amyloidosis.

3. Vascular Causes (Congestive splenomegaly) :

Right–sided heart failure and Portal hypertension (Cirrhosis, Portal vein thrombosis, and Budd-Chiari syndrome).

4. Hematological Diseases :

Hemolytic Anemia (Sickle cell disease, Thalassemia and Spherocytosis), and Autoimmune idiopathic thrombocytopenia.

5. Metabolic Diseases:

Gaucher disease, Niemann-Pick disease, and Mucopolysaccharidoses.

6. Neoplastic Diseases :

CML, CLL, Myelofilorosis, Lymphomas (HL and NHL), Polycythemia rubra vera, Hairy cell leukemia, Multiple myeloma, Metastatic tumor, Simple cyst, Hemangioma, and Fibroma.

7. Idiopathic splenomegaly

Thymus

☒ Site: Anterior – superior mediastinum.

☒ Size: Infant and children – large (30 - 40 gm).

Adult – Atrophied (15 gm)

Thymic Enlargement :

1. True Thymic Hyperplasia -rare
2. Thymic Follicular Hyperplasia (Thymitis): It is seen in Myasthenia gravis, SLE, Rheumatoid arthritis, and Autoimmune diseases .
3. Tumors :

❖ Thymomas: Primary Epithelial Tumor of the thymus.

- Benign Encapsulated (Non-invasive) Thymoma (70% of cases).
- Malignant Thymoma (30% of cases) :

☒ Type - I: Invasive Thymoma (25% of cases).

☒ Type - II: Thymic Carcinoma (5% of cases).

Mostly Squamous Cell Carcinoma.

❖ Lymphomas :

- Lymphoblastic Lymphoma + ALL.
- HL, usually Nodular Sclerosis subtype.
- NHL, usually Diffuse Large B-Cell lymphoma subtype.

❖ Germ Cell Tumors :

- Teratoma.
- Seminoma (Germinoma).

❖ Carcinoid tumor.

THANK YOU