Lymphoma

Lymphomas are a group of diseases caused by malignant lymphocytes (T, B, or NK) that accumulate in lymph nodes and cause the characteristic clinical features of lymphadenopathy

- Although having different characteristics from their normal counterparts, the neoplastic cells of many lymphomas have the features of lymphoid cells at a particular stage of differentiation.

- Lymphomas arise as a result of a series of mutations in a single lymphoid cell.

The major subdivisions of lymphomas are:

- **Hodgkin's lymphoma (HL)** and
- **non-Hodgkin's lymphoma (NHL)**

This is based on the histological presence of ***Reed-Sternberg (RS) cells in Hodgkin's lymphoma***

The biologic behavior and treatment of Hodgkin lymphoma differ from those of most NHLs, thus making the distinction between the two is of practical importance.

- B- and T-cell tumors are composed of cells derived from specific stage of normal lymphocyte differentiation.
- All lymphomas are derived from a single transformed cell and thus are by definition monoclonal.

➢ ***Hodgkin's lymphoma***

Hodgkin lymphoma (HL) include distinctive group of neoplasms that arise almost invariably in a single lymph node or chain of lymph nodes and spread characteristically in a stepwise fashion to the anatomically contiguous nodes.

■ HL accounts for 30% of all lymphomas

■ Molecular studies have shown that it is a tumor ***of B-cell origin***

■ It is characterized morphologically by the presence of distinctive neoplastic giant cells called **Reed-Sternberg (RS) cells**, and large mononuclear cells called Hodgkin's cells in a reactive background composed of lymphocytes, histiocytes (macrophages), and granulocytes.

■ The neoplastic Reed-Sternberg cells typically make up a minor fraction (1 - 5%) of the total tumor cell mass, making HL more difficult to study than typical NHLs.

■ The neoplastic RS-cells are derived from **germinal center or post-germinal center B cells** in the vast majority of cases,

■ The EBV genome is present in the RS cells in up to 70% of cases of the mixed-cellularity type and a smaller fraction of the nodular sclerosis type. Thus, EBV infection is likely to be a contributing step to the development of Hodgkin lymphoma, particularly the mixed-cellularity type.

■ The disease can present at any age but is rare in children and has a peak incidence in young adults. There is an almost 2 : 1 male predominance

■The usual clinical presentation is with painless asymmetrical lymphadenopathy–most commonly in the neck. Typically the disease is localized initially to **a single** peripheral lymph node region and its subsequent **progression is by contiguity** within the lymphatic system.

■ Constitutional symptoms of fever, weight loss & sweating are prominent in patients with widespread disease. Alcohol-induced pain in the areas where disease is present occurs in some patients.

Diagnosis and histological classification:

❖ The diagnosis is made by histological examination of an excised lymph node.

❖ **The histologic diagnosis of Hodgkin lymphoma rests on the definitive identification of Reed-Sterberg cells or their variants in the appropriate background of reactive cells.**

Morphology of Reed –Sternberg cells:

The **Reed-Sternberg (RS) cell** is a large cell with an enlarged multilobated nucleus, prominent nucleoli, and abundant, usually slightly eosinophilic, cytoplasm. **Particularly characteristic are cells with two mirror-image nuclei or nuclear lobes, each containing a large (inclusion-like) acidophilic nucleolus surrounded by a distinctive clear zone; together they give an owl-eye appearance. The nuclear membrane is distinct.**

Such "classic" RS cells are common in the mixed-cellularity subtype, uncommon in the nodular sclerosis subtype, and rare in the lymphocyte-predominance subtype.

❖ Blood tests may show anaemia, neutrophilia, eosinophilia & raised erythrocyte sedimentation rate (ESR) or lactate dehydrogenase (LDH).

Classification:

Five subtypes of Hodgkin lymphoma are recognized:

(1) Nodular sclerosis.

(2) Mixed cellularity.

(3) Lymphocyte predominance.

(4) Lymphocyte rich.

(5) Lymphocyte depletion.

} **Uncommon**

WHO classification of Hodgkin lymphoma.

- ***Nodular lymphocyte - predominant Hodgkin lymphoma***

-***Classical Hodgkin lymphoma***

are subclassified into 4 pathologic subtypes based upon Reed-Sternberg cell morphology and the composition of the reactive cell infiltrate seen in the lymph node biopsy specimen.

Nodular sclerosis classical Hodgkin lymphoma

Mixed- cellularity classical Hodgkin lymphoma

Lymphocyte- rich classical Hodgkin lymphoma (rare)

Lymphocyte- depleted classical Hodgkin lymphoma (rare)

- **Nodular Sclerosis Hodgkin Lymphoma:**

- The most common form**.**

- It is equally frequent in men and women**.**

- Most of the patients are adolescents or young adults**.**

- has a striking tendency to involve the lower cervical, supraclavicular, and mediastinal lymph nodes**.**

- The overall prognosis is excellent**.**

Morphology:

A variant of the RS cell, the **lacunar cell**. This cell is large and has a single multilobate nucleus with multiple small nucleoli and an abundant, pale-staining cytoplasm.

-In formalin-fixed tissue, the cytoplasm often retracts, giving rise to the appearance of cells lying in empty spaces, or lacunae**.**

There are varying proportions of lymphocytes, eosinophils, histiocytes.

- Classic RS cells are infrequent**.**

-There are collagen bands that divide the lymphoid tissue into circumscribed nodules.

- **Mixed-Cellularity Hodgkin Lymphoma:**

- Patients older than the age of 50 year.

-Male predominance.

- **Classic RS cells are plentiful** within a distinctive mixed cellular infiltrate of small lymphocytes, eosinophils, plasma cells, and benign histiocytes.

- Compared with the other subtypes, more patients with mixed cellularity have disseminated disease and systemic manifestations**.**

- **Lymphocyte-depleted HL**

- (< 1% of cases)

- Characterized by the presence of large numbers of RS cells that are often bizarre morphologically.

- It is associated with older age and HIV positive status.

- Patients usually present with advanced-stage disease.

- **Lymphocyte-rich HL**

- (5%) of cases.

- RS cells of the classic or lacunar type are observed, with a background infiltrate of lymphocytes.

- Clinically, the presentation and survival patterns are similar to mixed cellularity HL.

- **Nodular Lymphocyte-Predominance Hodgkin Lymphoma:**

- This subgroup, comprising about 5% of Hodgkin lymphoma.

- Affected LN in a nodular appearance.

-It is characterized by a large number of small resting lymphocytes admixed with a variable number of benign histiocytes**.**

-Eosinophils, neutrophils, and plasma cells, are scanty or absent, and classic RS cells are extremely difficult to find.

- Lymphohistiocytic (L&H) variant RS cells that have a delicate multilobed, puffy nucleus that has been likened in appearance to popcorn (**"popcorn cell"**), in a lympho-histiocytic background.

- Unlike classic RS cells, L&H cells are positive for B-cell antigens (CD19 & 20), and are negative for CD15 & 30).

- It presents mostly as isolated cervical or axillary lymphadenopathy and have excellent prognosis.

■ In all subtypes, involvement of the spleen, liver, bone marrow, and other organs may appear in the course of the disease.

➢ ***Non-Hodgkin's lymphoma***

These are a large group of clonal lymphoid tumours, about 85% are of B cell origin and 15% of T or NK (natural killer) cell origin.

-They are characterized by an irregular pattern of spread and a significant proportion of patients develop extranodal disease.

- The aetiology of the majority of cases of non-Hodgkin lymphomas (NHL) is unknown although infectious agents are an important cause in particular subtypes

Table Infections associated with haemopoietic malignancies.

Infection	**Organism**	**Tumour**
Virus	HTLV–1	Adult T-cell leukaemia/lymphoma
	Epstein–Barr virus	Burkitt and Hodgkin lymphomas; post-transplant lymphoproliferative disease (PTLD)
	HHV–8	Primary effusion lymphoma
	HIV–1	High-grade B-cell lymphoma, primary CNS lymphoma, Hodgkin lymphoma
	Hepatitis C	Marginal zone lymphoma
Bacteria	Helicobacter pylori	Gastric lymphoma (mucosa-associated lymphoid tissue MALT)
Protozoa	Malaria	Burkitt lymphoma

Cell of origin:

▪ B-cell lymphomas tend to mimic normal B cells at different stages of development.

▪ T-cell lymphomas resemble precursor T cells in bone marrow or thymus, or peripheral mature T cells.

Classification of non-Hodgkin lymphoma:

The lymphomas are classified within a group of mature B-cell and T-cell neoplasm.

For many years clinicians have subdivided lymphomas into low and high-grade disease.
-In general terms, the low grade disorders are relatively indolent, respond well to chemotherapy but are very difficult to cure whereas high-grade lymphomas are aggressive and need urgent treatment but are often curable.

-Low grade lymphoma: e.g.

Follicular lymphoma, mantle cell lymphoma.

-High Grade Lymphoma: e. g.

Diffuse Large B-Cell Lymphoma, Burkitt's lymphoma

The WHO Classification of lymphoid neoplasms

The World Health Organization (WHO) classification of lymphoid neoplasms considers the morphology, cell of origin (determined by immunophenotyping), clinical features, and genotype (e.g., karyotype, presence of viral genomes) of each entity.

1. Hodgkin lymphoma.
2. Non-Hodgkin's lymphoma
   a. Precursor B-cell neoplasms (neoplasms of immature B cells)
   b. Peripheral B-cell neoplasms (neoplasms of mature B cells)
   c. Precursor T-cell neoplasms (neoplasms of immature T cells)
   d. Peripheral T-cell and NK-cell neoplasms (neoplasms of mature T cells and NK cells)

PERIPHERAL B-CELL NEOPLASMS

i. Chronic lymphocytic leukemia/small lymphocytic lymphoma
ii. B-cell prolymphocytic leukemia
iii. Lymphoplasmacytic lymphoma
iv. Splenic and nodal marginal zone lymphoma

v. Extranodal marginal zone lymphoma
vi. Mantle cell lymphoma
vii. Follicular lymphoma
viii. Hairy cell leukemia
ix. Plasmacytoma/plasma cell myeloma
x. Diffuse large B-cell lymphoma
xi. Burkitt lymphoma

PERIPHERAL T-CELL AND NK-CELL NEOPLASMS

I. T-cell prolymphocytic leukemia
II. T-cell granular lymphocytic leukemia
III. Mycosis fungoides/Sézary syndrome
IV. Peripheral T-cell lymphoma, unspecified
V. Anaplastic large-cell lymphoma
VI. Angioimmunoblastic T-cell lymphoma
VII. Enteropathy-type T-cell lymphoma
VIII. Panniculitis-like T-cell lymphoma
IX. Hepatosplenic γδ T-cell lymphoma
X. Adult T-cell leukemia/lymphoma
XI. Extranodal NK/T-cell lymphoma
XII. Aggressive NK-cell leukemia

- **Some neoplasms are common and collectively make up the vast majority of lymphoid neoplasm (more than 90%),**

these include

1. Precursor B- and T-cell lymphoblastic leukemia/lymphoma—commonly called acute lymphoblastic leukemia (ALL)
2. Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL)
3. Follicular lymphoma
4. Mantle cell lymphoma
5. Extranodal marginal zone lymphoma
6. Diffuse large B-cell lymphomas
7. Burkitt's lymphoma
8. Multiple myeloma and related plasma cell dyscrasias
9. Hodgkin lymphoma

Clinical features of non-Hodgkin's lymphomas:

I. *Superficial lymphadenopathy***:** asymmetric painless enlargement of lymph nodes in one or more peripheral lymph node regions.

II. *Constitutional symptoms* Fever, night sweats and weight loss occur less frequently than in Hodgkin's disease.

III. *Oropharyngeal involvement*.

IV. *Features due to* anaemia, neutropenia or thrombocytopenia.

V. *Organs* involvement, the liver and spleen are often enlarged. The gastrointestinal tract is the most commonly involved extranodal site after the bone marrow. Also Skin, brain, testis or thyroid can be involved.

Clinical Differences Between Hodgkin and Non-Hodgkin Lymphomas:	
Hodgkin Lymphoma	**Non-Hodgkin Lymphoma**
1. More often localized to a single axial group of nodes (cervical, mediastinal, para-aortic	1.More frequent involvement of multiple peripheral nodes
2. Orderly spread by contiguity	2.Noncontiguous spread
3. Mesenteric nodes and Waldeyer ring rarely involved	3.Mesenteric nodes and Waldeyer ring commonly involved
4. Extranodal involvement uncommon	4. Extranodal involvement common

Investigations

- **Histology**

Lymph node biopsy or of other involved tissue is the definitive investigation.

- Morphological examination is assisted by Immunophenotypic and genetic analysis.
- A fine needle aspiration may be performed to exclude another cause of lymphadenopathy (e.g.tuberculosis,carcinoma) but is not useful in establishing a diagnosis of lymphoma.

- **Laboratory investigations:** -

i. In advanced disease with marrow involvement, there may be anaemia, neutropenia or thrombocytopenia.

ii. Lymphoma cells (e.g. mantle zone cells, 'cleaved follicular lymphoma' or 'blast' cells) may be found in the peripheral blood in some patients.
iii. Trephine biopsy of marrow to see if there is bone marrow involvement.
iv. Increase LDH and uric acid.
v. Immunoglobulin electrophoresis may reveal a paraprotein.

■ Specific subtypes of non-Hodgkin's lymphoma:

● Low-grade non-Hodgkin's lymphoma:

1) ***Follicular lymphoma:*** 40% of adult lymphomas. It is often characterized by a benign course for many years**.** It is associated with the t(14,18) translocation (fuses the *BCL2* gene to the IgH locus on chromosome 14 and leads to the inappropriate expression of BCL2 protein, which functions to prevent apoptosis.)

Follicular lymphoma occurs predominantly in older persons (rarely before age 20 years) and affects males and females equally.

The natural history is prolonged (median survival, 7-9 years), but follicular lymphoma is not easily curable, a feature that is common to most of the **indolent lymphoid malignancies**

2) ***Mantle cell lymphoma****:* it is associated with a t(11,14) translocation that results in over-expression of **cyclin D_1.** It is of aggressive behavior.

3) ***Marginal zone lymphomas:*** are typically extranodal.

Mucosa associated lymphoid tissue (MALT) lymphomas come into this category at sites such as the stomach or thyroid. Gastric MALT lymphoma is the most common form and is preceded by *Helicobacter (H.) pylori* infection.

4) ***Lymphocytic lymphomas:*** Lymphocytic lymphomas are closely related to CLL

● High Grade Lymphoma:

1. Diffuse Large B-Cell Lymphoma:

It is the most common type of NHL lymphoma. It is considered as heterogeneous group of mature B cell tumors that share a similar large-cell morphology and aggressive clinical behavior.

Highly associated with rearrangements or mutations of BCL6 gene.

2. ***Burkitt's lymphoma*****:** is one of the most highly proliferative subtypes of any tumours. It is associated with ***translocations of the* c-MYC *gene on chromosome 8*, as result of translocation (t(8;14)).**

Endemic (African) Burkitt's lymphoma is seen in areas with chronic malaria exposure and is associated with Epstein-Barr virus (EBV) infection. Typically, the patient, usually a child, presents with massive lymphadenopathy of the jaw which is initially very responsive to chemotherapy although long-term cure is uncommon

Sporadic cases may occur elsewhere in the world. It affects mainly children and adolescents, and has a greater tendency for involvement of the abdominal cavity (gastrointestinal tract, retroperitoneum, and ovaries) than the endemic form.

◙ **T-cell lymphoma** are less common and include: mycosis fungoides, peripheral T-cell lymphoma, anaplastic large cell lymphoma, enteropathy–associated T-cell lymphomas, and others.

Clinical Staging of Hodgkin and Non-Hodgkin Lymphomas (Ann Arbor Classification)*

Stage I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or tissue (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm alone (II) or with involvement of limited contiguous extralymphatic organs or tissue (II_E)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (III_S), limited contiguous extralymphatic organ or site (III_E), or both (III_{ES})
Stage IV	Multiple or disseminated foci of involvement of one or more extralymphatic organs or tissues with or without lymphatic involvement

---All stages are further divided on the basis of the absence (A) or presence (B) of the following systemic symptoms: significant fever, night sweats, unexplained loss of more than 10% of normal body weight.