Lymphoreticular system pathology

DR. AYSER HAMEED

LEC.3

Non-Hodgkin lymphoma-Clinical features

- Two-thirds of NHLs and (virtually all Hodgkin lymphomas) present as **enlarged non-tender lymph nodes** (often > 2 cm). The remaining one-third of NHLs present with symptoms related to the **involvement of extranodal sites** (e.g., skin, stomach, or brain).
- The lymphocytic leukemias most often come to attention because of signs and symptoms related to the **suppression of normal hematopoiesis** by tumor cells in the bone marrow
- Symptoms related to **proteins secreted** from the tumor cells or from immune cells that are responding to the tumor→ **Less likely than Hodgkin lymphoma to have B symptoms (only 20% versus 40% in Hodgkin lymphoma)**
- Lymphoid neoplasms often **disrupt normal immune function.** Both immunodeficiency and autoimmunity may be seen

Risk factors and etiology in the development of NHLs

 The etiology of the majority of cases of non-Hodgkin lymphomas (NHL) is unknown

1. **infectious agents** are an important cause in particular subtypes, see next table
2. **immunodeficiency** (primary or secondary)
3. **autoimmune disorders** (Sjogren, rheumatoid arthritis, Hashimoto thyroiditis)
4. **radiation**
5. **chemotherapy**

Table: Risk factors and etiology in the development of NHLs

Infection	Organism	Tumour
Virus	HTLV–1	Adult T-cell leukemia/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

The WHO Classification of lymphoid neoplasms

The World Health Organization (WHO) classification of lymphoid neoplasms considers the **morphology**, **cell of origin** (determined by immunophenotyping i.e. the study of surface molecules exhibited by tumor cells like CD3 for T-cells and CD20 for B-cells…etc), **clinical features**, and **genotype** (e.g., karyotype, presence of viral genomes) of each entity.

Table 12.7 WHO Classification of Lymphoid Neoplasms[a]

Precursor B Cell Neoplasms
Precursor B cell leukemia/lymphoma (B-ALL)
Peripheral B Cell Neoplasms
B cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
B cell prolymphocytic leukemia
Lymphoplasmacytic lymphoma
Mantle cell lymphoma
Follicular lymphoma
Extranodal marginal zone lymphoma
Splenic and nodal marginal zone lymphoma
Hairy cell leukemia
Plasmacytoma/plasma cell myeloma
Diffuse large B cell lymphoma (multiple subtypes)
Burkitt lymphoma
Precursor T Cell Neoplasms
Precursor T cell leukemia/lymphoma (T-ALL)
Peripheral T/NK Cell Neoplasms
T cell prolymphocytic leukemia
T cell granular lymphocytic leukemia
Mycosis fungoides/Sézary syndrome
Peripheral T cell lymphoma, unspecified
Angioimmunoblastic T cell lymphoma
Anaplastic large cell lymphoma
Enteropathy-type T cell lymphoma
Panniculitis-like T cell lymphoma
Hepatosplenic γδ T cell lymphoma
Adult T cell lymphoma/leukemia
Extranodal NK/T cell lymphoma
Aggressive NK cell leukemia
Hodgkin Lymphoma
Nodular sclerosis
Mixed cellularity
Lymphocyte-rich
Lymphocyte-depleted
Lymphocyte predominant

NK, Natural killer; *WHO*, World Health Organization.
[a]Entries in *italics* are among the most common lymphoid tumors.

Reference: Kumar, Vinay, et al. **Robbins Basic Pathology**.

Investigation and diagnosis

1. **Histology**

 Lymph node biopsy of other involved tissue is the definitive investigation. Morphological examination is assisted by Immunophenotypic and genetic analysis.

 A fine needle aspiration (aspirating cells from an enlarged lymph node using a syringe)may be performed to exclude another cause of lymphadenopathy (e.g.tuberculosis, carcinoma) but less useful in establishing a diagnosis of lymphoma

2. **Hematological investigations:** -

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

 Blood film: of paramount importance in the leukemias and if lymphoma cells spill out to the circulation.

 Trephine biopsy of marrow to see if there is bone marrow involvement.

3. **Biochemical tests:** Increase LDH and uric acid.

4. **Immunological tests:** immunoglobulin electrophoresis may reveal a paraprotein. (immunoglobin secreted by neoplastic plasma cells)

Specific subtypes of 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 **indolent lymphoid malignancies and eventually could transform into more aggressive type**

2. **Mantle cell lymphoma**

 6% of adult lymphomas B-cell origin

 Small to intermediate-sized cells resembling/originating from the mantle zone

 diffuse growth pattern.

- associated with a t (11,14) translocation that results in over-expression of **cyclin D_1**
- moderately aggressive.

3. Marginal zone lymphomas:

- This indolent B cell tumor arises most commonly in epithelial tissues such as the stomach, salivary glands, small and large bowel, lungs, orbit, and breast. (MALT lymphomas is a form of extranodal marginal zone lymphoma)
- ~5% of adult lymphomas
- Associated with chronic inflammation like 1- autoimmune disease as in thyroiditis or stomach in association with *H. pylori* gastritis)

4. <u>Diffuse Large B-Cell Lymphoma:</u>

- It is the most common type of NHL lymphoma
- A 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 the *BCL6* gene or *BCL2*.

5. *<u>Burkitt's lymphoma</u>*<u>:</u>

- is one of the most highly proliferative subtypes of any tumor. It is associated with ***translocations of the* c-MYC *gene on chromosome 8*, as a 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 a 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.

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

Stage I	Involvement of a single lymph node region (I) or involvement of a single extra lymphatic 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 extra lymphatic 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 extra lymphatic organ or site (III_E), or both (III_{ES})
Stage IV	Multiple or disseminated foci of involvement of one or more extra lymphatic organs or tissues with orwithout lymphatic involvement

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

Disorders of the Spleen

- The spleen is frequently involved in a wide variety of systemic diseases.
- In virtually all instances the spleen responds by enlarging (splenomegaly), an alteration that produces a set of stereotypical signs and symptoms
- Evaluation of the extent of splenomegaly can give clues to causes:

1. ***Massive splenomegaly*** (weight > 1000 g):

- Myeloproliferative neoplasms (CML)
- certain indolent leukemia (CLL);
- many lymphomas
- infectious diseases (e.g., malaria);

2. ***Moderate splenomegaly*** (weight 500–1000 g):

- Chronic congestive splenomegaly (portal hypertension);
- acute leukemias
- Hemolytic anemias

3. ***Mild splenomegaly*** (weight < 500 g)

- Acute splenitis;
- acute splenic congestion;
- Infectious mononucleosis;

Hypersplenism

 Hypersplenism is a clinical syndrome that can be seen in any form of splenomegaly (it does not imply a specific causal mechanism). It is characterized by:

1. Enlargement of the spleen
2. Reduction of at least one cell line in the blood in the presence of normal bone marrow function(anemia, leukopenia, or thrombocytopenia which is the most common)
3. Evidence of increased release of premature cells, such as reticulocytes or immature platelets, from the bone marrow into the blood.

Hyposplenism:

 Patients with functional hyposplenism have impaired immunity to blood-borne bacterial and protozoal infections, and persistent thrombocytosis

.