Pathology of the Lymphoid System

Lymph Node:

I. Non-Neoplastic Conditions:

►Reactive Lymphadenitis: Any immune response against foreign antigens (infectious &noninfectious inflammatory stimuli) is often associated with lymph node enlargement(lymphadenopathy). The infections that cause lymphadenitis are numerous and varied

and may be acute or chronic. In most instances, the histological appearance of the nodes is entirely nonspecific i.e. different etiologies are associated with similar microscopic changes.

■Acute Nonspecific Lymphadenitis:

Grossly: inflamed nodes are swollen & congested i.e. gray-red.

Microscopically: there are large germinal centers containing numerous mitotic figures. When

the cause is a pyogenic organism, a neutrophilic infiltrate is seen about the follicles and within the lymphoid sinuses. With severe infections, the centers of follicles can undergo suppurative necrosis. The overlying skin is frequently red, and penetration of the infection to the skin can produce draining sinus.

■Chronic Nonspecific Lymphadenitis:

This condition can assume one of three patterns, depending on the causative agent:

1. Follicular hyperplasia
2. Paracortical hyperplasia
3. Sinus histiocytosis

- Follicular Hyperplasia: is associated with infections or inflammatory processes that

activate B cells in the B-cell areas i.e. the follicles, & thus create the follicular (or germinal

center) reaction. The cells in the reactive follicles include the activated B cells (called

follicular center cells), scattered phagocytic macrophages containing nuclear debris and

follicular dendritic cells (function in antigen display to the B cells).

Causes of follicular hyperplasia include:

*Rheumatoid arthritis. *Toxoplasmosis. *Early stages of HIV infection.

- Paracortical Hyperplasia: The paracortex is the zone situated between the cortex and the medulla, which contains the mobile pool of T lymphocytes responsible for cell-mediated immune responses. Paracortical hyperplasia is characterized by reactive changes within the Tcell regions of the lymph node, which is reflected microscopically as expanded zones between the cortical follicles. On immune activation parafollicular T-cells transform into large proliferating immunoblasts.

Paracortical hyperplasia is encountered in:

*Viral infections (such as EBV).

*Following certain vaccinations.

*Immune reactions induced by certain drugs

●Sinus Histiocytosis: is characterized by distention and prominence of the lymphatic sinusoids, owing to a marked hypertrophy of lining endothelial cells and an infiltrate of macrophages.

Sinus histiocytosis is often encountered in:

*Lymph nodes draining cancers and may represent an immune response to the tumor or its products.

■Granulomatous lymphadenitis:

Immune reactions are usually involved in the development of granulomas. There is often

strong activation of T lymphocytes leading to macrophage activation, which can cause injury

to normal tissues. Granulomatous inflammation is a distinctive pattern of chronic inflammation that is encountered in a limited number of infectious and some noninfectious condition

The causes of granulomatous lymphadenitis include:

- Infections.
- Foreign body reactions.
- Malignancy.

Among the infectious causes are: *Tuberculosis. *Atypical mycobacteriosis.

*Sarcoidosis. *Fungal infections. *Toxoplasmosis. *Syphilis & Leprosy. *Brucellosis.

- Malignancy related granulomatous lymphadenitis: occurs whether the neoplasm is:

*Primary (Hodgkin & nonHodgkin lymphomas), or

*Secondary (metastatic carcinoma).

It occurs whether the node is involved by the malignancy or not.

II. Lymphoid Neoplasms:

All lymphoid neoplasms have the potential to spread to lymph nodes and various tissues

throughout the body, especially the liver, spleen, and bone marrow. In some cases lymphomas

spill over into the peripheral blood, creating a leukemia-like picture. Conversely, leukemias of

lymphoid cells, originating in the bone marrow, can infiltrate lymph nodes and other tissues,

creating the histologic picture of lymphoma.

Two groups of lymphomas are recognized:

- Hodgkin lymphoma and (HL).
- Non-Hodgkin lymphomas (NHL).

According to the Iraqi Cancer Registry (2009); NHL ranks the 6th, and represents 4.83% of the top ten cancers by primary site in Iraq.

The behavior and treatment of Hodgkin lymphoma differ from those of most NHLs,

thus making the distinction between the two of practical importance.

It has been shown that NHLs is often widely disseminated at the time of diagnosis, even

when the disease appears clinically localized, that is why only systemic therapies are

curative.

In contrast, Hodgkin lymphoma often presents at a single site and spreads in apredictable fashion to neighboring lymph node groups. For this reason, early in the disease, local therapy may be effective.

The WHO has established a widely accepted classification that depends on a combination of:

*Clinical. *Microscopic. *Immunophenotypic. *Genetic features (e.g., cytogenetic, molecular, presence of viral genomes, etc.).

B- and T-cell tumors are composed of cells derived from specific stages of their normal differentiation pathways. The diagnosis and classification of these tumors relies heavily on tests (e.g. immunohistochemistry & flow cytometry) that detect specific antigens (e.g., B-cell, T-cell markers).

■Non-Hodgkin lymphomas (NHL):

●Precursor B- and T-Cell Lymphoblastic Leukemia/Lymphoma: These are aggressive tumors, composed of immature lymphocytes (lymphoblasts). They are microscopically indistinguishable. Both pre-B- and pre-T-lymphoblastic lymphomas usually take on the clinical appearance of an acute lymphoblastic leukemia (ALL) at some time during their course. As a group, ALLs constitute 80% of childhood leukemia, peaking in incidence at age of 4 years, with most of the cases being of pre-B-cell origin. The pre-T-cell tumors, which initially present as thymic tumors, are most common in adolescent males of between 15 and20 years of age.

- Small Lymphocytic Lymphoma/Chronic Lymphocytic Leukemia (SLL/ CLL): These

two disorders differ only in the extent of peripheral blood involvement.

If there is peripheral blood lymphocytosis > 4000/µL, the patient is diagnosed with chronic lymphocytic leukemia (CLL); if not, a diagnosis of small lymphocytic lymphoma (SLL) is made.

- Follicular Lymphomas: The tumor likely arises from germinal center B cells. The bone

marrow is almost always involved at the time of diagnosis.

- Diffuse Large B-Cell Lymphoma (DLBCL): this is the most important type of NHL lymphoma in adults (50% of adult NHL).

- Burkitt Lymphoma: is endemic in some parts of Africa and sporadic elsewhere. Both the African and nonendemic forms are identical, although there are clinical and virologic differences.

*In endemic areas: tumor cells in almost all patients carry EBV genome.

*In nonendemic areas: 80% of tumors DO NOT harbor the EBV genome.

■Hodgkin Lymphoma (HL): encompasses a 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.

Classification: HL has been classified into:

1. Classical HLs.
2. Nodular lymphocyte predominant HL.

► Classical Hodgkin's 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.

Microscopic features: The characteristic microscopic feature is the presence of distinctive neoplastic giant cells called Reed-Sternberg (RS) cells in a reactive background of prominent inflammatory response composed of a variable number of lymphocytes, macrophages, eosinophils, plasma cells and fibroblasts.

►Classical HL: Under this heading are the following subtypes:

●Nodular Sclerosis Hodgkin Lymphoma: is the most common form. It is equally frequent in men and women and has a striking tendency to involve the lower cervical, supraclavicular, and mediastinal lymph nodes. Most of the patients are adolescents or young adults, and the overall prognosis is excellent.It is characterized microscopically by the presence of a particular variant of the RS cell,

the “lacunar cell”.

- Mixed-Cellularity Hodgkin Lymphoma (MCHL): is the most common form of Hodgkin

lymphoma in patients older than the age of 50 years with a male predominance. Classic RS

cells are plentiful within a distinctive mixed cellular infiltrate, which includes small lymphocytes, eosinophils, plasma cells, and benign histiocytes. Compared with the other subtypes, patients with mixed cellularity have more disseminated disease and systemic manifestations.

- Lymphocyte-depleted Hodgkin disease (LDHL) (< 1% of cases): it is characterized by the presence of large numbers of RS that are often of bizarre morphology. Reactive cells are infrequent and fibrosis may be extensive. It is associated with older age and HIV positive status.

- Lymphocyte-rich HL (LRHL) (5% of cases): RS cells of the classic or lacunar type are observed with

abackground infiltrate of B-lymphocytes.

The histologic diagnosis of Hodgkin lymphoma rests on the definitive identification of RS cells or their variants in the appropriate background of reactive cells.Immunophenotyping plays an important adjunct role in helping to distinguish Hodgkin lymphoma from reactive conditions and other forms of lymphoma.

Clinical Staging of Hodgkin (and Non-Hodgkin Lymphoma) (Ann Arbor Classification):

Stage I: involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or tissue (IE).

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 (IIE).

Stage III: involvement of lymph node regions on both sides of the diaphragm (III), which

may include the spleen (IIIS), limited contiguous extralymphatic organ or site (IIIE), or both

(IIIES).

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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

Spleen:

Splenomegaly: The spleen is frequently secondarily involved in a wide variety of systemic diseases. In virtually all instances, the response of the spleen causes its enlargement(splenomegaly). As an aid to diagnosis, splenomegaly is classified according to the degree of its enlargement:

- Massive splenomegaly (weight more than 1000 gm):
  - Chronic myeloproliferative disorders (chronic myeloid leukemia & primary myelofibrosis).
  - Chronic lymphocytic leukemia.
  - Hairy cell leukemia.
  - Lymphomas.
  - Malaria.

■Moderate splenomegaly (weight 500-1000 gm):

●Chronic congestive splenomegaly (portal hypertension or splenic vein obstruction).

●Acute leukemias.

●Hereditary spherocytosis.

●Thalassemia major.

●Autoimmune hemolytic anemia.

■Mild splenomegaly (weight <500 gm):

●Acute splenitis.

●Acute splenic congestion.

●Infectious mononucleosis.

●Miscellaneous acute febrile disorders, including septicemia, SLE, and intra-abdominal infections.