Pathology of lymphatic system

BY

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LYMPHOID TISSUE

3 types

**Diffuse lymphatic tissue**
No capsule present
Found in connective tissue of almost all organs

**Lymphatic nodules**
No capsule present
Oval-shaped masses
Found singly or in clusters

**Lymphatic organs**
Capsule present
Lymph nodes, spleen, thymus gland
1- LYMPH NODE

[Diagram of a lymph node with labeled parts such as cortex, medullary cords, medullary sinus, paracortical area, secondary lymphoid follicles, and germinal center.]
Lymph node histology
lymphadenopathy
Causes of lymphadenopathy

1- Reactive lymphadenopathy

2- Malignant lymphomas (primary)
   Non-Hodgkin’s lymphoma-NHL
   Hodgkin’s lymphoma

3- Metastatic tumors (secondary)
I - REACTIVE LYMPHADENOPATHY

Reactive lymphadenopathy = Reactive lymphadenitis
Reactive processes are analyzed by their architectural features into
Reactive lymphoid hyperplasia with
1) Follicular hyperplasia
2) Parafollicular hyperplasia
3) Sinus histocytosis

Reactive processes are analyzed by their Etiological features into
1) Infectious
   a) acute ....acute lymphadenitis due to draining inflamed area
   b) chronic
   Non specific ....non specific lymphadenitis
   Specific ......due to certain AE.

2) Immunological
   Rheumatoid arthritis
   Lupus erythematousus
   Sjögren's syndrome

3) Unknown causes
   Sarcoidosis
I-REACTIVE LYMPHADENOPATHY
REACTIVE LYMPHOID HYPERPLASIA

It is non-specific response and is categorized into three types depending upon the pattern. These are:
follicular hyperplasia,
paracortical hyperplasia and
sinus histiocytosis.
Some types characteristic of certain diseases, but most not

1-Follicular hyperplasia-
Characterized by
Increases number and Marked enlargement and prominence of the germinal centers of lymphoid follicles
(proliferation of B-cell areas),

it may be Reactive non specific or
associated with(specific)

Collagen vascular diseases
Systemic toxoplasmosis
Syphillis
HIV
2- Interfollicular hyperplasia- paracortex

Characterized by

Expansion of the paracortex (T-cell area) with T-lymphocytes transformed immunoblasts, eosinophils and plasma cells.

it may be Reactive non specific or associated with (specific)

Skin diseases
Viral infections (EBV causing IMN)
Drug reactions
3-Sinus histiocytosis
Characterized by
Expansion of the sinuses by proliferating large histiocytes containing phagocytosed material.; it may be Reactive non specific or associated with (specific)

Adjacent cancer
Infections
**FOLLICULAR HYPERPLASIA**

*Figure 41-9* Reactive germinal center. This reactive follicle exhibits polarization, that is, a dark zone at the top with gradation to a light zone at the bottom. Thercingible body macrophages impart a starry sky appearance.
Para cortical hyperplasia
Sinus Histiocytosis

Figure 41-20: Sinus histiocytosis with massive lymphadenopathy: high-power magnification. The distinctive histiocytes have a vesicular nucleus, one or several prominent nucleoli, and abundant cytoplasm exhibiting lymphophagocytosis. Numerous admixed plasma cells are present.
LYMPHADENITIS
II- PRIMARY MALIGNANCIES
LYMPHOMAS
Hodgkin's lymphoma

The disease originally described by Thomas Hodgkin in (1798-1866)

It is a type of malignant lymphoma in which Reed–Sternberg cells are present in a ‘characteristic background’ of reactive inflammatory cells of various types, accompanied by fibrosis of a variable degree.
Pathobiology

EBV infection
smaller family size
higher socio-economic status
possible genetic predisposition
other: HIV? occupation? herbicides?
EPIDEMIOLOGY

Less common; ~ 10,000 cases per year
Age incidence bimodal,
   one peak in late adolescence 15 Y, young adulthood 35 Y,
   second peak beginning in 5th decade
Bimodal curve shifts to younger ages in poorer countries
CLINICAL MANIFESTATION

- Painless lymphadenopathy
- contiguous spread
- extranodal sites relatively uncommon except in advanced disease
- “B” symptoms
Patterns of spread

Hodgkin's lymphoma spreads contiguously via lymphatics
**RS cell**
Various appearances of *lacunar cells* in nodular sclerosis Hodgkin lymphoma.
Hodgkin's lymphoma classification

REAL / WHO 2001 classification

- Nodular lymphocyte predominant
- Classical
  1. Lymphocyte-predominance type.
  2. Nodular-sclerosis type.
  4. Lymphocyte-depletion type.
1- NODULAR LYMPHOCYTE PREDOMINANT

- Usually presents with limited disease in the neck of young adults
- Associated with L & H (lymphocytic and histiocytic) or "popcorn cell" variant RS cell
- Scant background formed mainly of small lymphocytes.
A and B, Lymphocyte predominant Hodgkin lymphoma.

A, Low-power view showing a mottled appearance of the node.
B, High-power view showing the lymphocytic and/or histiocytic (L&H) type of cell (‘popcorn’ cell) that is characteristic of this condition.
2- classical HL

1- Nodular sclerosing HL
- *Most common type* Hodgkin's lymphoma in US/Europe
- Usually presents in the *anterior mediastinum* and neck of young adult females
- Characterized by *fibrotic capsule* and bands subdividing tissue and
  *Lacunar* variant Reed Sternberg cell
Nodular sclerosing HL
other Histologic subtypes

2- Mixed cellularity
- More extensive disease
- Older patients than NS and LP
- *More R-S cells, eosinophils, plasma cells*
- Mononuclear variant R-S cells
- Inherently more aggressive disease

4- lymphocyte rich
Usually presented with *lower stage*
*Rich in lymphocytes*, with Scattered RS cells

5- Lymphocyte depleted
- Often presents in retroperitoneum, *older patients*
- Accompanied by less lymphocytes, sclerosis and *pleomorphic RS cell variants*
- Also more aggressive disease
lymphocyte rich
Mixed cellularity Hodgkin lymphoma.

Several Reed–Sternberg cells are admixed with a polymorphic lymphoid infiltrate rich in eosinophils.
Lymphocyte depletion type of Hodgkin lymphoma.

Numerous atypical RS cells are present in a densely fibrotic stroma. Lymphocytes are scanty.
INVESTIGATIONS

- Lymph node biopsy
- Bone marrow aspiration and biopsy
- Clinical staging investigations (CT, MRI scan, x ray, us)
- Immunohistochemistry
- Flow cytometry
- Molecular Genetic studies
- FISH
- Cytogenetics
Clinical staging of HL lymphomas

Defines extent of disease; determines therapy and prognosis
Based on physical, radiologic examination, bone marrow biopsy and aspiration

*******Ann Arbor Staging system

**B symptoms:** fever, weight loss > 10% body weight, night sweats
Stages of Non-Hodgkin’s Lymphoma

Stage I (early disease): the cancer is found only in a single lymph node region OR one organ or area outside the lymph node.

Stage II (locally advanced disease): the cancer is found in two or more lymph node regions on one side of the diaphragm (the breathing muscle that separates the abdomen from the chest), OR the cancer is found in one lymph node region plus a nearby area or organ.

Stage III (advanced disease): the disease involves lymph nodes both above and below the diaphragm OR one nodal area and one organ on opposite sides of the diaphragm.

Stage IV (widespread disease): the lymphoma is outside the lymph nodes and spleen AND has spread to one or more organs such as bone, bone marrow, skin, or other organs.
Stage subdivision:

- **A**: Asymptomatic
- **B**: Unexplained weight loss >10% in 6m and/or fever and/or night sweats

**Extralymphatic** = tissue other than lymph nodes, thymus, spleen, Waldeyer's ring, appendix & Peyer's patches
Prognosis

- Hodgkin's lymphoma is a curable malignancy
- Overall cure rate approximately 80%
- With modern therapy, prognosis based more on staging, bulk of disease, than morphologic subtype
- Lymphocyte depletion and mixed cellularity had the worst prognosis
Non-Hodgkin's lymphomas-NHLs

- Approximately 40,000 cases per year, 20,000 deaths
- It forms 75% of cases of lymphoma
Clinical presentation

- Enlarging mass(es), typically painless, swelling of lymph nodes
- located in the neck, underarm and groin.
- Common primary extranodal spread

- Hollow organ obstruction, ulceration and perforation

- Solid organ infiltration: kidneys, liver, bone marrow
- Systemic symptoms
  - Fever
  - Night sweats
  - Weight loss
- If marrow infiltrated, can have leukemic component
Classification of NH lymphomas

- **Working Formulation**
  - Low grade = indolent
  - Intermediate and high = aggressive

- **R.E.A.L./W.H.O. Classification**
  
  **B cell neoplasms**
  - Precursor B cells-related to acute leukemia
  - Peripheral B cell lymphomas- the majority of B cell lymphomas

  **T cell and Natural Killer cell neoplasms**
  - Precursor T cells
  - Peripheral T cell and NK neoplasms
R.E.A.L. Classification (1994)

1. Leukaemias and lymphomas of B-cell origin (Pan B CD19,20 positive)
   (A) Indolent B-cell malignancies
   (B) Aggressive B-cell malignancies

II. Leukemias and lymphomas of T-cell origin (CD2,7 positive)
   (A) Indolent T-cell malignancies
   (B) Aggressive T-cell malignancies
Working Formulations For Clinical Usage (1982)

I. Low-grade
1) Small lymphocytic
2) Follicular, predominantly small cleaved cell
3) Follicular, mixed small and large cleaved cell

II. Intermediate grade
1) Follicular predominantly large cell
2) Diffuse, small cleaved cell
3) Diffuse, mixed small and large cell
4) Diffuse, large, cell

III. High - Grade
1) Large cell. immunoblastic
2) Lymphoblastic
3) Small non-cleaved cell (Burkitt's)

IV. Miscellaneous
1. Adult T-cell leukaemia/lymphoma
2. Cutaneous T-cell lymphoma
3. Histiocytic (Histiocytic medullary reticulosis)
R.E.A.L. Classification (1994)

1. Leukaemias and lymphomas of B-cell origin (Pan B CD19,20 positive)
   ○ (A) Indolent B-cell malignancies
     i) Chronic lymphocytic leukaemia/small lymphocytic lymphoma
     ii) Hairy cell leukaemia
     iii) Follicular lymphomas (grade I small cleaved, grade II mixed small and large)
     iv) Lymphoplasmacytoid lymphoma/Waldenstrom's macroglobulinaemia
     v) Marginal zone lymphoma {lymphoma of mucosa associated lymphoid tissue (MALT), splenic lymphoma)

   ○ B) Aggressive B-cell malignancies
     i) Diffuse large cell lymphoma
     ii) Follicular large cell lymphoma (grade III)
     iii) Mantle cell lymphoma
     iv) Burkitt's lymphoma
     v) Plasmacytoma/myeloma

II. Leukemias and lymphomas of T-cell origin (CD2,7 positive)
   ○ A) Indolent T-cll malignanciel
     i) T-CLL, T-prolymphocytic leukaemia
     ii) Cutaneous T-cell lymphoma

   ○ B) Aggressive T-cell malignancies
     i) Peripheral T-cell NHL
     ii) Angioimmunoblastic T-cell lymphoma
     iii) Intestinal T-cell lymphoma
     iv) Adult T-ALL
DIFFERENT TYPES OF CELLS INVOLVED IN NHL
# Frequency of Lymphomas

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>% of total cases</th>
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<tbody>
<tr>
<td>Diffuse large B-cell lymphoma</td>
<td>30.6%</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>22.1%</td>
</tr>
<tr>
<td>MALT lymphoma</td>
<td>7.6%</td>
</tr>
<tr>
<td>Mature T-cell lymphomas (except ALCL)</td>
<td>7.6%</td>
</tr>
<tr>
<td>Chronic lymphocytic leukaemia/small lymphocytic lymphoma</td>
<td>6.7%</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>6.0%</td>
</tr>
<tr>
<td>Mediastinal large B-cell lymphoma</td>
<td>2.4%</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma</td>
<td>2.4%</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>2.50%</td>
</tr>
<tr>
<td>Nodal marginal zone lymphoma</td>
<td>1.8%</td>
</tr>
<tr>
<td>Precursor T lymphoblastic</td>
<td>1.7%</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
<td>1.2%</td>
</tr>
<tr>
<td>Other types</td>
<td>7.4%</td>
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B CELL LYMPHOMA
1- Follicular lymphoma

This tumor comprises up to 40% in the United States.
Most cases occur in elderly

Grossly
the most distinctive feature is the nodular pattern of growth.
Homogeneous population of small cleaved cells in follicular lymphoma

Even distribution of neoplastic follicles in follicular lymphoma

Retain follicular structure
2- Marginal zone B-cell lymphoma

- marginal zone lymphoma of mucosa-associated lymphoid tissue (usually abbreviated as MALT lymphoma).
- This tumor was originally described at extranodal sites in relation to mucosae or glandular epithelia, such as gastrointestinal tract, salivary and lacrimal glands, lung, thyroid, conjunctiva, bladder, and skin.
Lymph node involvement by marginal zone B-cell lymphoma.
There are numerous residual germinal centers.

MALT lymphoma
3-Small lymphocytic lymphoma

- occurs in middle-aged and elderly individuals
- Indolent in behavior
Low-power view of small lymphocytic lymphoma. A monotonous proliferation of small lymphocytes effaces the architecture of the node.
Examples: aggressive B cell lymphoma

1-Diffuse large B-cell lymphoma

- Diffuse large B-cell lymphoma (DLBCL) is the most complex and heterogeneous of all the non-Hodgkin lymphomas
- DLBCL occurs both in children and adults, but mostly in the latter
- Approximately 40% of the cases present in extranodal sites, such as the digestive system, skin, and skeletal system.
- When the liver or spleen is involved, it is usually in the form of scattered large tumor masses
Medium- (A) and high-power (B) views of diffuse large B-cell lymphoma of large cleaved type.
Burkitt lymphoma is a high-grade malignant lymphoma composed of germinal center B cells which can present in three clinical settings:

1. **Endemic.**
   This occurs in the equatorial *strip of Africa* and is the most common form of childhood malignancy in this area.
   The patients characteristically present with *jaw and orbital lesions*. Involvement of the gastrointestinal tract, ovaries, kidney, and breast are also common.

2. **Sporadic.**
   This is seen throughout the world.
   It affects mainly children and adolescents, and has a greater tendency for involvement of the *abdominal cavity* than the endemic form.

3. **Immunodeficiency-associated.**
   This is seen primarily in association with HIV infection and often occurs as the initial manifestation of the disease. Mainly in GIT, CNS.
Burkitt lymphoma with characteristic starry sky appearance.
4- Mantle cell lymphoma

- it usually occurs in middle-aged and elderly individuals
High-power view of mantle cell lymphoma. The nuclear contours, being intermediate between that seen in small cleaved follicular lymphoma and that of small lymphocytic lymphoma.
T CELL LYMPHOMA

- Represent 20% all lymphomas
- Most diseases had high stage, highly aggressive occurring primarily at extranodal sites as skin, midline facial area, liver
- poorer response to therapy than B cell lymphomas of all grades
Peripheral large T-cell lymphoma
Clinical staging of NHL lymphomas

***** Ann Arbor Staging system

B symptoms: fever, weight loss > 10% body weight, night sweats

N.B:
The concept of staging is much less helpful in NHL.
Prognosis

**Indolent**
- Small lymphocytic lymphoma/CLL
- Follicular lymphoma, Grades 1/2
- Extranodal Marginal zone lymphoma of MALT type
- Nodal marginal zone lymphoma
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Lymphoplasmacytic lymphoma
- Plasma cell myeloma
- Plasmacytoma
- Cutaneous T cell lymphoma
- Cutaneous CD30+ anaplastic large cell lymphoma
- Cutaneous T cell lymphoma
- Cutaneous CD30+ anaplastic large cell lymphoma

**Aggressive**
- Prolymphocytic leukemia
- Large B cell lymphoma
- Burkitt lymphoma
- Mantle cell lymphoma
- Anaplastic large cell lymphoma
- All peripheral T cell lymphomas
III-Secondary Metastatic Tumors

Metastatic Tumors
Carcinoma
Malignant melanoma
Germ cell tumor
Sarcoma
Unknown primary site
Childhood tumors