Lymphoma

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THE LYMPHOMAS

- The lymphomas are a heterogeneous group of biologically and clinically distinct neoplasms that originate from cells in the lymphoid tissue.
- Lymphoma is the 5th most common malignancy and the most common form of hematological malignancy in the developed world.
- They have been historically divided into 2 distinct categories: Hodgkin's and Non-Hodgkin's Lymphoma.
- 85% of lymphomas originate from mature B cells and 15% derive from the T-cell lineage.

THE LYMPHOMAS

- Variable c/p (Asymptomatic-medical emergency)
- Most commonly patients have peripheral lymphadenopathy or symptoms due to occult lymph nodes, although approximately 20% arise at primary extra-nodal sites.
- A relatively small proportion present with lymphoma-associated ‘B’ symptoms of weight loss, fever and sweats.

ANATOMY OF THE LYMPHOID SYSTEM

Lymphoid Tissues can be divided into 2 major categories :

1) CENTRAL or PRIMARY LYMPHOID TISSUES :

- These are tissues in which the lymphoid precursor cells mature to a stage at which they are capable of performing their function in response to an antigen
- Includes Bone Marrow and Thymus

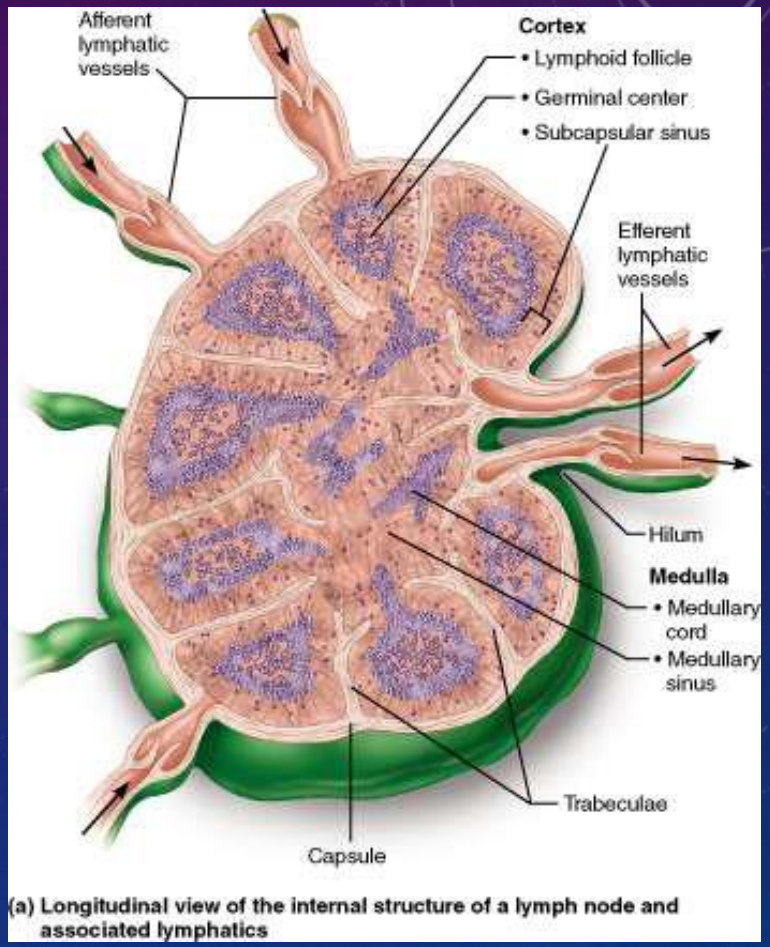
2) PERIPHERAL or SECONDARY LYMPHOID TISSUE

- These are tissues in which antigen specific reactions occur
- Includes Lymph Nodes, Spleen and Mucosa Associated Lymphoid Tissue

LYMPH NODE

Divided into a capsule, cortex, medulla and sinuses.

- Sinuses contain numerous macrophages which filter the lymph fluid, identify and process antigens and present them to lymphocytes.
- Cortex contains B cell follicles
- Paracortex contains high endothelial venules and T cell zones.
- Medulla contains sinuses.



(a) Longitudinal view of the internal structure of a lymph node and associated lymphatics

MUCOSA ASSOCIATED LYMPHOID TISSUE(MALT)

Specialized lymphoid tissue , found in association with certain epithelia, in particular:

a) Naso and Oro-Pharynx : Adenoids, palatine tonsils

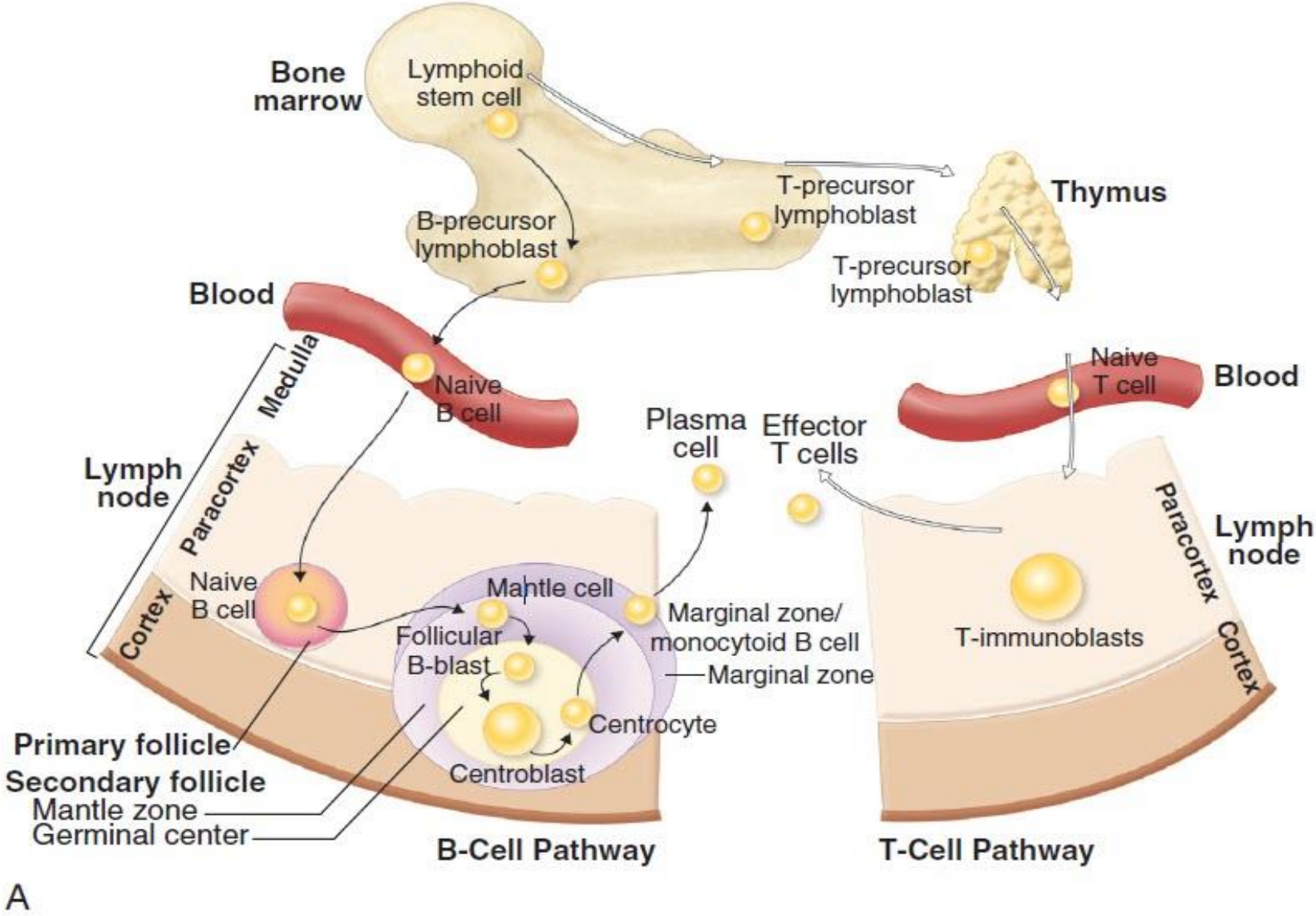
b) Gastro-Intestinal tract : Peyer's patches of distal ileum and mucosal lymphoid aggregates in colon and rectum.

c) Lung : Bronchus associated lymphoid tissue

FUNCTION

- Response to intra-luminal antigens
- Generation of mucosal immunity

NORMAL B- AND T-CELL DIFFERENTIATION.



THE 2016 WHO CLASSIFICATION OF LYMPHOID TUMORS

Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

Mature B-cell neoplasms
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- Monoclonal B-cell lymphocytosis*
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- *Splenic B-cell lymphoma/leukemia, unclassifiable*
  - *Splenic diffuse red pulp small B-cell lymphoma*
  - *Hairy cell leukemia–variant*
- Lymphoplasmacytic lymphoma
  - Waldenström macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS), IgM*
- μ heavy-chain disease
- γ heavy-chain disease
- α heavy-chain disease
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extraosseous plasmacytoma
- Monoclonal immunoglobulin deposition diseases*
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
  - *Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - In situ follicular neoplasia*
  - Duodenal-type follicular lymphoma*
- Pediatric-type follicular lymphoma*
- *Large B-cell lymphoma with IRF4 rearrangement**
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma
  - In situ mantle cell neoplasia*
- Diffuse large B-cell lymphoma (DLBCL), NOS
  - Germinal center B-cell type*
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the central nervous system (CNS)
- Primary cutaneous DLBCL, leg type
- EBV$^+$ DLBCL, NOS*
- *EBV$^+$ mucocutaneous ulcer**
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK$^+$ large B-cell lymphoma
- Plasmablastic lymphoma
- Primary effusion lymphoma
- *HHV8$^+$ DLBCL, NOS**
- Burkitt lymphoma
- *Burkitt-like lymphoma with 11q aberration**
- High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
- High-grade B-cell lymphoma, NOS*
- B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

Mature T and NK neoplasms
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- *Chronic lymphoproliferative disorder of NK cells*
- Aggressive NK-cell leukemia
- Systemic EBV$^+$ T-cell lymphoma of childhood*
- Hydroa vacciniforme–like lymphoproliferative disorder*
- Adult T-cell leukemia/lymphoma
- Extranodal NK-/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma*
- *Indolent T-cell lymphoproliferative disorder of the GI tract**
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous γδ T-cell lymphoma
- *Primary cutaneous CD8$^+$ aggressive epidermotropic cytotoxic T-cell lymphoma*
- *Primary cutaneous acral CD8$^+$ T-cell lymphoma**
- *Primary cutaneous CD4$^+$ small/medium T-cell lymphoproliferative disorder**
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- *Follicular T-cell lymphoma**
- *Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma, ALK$^+$
- Anaplastic large-cell lymphoma, ALK$^-$*
- *Breast implant–associated anaplastic large-cell lymphoma**

Hodgkin lymphoma
- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte-depleted classical Hodgkin lymphoma

Posttransplant lymphoproliferative disorders (PTLD)
- Plasmacytic hyperplasia PTLD
- Infectious mononucleosis PTLD
- Florid follicular hyperplasia PTLD*
- Polymorphic PTLD
- Monomorphic PTLD (B- and T-/NK-cell types)
- Classical Hodgkin lymphoma PTLD

Histiocytic and dendritic cell neoplasms
- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Indeterminate dendritic cell tumor
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor
- Disseminated juvenile xanthogranuloma
- Erdheim-Chester disease*

HODGKIN'S LYMPHOMAS

- Hodgkin lymphoma (formerly, Hodgkin disease) is a potentially curable lymphoma with distinct histology (by the presence of a Reed-Sternberg cell), biologic behavior, and clinical characteristics.
- **Incidence**
  - Hodgkin's lymphoma (HL) has an incidence of approximately 3 per 100 000 in the Western world.
  - Sex: male predominance, approximately 1.3 : 1.
  - Age: the incidence varies with age, with a clear **bimodal** distribution that is consistent across most countries and studies. The initial peak is in young adults (15-35 years) and older adults (>55 years).

AETIOLOGY

- The etiology of HL is unknown.
- Infectious agents, particularly Epstein-Barr virus (EBV) and HIV
- Genetic predisposition plays a role: 1% of patients with Hodgkin lymphoma have a family history of the disease and siblings of a patient have a 3- to 7-fold increased risk of developing the disease.

CLINICAL FEATURES

- Asymptomatic.
- Lymphadenopathy:
  - Painless lymphadenopathy in most of cases (80%),
  - Usually cervical, supraclavicular, axillary.
  - HL arises in a single node or chain of nodes and spreads first to anatomically contiguous lymphoid tissue.
  - Lymph nodes feel rubbery and more firm than inflammatory adenopathy.

CLINICAL FEATURES

B symptoms

- About 33 % present with B symptoms overall.

1- Fever(>38^C)

- May first present as fever of unknown origin.
- Fever persists for days to weeks followed by afebrile intervals and then recurrence. This pattern is called Pel Ebstein fever.

2- Recurrent Drenching night sweats.

3- Weight loss (>10% in 6 months).

CLINICAL FEATURES

Mediastinal Lymphadenopathy:

- At the time of presentation present in 75% of cases.
- Bulky mediastinal disease (masses greater than one-third the diameter of the intrathoracic cavity) may cause dysphagia, dyspnea, cough, stridor, or the superior vena cava (SVC) syndrome.
- Superior Vena Cava (SVC) Syndrome
  - Dyspnea is the most common symptom,
  - Dysphagia, Cough, Chest pain,
  - Facial swelling, Fullness of face, congested neck veins, Arm swelling,
  - Patients with cerebral edema may have headaches, confusion, or possibly coma,

CLINICAL FEATURES

- Other less common manifestations are :

  Pruritis,

  Alcohol induced pain over involved lymph nodes, nephrotic syndrome,

  Erythema nodosum,

  CNS manifestations may be due to paraneoplastic syndromes, including cerebellar degeneration, neuropathy or guillain-barre syndrome

  Immune hemolytic anaemia,

  Thrombocytopenia,

  Hypercalcemia.

DIAGNOSIS

- History Taking:
  - Swellings
  - B symptoms
  - Previous infection
  - Immune deficiencies
  - Exposure to toxins
  - Familial

DIAGNOSIS

- Examination:
  - Lymph node (size, number, location, consistency, fixed or not).
  - Liver and spleen (size)
  - Skin involvement
  - Pulmonary findings
  - Neurological signs

DIAGNOSIS

Laboratory:

1- CBC with differential count and blood film

- Normal/ NNA/Lymphopenia/lymphocytosis.

2- ESR

Usually raised/ Indicator of disease activity.

3- Liver Biochemistry

- Often abnormal with or without liver involvement.
- Cholestatic Jaundice in LN of porta hepatis involvement.

DIAGNOSIS

4- Serum LDH

-Raised level is adverse prognostic factor.

5- Uric acid

-Normal or raised (Tumor lysis syndrome).

6- Renal function and Electrolytes

7- Virology: HIV, hepatitis B and C

-when potentially immunosuppressive therapy is to be recommended.

8- Fertility (Pregnancy test if married female)

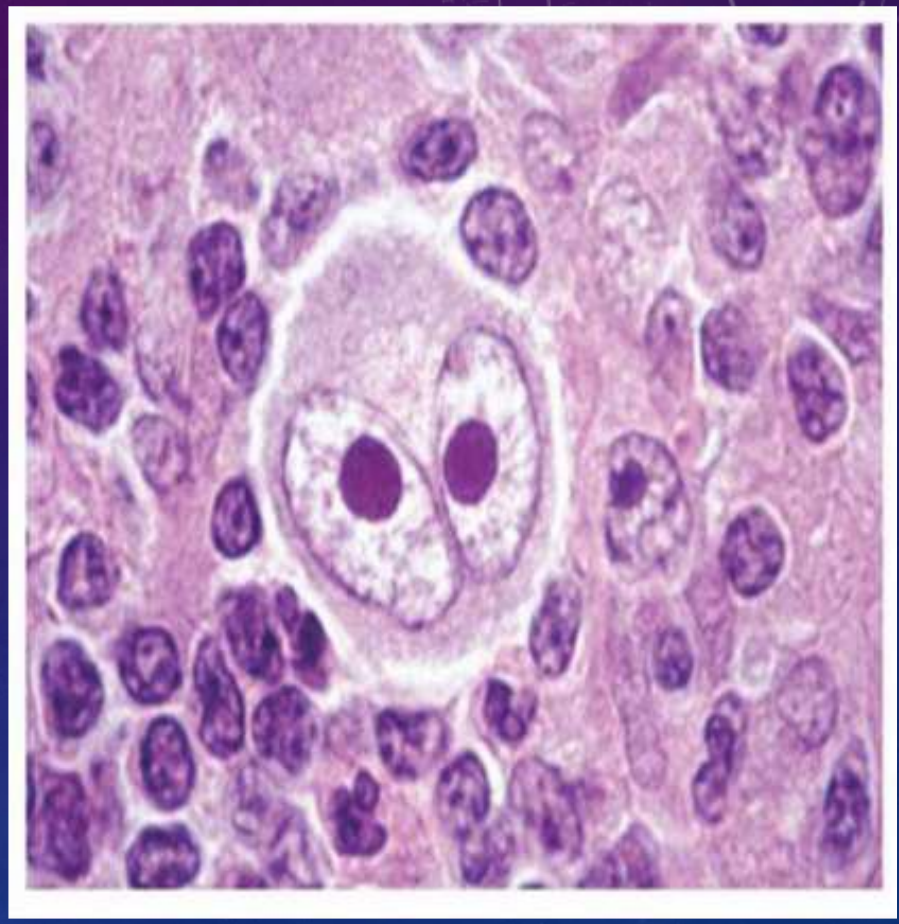
DIAGNOSIS

- Imaging:
  1- Chest X-ray for mediastinal widening.
  2- CT scan of chest, abdomen, pelvis ± neck
  - It is the investigation of choice for staging.
  3- PET scan (It is the examination of choice for detecting disease activity during and after treatment, to stage a patient accurately and to establish sites of extranodal disease.)
  4- Cardiac evaluation (ECG, Echo)

DIAGNOSIS

- **Histopathological diagnosis:**

- Lymph node biopsy is required for a definitive diagnosis.
- The hallmark of HL is the Reed–Sternberg cell. (Large malignant B cells have two mirror-image nuclei "owl-eye" Appearance and surrounded by large numbers of reactive non malignant T cells, plasma cells and oesinophils).
- CD30 and CD15 are almost always expressed in the majority of cases of classical HL.



WHO PATHOLOGICAL CLASSIFICATION OF HL

- **Nodular lymphocyte-predominant HL (5%)**
- **Classical Hodgkin's lymphoma:**
  - **Nodular sclerosis HL …. (70%)**
  - **Lymphocyte-rich HL …. (5%)**
  - **Mixed cellularity HL ….. (25%)**
  - **Lymphocyte-depleted HL…..Rare**

DIAGNOSIS

- BM examination:
  - BMA & BMB are recommended only for patients with:

  1- Advanced stage disease (stage III, IV),

  2- B symptoms, or

  3- Any abnormality on CBC that is suspicious for bone marrow involvement (anaemia).

STAGING (ANN ARBOR STAGING OF HL)

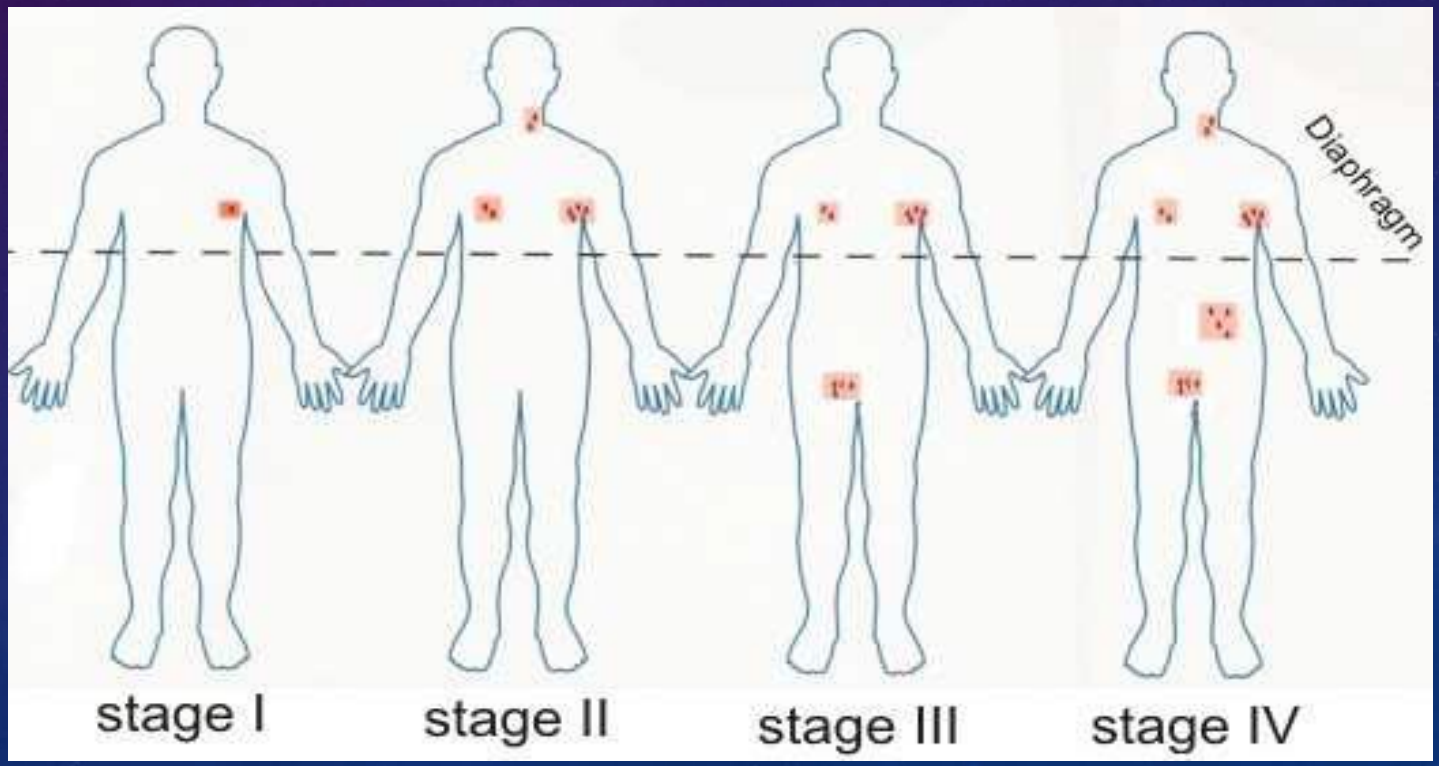
I - Single LN region or extranodal structure (spleen, thymus).

II - Two or more on the same side of diaphragm or localized contagious involvement of only one extranodal structure and ln regions on the same side of diaphragm.

III - In regions on both sides of diaphragm +\- involvement of spleen.

IV - Diffuse involvement of one or more of exranodal tissues (liver, bone marrow or lung) +\- ln invlovement.

- *A and B for each stage as regards absence or presence of B symptoms*



➢ DD of cervical lymphadenopathy

- Acute infections:

  -pyogenic infections.

  -IMN, CMV.

  -Cat scratch diseases.

  -Toxoplasosis.

- Chronic infections:

  -T.B , Syphilis.

  -HIV, sarcoidosis.

- Connective tissue diseases:

- SLE, rheumatoid arthritis.

- Drugs: Phenytoin

- 1ry LN malignancy:

-Lymphoma.

-CLL.

-ALL.

- 2ry LN malignancy:

-Thyroid, breast , lung.

- Miscellaneous:

- kawasaki disease.

WORSE PROGNOSTIC FACTORS

- Age ≥ 45 years
- Male sex
- Hemoglobin less than 10.5 g/dL
- Serum albumin less than 4 g/dL
- Stage IV disease (Ann Arbor classification)
- White blood cell (WBC) count greater than 15,000/mm^3
- Absolute lymphocyte count less than 600/mm^3, less than 8% of the total WBC count, or both

TREATMENT

- Specific treatment is based on the anatomical distribution of disease, its ‘bulk’ and ‘B’ symptoms.
- 90% of patients with early stage achieve complete remission, while 50-70% of those with advanced disease can be cured.
- Treatment methods
  1. Radiotherapy
  2. Chemotherapy
  3. Combined treatment modality
  4. Hematopoietic stem cell transplantation.

EARLY STAGE (IA, IIA + NO BULK)

- Chemotherapy **ABVD**
  - (doxorubicin, bleomycin, **vinblastine,** and dacarbazine)
  - 2-4 cycles
- followed by involved field irradiation.

ADVANCED DISEASE (STAGES IB, IIB, OR ANY STAGE III OR IV OR BULKY DISEASE)

- This is also curable for a significant proportion of patients, the median survival exceeding 5 years for 50-60 % .
- Cyclical combination chemotherapy with or without irradiation to sites of ‘bulk’ disease is the treatment of choice for all these patients.
- The ‘gold standard’ combination is ABVD given to a total of 6-8 cycles.
- All patients with mediastinal bulk receive irradiation.

ADVANCED DISEASE (STAGES IB, IIB, OR ANY STAGE III OR IV OR BULKY DISEASE)

- The major potential toxicity in the short term being myelosuppression and mucositis with a mortality of ~ 1%.
- Long-term risks → the heart and lungs affection, infertility and second malignancy.
- Autologous bone marrow transplant may be considered in resistant and relapsing disaese.

NON-HODGKIN'S LYMPHOMA (NHL)

- NHL represents a monoclonal proliferation of lymphoid cells of B cell origin (80%) or T cell origin (20%).
- **The incidence**
- The incidence of NHL is 5- 15/100000 per year in developed countries, an incidence which has increased over the last 20–30 years.
- There is a slight male predominance.
- The median age of presentation is 55–75 years.

AETIOLOGY

- NHLs may result from chromosomal translocations, infections, environmental factors, immunodeficiency states, and chronic inflammation.

Chromosomal translocations

- Chromosomal translocations and molecular rearrangements play an important role in the pathogenesis of many lymphomas
- Example: The t(14;18)(q32;q21) translocation is the most common chromosomal abnormality associated with NHL. This translocation occurs in 85% of follicular lymphomas and 28% of higher-grade NHLs. This translocation results in the juxtaposition of the *bcl* -2 apoptotic inhibitor oncogene at chromosome band 18q21 to the heavy chain region of the immunoglobulin (Ig) locus within chromosome band 14q32.

Infection

- Some viruses are implicated in the pathogenesis of NHL as Epstein-Barr virus (EBV) which is associated with Burkitt lymphoma and lymphomas in immunocompromised patients and sinonasal lymphoma. Also, Herpesvirus, Hepatitis C virus (HCV) and the human T cell lymphotropic virus are associated with NHL.
- Helicobacter pylori is an etiological factor in gastric MALT lymphoma.

AETIOLOGY

- **Environmental factors**
  - chemicals (eg, pesticides, herbicides, solvents, organic chemicals, hair dye),
  - Chemotherapy
  - Iradiation exposure
- **Immunodeficiency states**
  - Congenital and acquired immunodeficiency states
  - Induced immunodeficiency states (eg, immunosuppression)
  - Celiac disease has been associated with an increased risk of malignant lymphomas.
- **Chronic inflammation**
  - autoimmune disorders, such as Sjögren syndrome and Hashimoto thyroiditis, promotes the development of MALT.

CLASSIFICATION

- The NHLs are subclassified according to the cell of origin (T or B lineage) and the stage of lymphocytic maturation at which they develop (precursor or mature).
- NHL includes many subtypes, each with distinct epidemiologies; etiologies; morphologic, immunophenotypic, genetic, and clinical features; and responses to therapy.

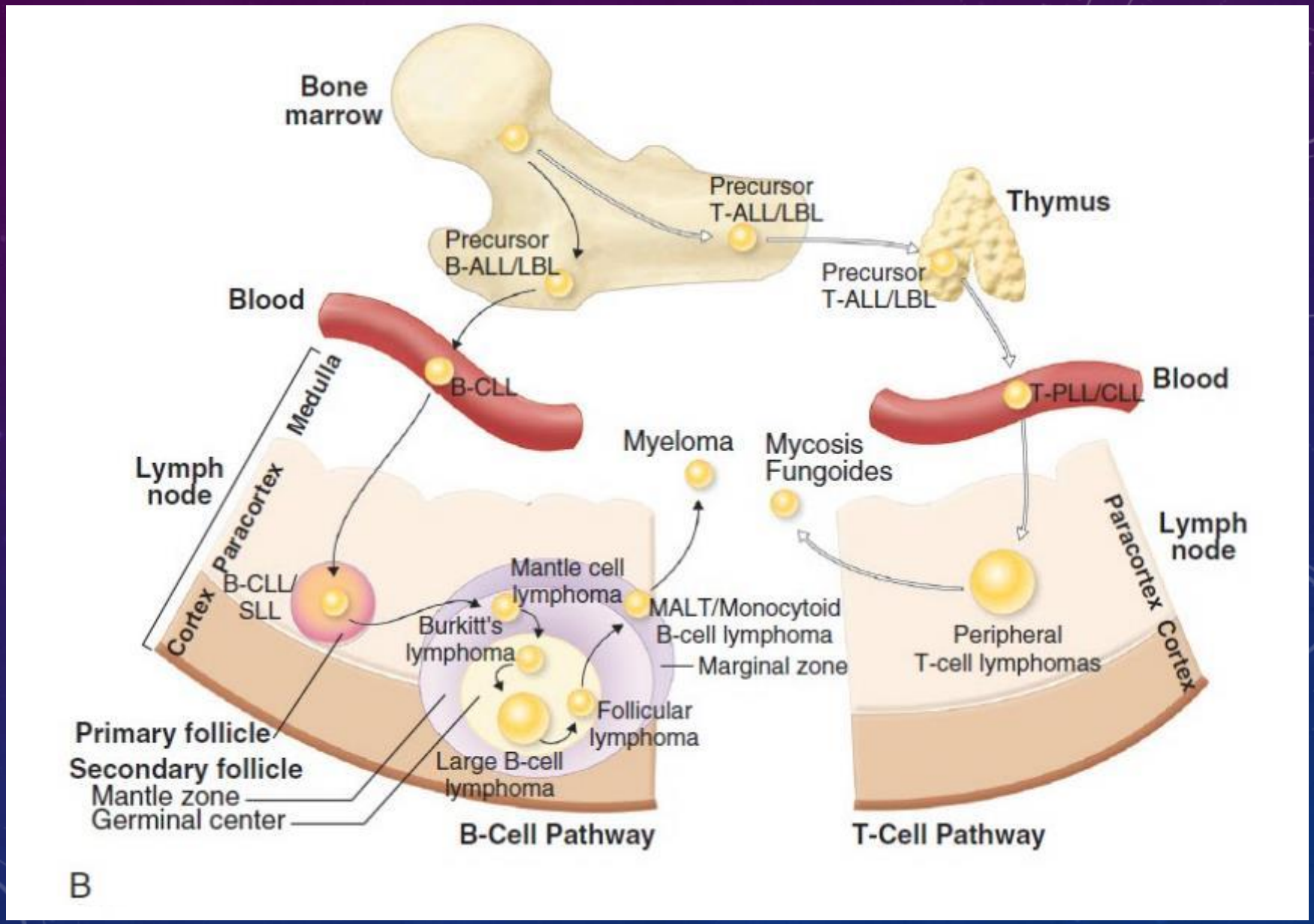
CLASSIFICATION

Mature B cell lymphomas:

- Diffuse large B cell (37%).
- Follicular (29%).
- MALT lymphoma (9%).
- CLL/SLL (12%).
- Mantle lymphoma (7%).
- Burkitt lymphoma (0.8%).

Mature T-cell and natural killer (NK) cell lymphomas:

- Primary T cell lymphoma NOS (29%).
- Angioimmunoplastic lymphoma (18%).
- Extranodal T cell or NK lymphoma (10%).
- Adult T-cell lymphoma or leukemia.
- Anaplastic large cell lymphoma.
- Primary cutaneous lymphoma.


Bone marrow
Precursor T-ALL/LBL
Thymus
Precursor B-ALL/LBL
Precursor T-ALL/LBL
Blood
B-CLL
Blood
T-PLL/CLL
Medulla
Lymph node
Paracortex
Myeloma
Mycosis Fungoides
Lymph node
Paracortex
B-CLL/ SLL
Mantle cell lymphoma
MALT/Monocytoid B-cell lymphoma
Marginal zone
Burkitt's lymphoma
Peripheral T-cell lymphomas
Cortex
Cortex
Follicular lymphoma
Primary follicle
Secondary follicle
Mantle zone
Germinal center
Large B-cell lymphoma
B-Cell Pathway
T-Cell Pathway
B

CLASSIFICATION

1- Low grade : slow rate of proliferation, asymptomatic for many months before presentation, run an indolent course, but is not curable by conventional therapy. (15%)

2- High grade : High rate of proliferation, rapidely produces symptoms , is fatal if untreated, but is potentially curable. (85%)

CLINICAL FEATURES

- *Unlike HL, NHL is often widely disseminated at presentation including extranodal sites.*
- This may involve the gastrointestinal tract, lung, brain, testes, thyroid and skin. Abdominal involvement may reveal hepatosplenomegaly.
- Skin involvement in T cell lymphomas.

CLINICAL FEATURES

- Peripheral lymphadenopathy:

  painless, superficial lymph node enlargement and may be associated with systemic symptoms (B symptoms). Fever, sweats, and weight loss.

- Compression symptoms may occurs (Gut obstruction, ascites, SVC obstruction and spinal cord compression).
- NHL is more likely to be stage III or IV at presentaion.

DIAGNOSIS

- History Taking:
  - B symptoms
  - Previous infection
  - Immune deficiencies
  - Exposure to toxins
  - Familial

DIAGNOSIS

- Examination:

  Lymph node (size and location).

  Liver and spleen (size)

  Skin involvement

  Pulmonary findings

  Neurological signs

DIAGNOSIS

- Laboratory:

1- CBC with differential count and blood film

- Normal/ NNA/Lymphopenia/Eosinophilia.

2- ESR

Usually raised/ Indicator of disease activity.

3- Liver Biochemistry

- Often abnormal with or without liver involvement.
- Cholestatic Jaundice in LN of porta hepatis involvement.

DIAGNOSIS

4- Serum LDH

-Raised level is adverse prognostic factor.

5- Uric acid

-Normal or raised (Tumor lysis syndrome).

6- Renal function and Electrolytes

7- Virology: HIV, hepatitis B and C

- HIV predisposes to NHL.
- when potentially immunosuppressive therapy is to be recommended.

DIAGNOSIS

- Imaging:
  1- Chest X-ray for mediastinal widening.
  2- CT scan of chest, abdomen, pelvis ± neck
    - It is the investigation of choice for staging.
  3- PET scan (It is the examination of choice for detecting disease activity during and after treatment, to stage a patient accurately and to establish sites of extranodal disease.)
  4- Cardiac evaluation (ECG, Echo)

DIAGNOSIS

- Histopathological diagnosis:
  - Lymph node or extranodal disease biopsy, is required for a definitive diagnosis.
- Immunophenotyping
- BM examination:
  - BMA & BMB are routinely recommended.

TREATMENT

Low- grade:

- Asymptomatic patients may not require ttt as there is no survival advantage with immediate treatment versus a watch-and-wait approach.
- Indication of treatment:

  1- Marked systemic symptoms.

  2- Compression syndromes.

  3- Marrow infiltration.

  4- Lymphadenopathy causing discomfort.

TREATMENT OF LOW GRADE NHL

- Options of therapy:

  1-Radiotherpay for stage I.

  2- Chemotherapy . Oral chlorambucil.

  3-Monoclonal antibody therapy…To target surface antigens on tumor cells ….Rituximab.

  4- BM transplantation in patients with relapsed disease.

TREATMENT OF HIGH GRADE NHL

- **Options of therapy:**
  - Chemotherapy: combination chemotherapy with CHOP regimen (cyclophosphmide, doxorubucin, vincrtistine, and prednisolone) .
  - Radiotherapy: for a residual localized bulky disease after chemotherpy and for spinal cord compression.
  - Monoclonal antibody therapy : When combined with CHOP chemotherapy **(R-CHOP)** increases the complete response rate.
  - BM transplantation: For relapsed chemosensitive disease.

Thank you