Disorders of Hematopoietic System
Lymphoproliferative Neoplasms

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Learning Objectives

➢ Introduction to lymphoid system
  - Anatomic distribution
  - Physiology

➢ Introduction to pathobiology

➢ Introduction to neoplastic lymphoid proliferations - clinical Presentation

➢ Overview of diagnostic concepts (pathology)
Subdivision of Hematopoietic Tumors

Anatomic distribution

- Bone marrow
- Blood
- Thymus
- Lymph nodes
- Spleen

Liquid

Tissue
Lymphoid System: Physiology

Important component of immune system

Cellular components and functions:
- B-lymphocytes and plasma cells: antibody mediated defense.
- T-lymphocytes and Natural Killer cells: cell mediated defense, and support B-lymphocyte function.

Deregulation of function:
- Immunodeficiency,
- Autoimmune disorders
- Malignancy
Lymphoid System: Pathobiology

Lymphocyte development is a complex process that occurs in discrete steps.

![Diagram showing the development of lymphoid and myeloid cells from pluripotent stem cells.]

- **Pluripotent stem cell**
  - Lymphoid stem cell
    - B stem cell → Pro B cell → B cell → Plasma cell
    - T stem cell → Prothymocyte → T cell
  - Myeloid stem cell
    - DC stem cell → Mature dendritic cell
- **Myeloid series**
  - Monocytes → Macrophages → Neutrophils
Lymphocytes Undergo Genomic Alterations During Normal Development

Despite the oncogenic dangers associated with genomic instability and mutation...

...lymphoid cells purposely alter their DNA during development to maximize the diversity and effector functions of their antigen receptors

Tsai AG, Lieber MR. BMC Genomics. 2010;11(suppl):S1.
T-Cell Gene Rearrangements: Genetic Permutations and Combinations

![Diagram of T-Cell Gene Rearrangements]

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<th>Gene segment</th>
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<th>IGL</th>
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<td>5c</td>
<td>61</td>
<td>13</td>
<td>5</td>
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</table>
Stages of T-cell development are defined by surface antigen expression.

Prothymocyte, Cortical thymocyte, Medullary thymocyte, T cell

*Terminal deoxynucleotidyl transferase.

Lymphoma subtypes arise from different stages of T-cell development\textsuperscript{1,2}

Lymphoid System: Pathobiology

Stages of B-cell development are defined by surface antigen expression\textsuperscript{1-3}

Lymphoid System: Pathobiology

**Lymph Node Section:**
- Hematoxylin and Eosin Stain

**Germinal Center** (lymphoma)

**Mantle zone** (lymphoma)

**Marginal zone** (lymphoma)

**T zone** (lymphoma)
**W.H.O. classification** Incorporates morphology, immunophenotype, genetic and clinical features

### B cell neoplasms (20 types)
- Small lymphocytic lymphoma/chronic lymphocytic leukemia
- B cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Plasma cell myeloma
- Monoclonal gammopathy of uncertain significance
- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma
- Primary amyloidosis
- Heavy chain diseases
- Extranodal marginal zone B cell lymphoma
- MALT
- Nodal marginal zone lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma/leukemia

### T cell neoplasms (16 types)
- T-cell PLL
- T-cell LGL leukemia
- Aggressive NK leukemia
- Adult T-cell leukemia/lymphoma
- Mycosis fungoides
- Sezary syndrome
- 1° cutaneous ALCL
- Lymphomatoid papulosis
- Blastic NK cell lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Angioimmunoblastic lymphoma
- Peripheral T-cell lymphoma, unspecified
- Anaplastic large cell lymphoma

### Hodgkin Lymphoma
- Classical HL
- NLPHL

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No simple way to remember this!!!
Frequency and distribution of lymphoproliferative neoplasms

- B-NHL: 88%
- T/NK-NHL: 12%

- Peripheral T-cell lymphoma, not otherwise specified
- Cutaneous T-cell lymphoma
- Anaplastic large cell lymphoma
- Angioimmunoblastic T-cell lymphoma
- NK-cell lymphoma

Information presented in the World Health Organization Classification of Tumors: Tumors of Hematopoietic and Lymphoid Diseases : www.LLS.org

4% of all Cancers
Clinical Presentation

- Unexplained/unintentional weight loss
- Unexplained fever
- Night sweats
- Rash
- Painless lymphadenopathy
- Skin rash
Enlargement of lymph nodes in lymphoma

Biopsy of suspected Lymph node for diagnosis
Examples of Skin Rash
Clinical Approach to Lymphoma Diagnosis

- Physical examination
- Complete blood count, peripheral blood smear review
- Chemistry: lactate dehydrogenase, beta 2 macroglobulin
- Radiology: X-ray, Ct scan, PET scan
- Tissue biopsy
- Bone marrow biopsy
Radiology

- Cervical lymph nodes
- Mediastinal mass
- Enlarged spleen

CT scan

PET scan

Fused PET-CT
Lymph Node Biopsy

Open biopsy
Tissue Biopsy: Microscopic Evaluation
Diagnostic Tests

Hematopathologists conduct diagnostic evaluation using special tests.

Immunohistochemistry

CD20

CD79a
Hematopathologists conduct diagnostic evaluation using special tests.
**Diagnostic Tests: FISH**

### Dual-fusion probes

**Metaphase chromosomes**

- **Normal**
  - Red and green probes bind to respective loci.
  - No fusion visible.

- **Abnormal**
  - Reciprocal translocation occurs.
  - One red and one green signal split in half.

**Interphase cells**

- Normal interphase nuclei show two red and two green signals.

- Neoplastic cell with a reciprocal translocation generates:
  - One green, one red, and two yellow (red/green) signals.
  - The latter represent derivative chromosomes.
Diagnostic Tests: FISH

**Break-apart probes**

*Metaphase chromosomes*:
- **Normal**
  - The red and green probes each bind to sequences upstream and downstream of the loci of interest. FISH analysis of normal interphase nuclei shows two yellow (red/green) signals.

*Abnormal*:
- In a neoplastic cell carrying a reciprocal translocation, one of the yellow (red/green) signals splits resulting in separated red and green signals, in addition to the yellow (red/green) signal from the normal chromosome.

*Only one FISH signal is shown per metaphase chromosome to aid clarity but in practice two signals (representing the two chromatids) can be visible*.

JMD May 2006, Vol. 8, No. 2
Lymphoma Classification: Clinical behavior

Mature High Grade B-cell Neoplasms

➢ Diffuse Large B-cell Lymphoma
➢ Burkitt Lymphoma
➢ B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
Heterogeneity of Diffuse Large B-cell Lymphoma

➢ Clinical Presentation
➢ Morphology
➢ Immunophenotype
➢ Molecular/ Cytogenetic features
➢ Response to treatment
Heterogeneity of Diffuse Large B-cell Lymphoma

➢ Clinical Presentation
  - Nodal Disease
  - Extra-nodal disease
    - Skin, soft tissue, bone, GI tract,
      CNS, organ involvement,
      mediastinum
  - Immunosuppression related
Diffuse Large B-cell Lymphoma: Gross

Forms a mass. Can be associated with necrosis in large lesions.
Relationship of DLBCL Subgroups to Normal B-Lymphocyte Differentiation and Activation

- CD21
- BCL6
- CD10
- c-MYC
- BCL2
- IRF4
Subtypes of DLBCL and Survival Characteristics

Figure 5. Clinically distinct DLBCL subgroups defined by gene expression profiling. a, Kaplan–Meier plot of overall survival of DLBCL patients grouped on the basis of gene expression profiling. b, Kaplan–Meier plot of overall survival of DLBCL patients grouped according to the International Prognostic Index (IPI). Low clinical risk patients (IPI score 0–2) and high clinical risk patients (IPI score 3–5) are plotted separately. c, Kaplan–Meier plot of overall survival of low clinical risk DLBCL patients (IPI score 0–2) grouped on the basis of their gene expression profiles.
Follicular Lymphoma

B-FL pattern: Absence of TM, proliferation of centroblasts/centrocytes
CD3 and CD20 Pattern

CD3: T-cell

CD20: B-cell

B-FL pattern: Absence of TM, proliferation of centroblasts/centrocytes
Diagnostic Approach: Immunohistochemistry

CD10: Follicular centre cell B-cells

BCL-2: antiapoptotic

BCL-6: nuclear stain, follicular centre B-cell

B-FL: CD3-; CD20+, BCL2+, CD10+, BCL-6 +
Marginal zone lymphoma
Marginal zone pattern

CD21: FDC
Marginal zone pattern

CD3: T-cells
Marginal zone pattern

CD79a: B-cells
Marginal zone pattern

Pan keratin
Metastatic/ sinusoidal pattern
Metastatic/ sinusoidal pattern
Treatment

- Combination chemotherapy
- Monoclonal therapy: Rituximab
- Transplant
Thank You