LYMPHOMA

BACHIR ALOBEID, M.D.
DEPARTMENT OF PATHOLOGY
Columbia University-College of Physicians & Surgeons
Lymphoma: Neoplastic proliferation of lymphoid cells
Normal development of lymphocytes
B-Cells
in the bone marrow
“hematogones”
PROGENITOR B CELL → PRE-PRE-B CELL → PRE-B CELL → IMMATURE B CELL → RESTING MATURE B CELL → ACTIVATED / DIFFERENTIATING B CELL → PLASMA CELL

**HEAVY CHAIN GENES REARRANGED**

**LIGHT CHAIN GENES REARRANGED**
T-Cells in the thymus “thymocytes”
Normal Lymph Node

- Normal compartments of the lymph node:
  1- cortex / follicles
  2- paracortex
  3- medullary cords
  4- sinuses
Laboratory Methods

- Gold standard method: Histomorphologic evaluation of the lymphoid tissues.
  - Sections of fixed tissue -embedded in paraffin- for routine H&E staining
Laboratory Methods

Ancillary studies:

- Immunophenotyping:
  1. Immunohistochemistry (IHC) and/or
  2. Flow cytometry
Lymphoid Markers

Examples of lymphoid markers commonly used in immunophenotypic studies:

Pan-hematopoietic: CD45, CD43

B-cell markers: CD19, CD20, CD22, CD79a, Pax5, MUM1

T-cell markers: CD2, CD3, CD5, CD7, CD4, CD8

Germinal center cells: CD10, Bcl-6, HGAL

Follicular dendritic cells: CD21, CD23, CD35

Plasma cells: CD138, CD38, MUM1

Immature lymphoid cells: TdT, CD10, CD34, CD1a

Activated lymphoid cells: CD30, CD23

NK-cells: CD56, CD57
Laboratory Methods

• Flow cytometry (multi-parametric) analysis is the method of choice to demonstrate the intensity of antigen expression and simultaneous expression of multiple antigens.

Requires: Cell suspensions and Flow Cytometer
Flow cytometry, dot blot
Laboratory Methods

• **IHC** is good to show the distribution and localization of different lymphoid elements in tissue sections.
Ancillary studies:

- Cytogenetic studies: Conventional Karyotype analysis, FISH analysis, SKY analysis
- Molecular analysis: Southern blot and PCR
- DNA microarray platforms
Chromosomes from a metaphase spread in karyotype format
SKY analysis
PCR

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DNA microarray platforms:
Useful to demonstrate gene expression patterns/profiles; important methodology for the diagnosis and classification of hematological malignancies in the future
LYMPHOID DISORDERS

1- Benign (reactive) Lymphadenopathies
2- Malignant Lymphoproliferative Disorders/Lymphomas
3- Atypical (borderline/grey zone) Lymphoproliferative Disorders
LYMPHOMAS

• **Non-Hodgkin Lymphoma (NHL):**
  1- *B-cell lymphomas (most common)*
  2- *T-cell and NK cell lymphomas*

• **Hodgkin Lymphoma (disease):**
  1- *Nodular Lymphocyte Predominance*
  2- *Classical Hodgkin Lymphoma*
Non-Hodgkin Lymphoma

• Definition:
Malignant neoplastic proliferation of lymphoid cells derived from a single transformed cell (monoclonal proliferation).
Non-Hodgkin Lymphoma

- Epidemiology:
  - More common in the developed countries
  - Frequency of different types varies around the world:
    B- vs NK/T-cell..
    Burkitt lymphoma..
    adult T-cell leukemia/lymphoma..
Non-Hodgkin Lymphoma

- Epidemiology, cont.: Individuals with immunodeficiencies/immune disorders are at higher risk:
  1. Congenital (primary) immunodeficiency
  2. Acquired immunodeficiencies (HIV-related, post-therapy)
  3. Autoimmune diseases.
Non-Hodgkin Lymphoma

- **Etiology:**
  - Infectious agents and development of lymphoma:
    - HTLV-1 infection and T-cell leukemia/lymphoma..
    - Epstein-Barr virus (EBV) and Burkitt’s lymphoma..
    - Human herpesvirus-8 (HHV-8) and primary effusion lymphoma
    - HCV and marginal zone lymphoma
    - H. Pylori and gastric MALT lymphoma
Non-Hodgkin Lymphoma

- Etiology, cont.:
  - Genetic alterations and development of lymphoma..
    - t(14;18) translocation and follicular lymphoma..
    - t(8;14) translocation and Burkitt’s lymphoma..
    - t(11;14) translocation and mantle cell lymphoma..
Non-Hodgkin Lymphoma

WHO Classification 2008:
An updated version of 2001 WHO classification.
Replaces all previous classifications.
Represents an international consensus.
Contains significant changes and updates.
WHO Classification

- **Precursor** (immature) B- and T-cell Lymphoid Neoplasms (leukemia/lymphoma):
  - Precursor lymphoblastic leukemia/lymphoma
- **Mature** (peripheral) B- and T-cell Lymphoid Neoplasms:
  - Mature B-cell lymphomas
  - Mature NK/T-cell lymphomas
Mature B-cell Neoplasms

- CLL/SLL
- B-cell prolymphocytic leukemia
- Splenic B-cell marginal zone lymphoma
- Hairy cell leukaemia
- Splenic B-cell lymphoma/HCL var.
- Lymphoplasmacytic lymphoma
- Multiple Myeloma
- Heavy Chain diseases
- Extra nodal marginal zone, MALT
- Nodal marginal zone lymphoma
- Follicular lymphoma
- Primary cutaneous follicular center lymphoma
- Lymphomatoid granulomatosis

- Diff large B-cell lymphoma NOS
  - T-cell/histiocyte rich
  - Primary DLBCL of CNS
  - Primary cutaneous, leg Type
  - EBV+ of the elderly
  - DLBCL associated with chronic inflammation

- Mediastinal lymphoma
- Intravasc large B-cell lymphoma
- ALK pos large B-cell lymphoma
- Plasmablastic lymphoma
- HHV8 assoc, Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell unclass. – Butkitt lymphoma
- B-cell unclass. –Hodgkin lymphoma
Mature T- and NK-cell neoplasms

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- chronic lymphoproliferative disorders of NK cells
- Aggressive NK cell leukaemia
- EBV+ T-cell lymphoma (children)
  - Systemic EBV+ T-cell lymphoproliferative disorders
  - Hydroa vacciniforme-like lymphoma
- Adult T-cell leukaemia/lymphoma
- Extranodal NK/T cell, nasal type
- Enteropathy assoc. T cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mucosis fungoides
- Sezary syndrome
- Prim cutaneous CD30 pos T-cell lymphoma
- Prim cut periphere T-cell lymph rare types
  - Gamma-delta t-cell lymphoma
  - CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
  - CD4+ small/med T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK+ 
- Anaplastic large cell lymphoma, ALK-
B cell neoplasms

- Precursor B lymphoblastic lymphoma/leukemias
- Small lymphocytic lymphoma
- Chronic lymphocytic leukemia
- Multiple myeloma
- Mantle cell lymphoma
- Follicular lymphoma
- Burkitt lymphoma
- Diffuse large B cell lymphoma
- Hodgkin lymphoma
- Diffuse large B cell lymphoma
- Marginal zone lymphoma
- Small lymphocytic lymphoma
- Chronic lymphocytic leukemia

T cell neoplasms

- Precursor T lymphoblastic lymphoma/leukemias
- Peripheral T cell lymphomas

LYMPH NODE
WHO Classification

• Immunodeficiency Associated Lymphoproliferative Disorders:
  1. Lymphoproliferative diseases associated with primary immune disorders
  2. Lymphomas associated with HIV infection
  3. Post-transplant lymphoproliferative disorders
  4. Other iatrogeneic immunodeficiency-associated lymphoproliferative disorders
Non-Hodgkin Lymphoma

- Clinical manifestations of NHL:
  1- Lymphadenopathy..
  2- Organomegaly (infiltration of organs)..
  3- Systemic/B symptoms (fever, night sweats, weight loss)..
Non-Hodgkin Lymphoma

- **Examples of NHL:**
  - Diffuse Large B-cell Lymphoma (DLBCL), most common lymphoma in the western hemisphere
  - Follicular Lymphoma (FL)
  - Burkitt Lymphoma (BL)
Non-Hodgkin Lymphoma

Diffuse Large B-cell Lymphoma

A diffuse proliferation of large neoplastic B lymphoid cells with a nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte
CD20
Recent studies using gene expression profiling (GEP) in DLBCL have identified patterns of gene expression, as well as individual genes that appear to have important prognostic significance, related to underlying tumor biology.

At least two types:

1- DLBCL of germinal center cell origin
   CD10+ and/or BCl-6+, MUM1-

2- DLBCL activated B-cell like
   CD10- and MUM1+

3- Other or third type..
Non-Hodgkin Lymphoma

Follicular Lymphoma
A neoplasm of follicle center B-cells
(a mixture of centrocytes/centroblasts),
which has at least a partially
follicular/nodular pattern of growth
Non-Hodgkin Lymphoma

Burkitt Lymphoma
A highly aggressive lymphoma often presenting at an extra-nodal site or in a leukemic phase, composed of monomorphic medium-sized B-cells with basophilic/vacuolated cytoplasm and numerous mitotic figures
Giemsan stain
Non-Hodgkin Lymphoma

• Therapy of NHL:
  1- Chemotherapy
  2- Radiotherapy
  3- Combined chemo- and radiotherapy
  4- Immune therapy: antibodies raised against B-cell antigens (anti-CD20/anti-CD22 antibodies)
Hodgkin Lymphoma

• **Definition:**
  Lymphoid neoplasm with a minority of neoplastic lymphoid cells (*Hodgkin cells*) in a predominant inflammatory/reactive background which may mask the tumor cell population.
Hodgkin Lymphoma

- Epidemiology & Etiology:
  - accounts approximately for 30% of all malignant lymphomas
  - bimodal age distribution
  - EBV has been postulated to play a role in the pathogenesis of classical HL
Hodgkin Lymphoma

• WHO Classification of HL:
  1- Nodular Lymphocyte Predominance
  2- Classical Hodgkin Lymphoma
Hodgkin Lymphoma

• Nodular Lymphocyte Predominance:
  - uncommon variant (6% of HL)
  - characteristic nodular pattern of growth
  - characteristic variant of Hodgkin cells (known as “popcorn” cells), which are CD20 positive B-cells of follicle center cell origin (CD10+, Bcl-6+)
Hodgkin Lymphoma

Classical Hodgkin Lymphoma:
Nodular sclerosis (NSHL)
Mixed cellularity (MCHL)
Lymphocyte depletion (LDHL)
Lymphocyte-rich classical Hodgkin lymphoma (LRCHL)
Hodgkin Lymphoma

Classical Hodgkin Lymphoma:

**Hodgkin cells**: derived from mature B-cells at the germinal center stage of differentiation

- typical Reed-Sternberg cells (binucleated cells)

- variants (mono- and multinucleated forms and lacunar cells)

**Immunophenotype**: CD30+, CD15+, Pax5+, and CD45 negative
Hodgkin Lymphoma

Classical Hodgkin Lymphoma:

**Nodular sclerosis (NSHL):**
- characterized by Reed-Sternberg cells and *lacunar cells* within a polymorphic reactive background, and a characteristic *fibrosis* (bands of collagen surrounding nodules)
Hodgkin Lymphoma

Classical Hodgkin Lymphoma:

**Mixed cellularity (MCHL):**
- classical Reed-sternberg cells in a mixed, polymorphic background; no lacunar cells or collagen bands

**Lymphocyte depletion (LDHL):**
- uncommon subtype
- rich in Hodgkin’s cells
Hodgkin Lymphoma

- Clinical manifestations of HL:
  1- Lymphadenopathy
  2- Organomegaly (infiltration of organs)
  3- Systemic/B symptoms (fever, night sweats, weight loss)
Hodgkin’s Lymphoma

- Therapy of HL:
  1- Chemotherapy
  2- Radiotherapy