someday is today | LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers

NHL: Keys to an Accurate Diagnosis

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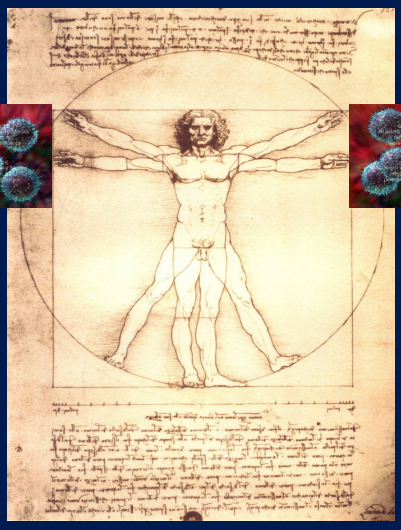
Facts and Figures: Non-Hodgkin Lymphomas

- **Most common blood cancer**
- **7th most common cancer in females, and 6th most common in common cancer in males[1]**
- **70,800 new cases expected in 2014[1]**
- **18,990 people expected to die from NHL in 2014[1]**
- **85% are B-cell disorders[2]**

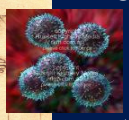
[1] The Leukemia & Lymphoma Society. Facts Spring 2014. Available at http://www.lls.org/content/nationalcontent/resourcecenter/freeeducationmaterials/generalcancer/pdf/facts.pdf Accessed on December 12, 2014.
[2] ACS. Detailed Guide (revised January 21, 2000): Non-Hodgkin's Lymphoma.

The Immune System

T- CELLS



B- CELLS



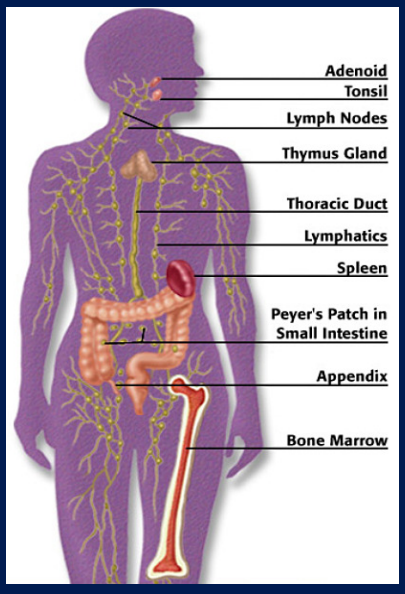
Cellular immunity:

helper + cytotoxic T-cells

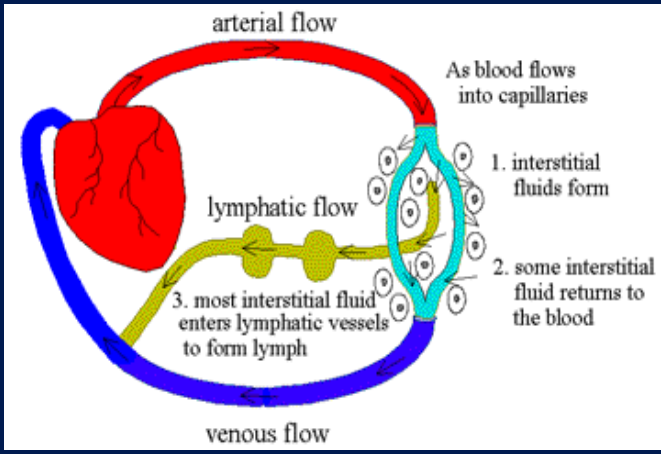
Humoral immunity:

antibodies

Lymphatic System

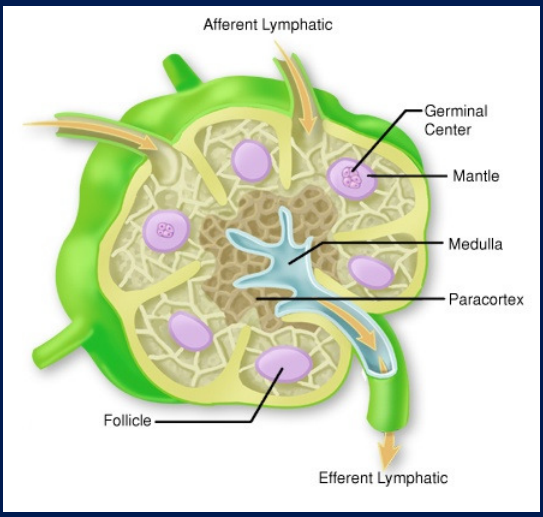


Lymphatic Circulation

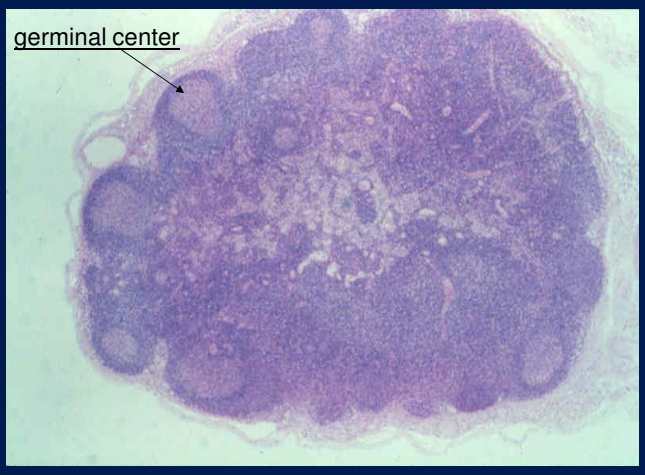


http://www.mhhe.com/biosci/ap/histology_mh/fluidct.htm

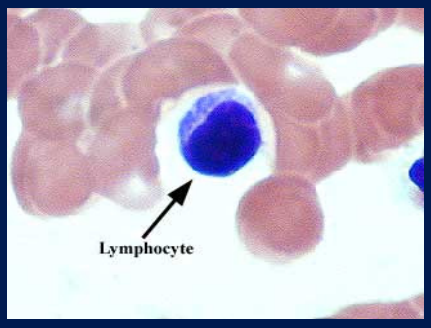
Lymph Node Anatomy



Lymph Node: Microscopic View



Lymphocyte: Microscopic View

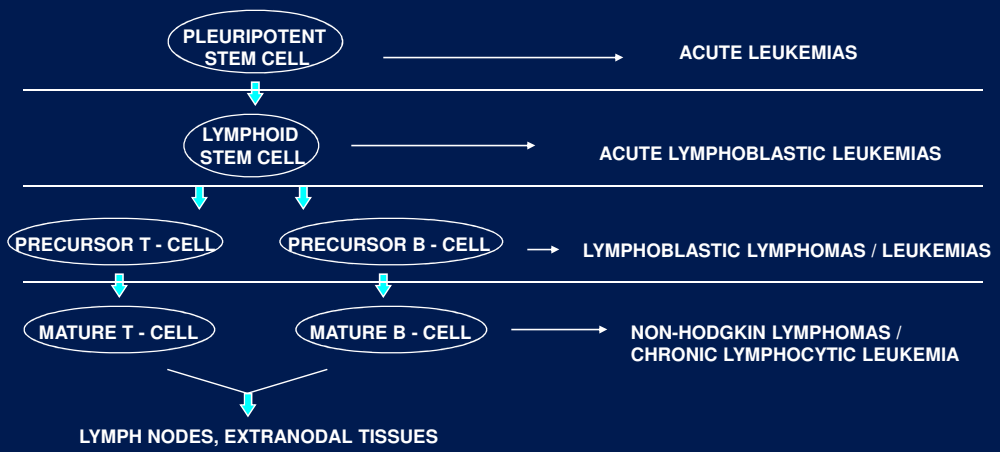


Causes of Non-Hodgkin Lymphomas

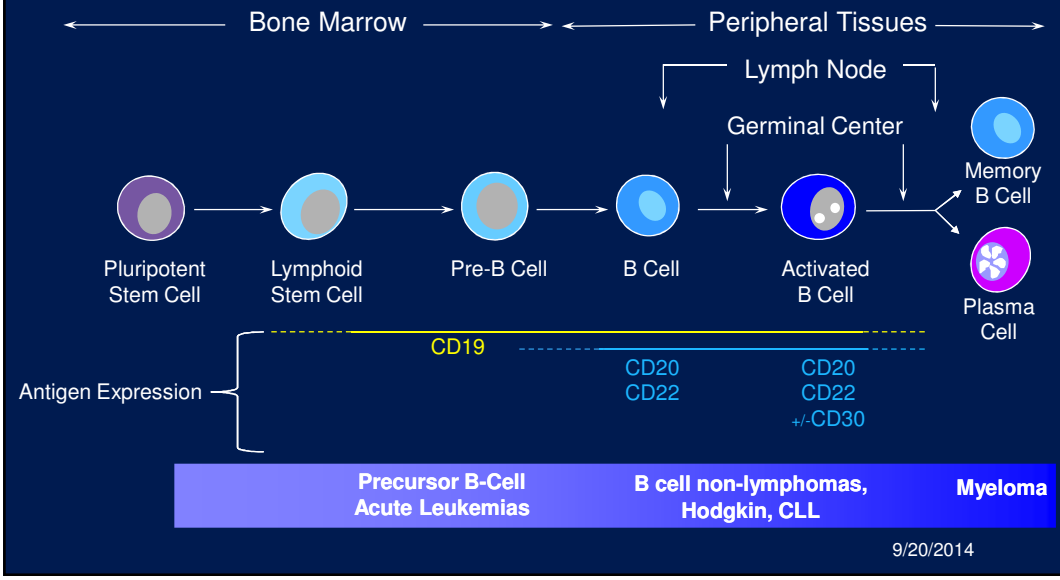
Possible cause(s):

- chemical exposures (pesticides, fertilizers or solvents)
- individuals with compromised immune systems
- heredity
- infections
- most patients have no clear risk factors
- IN MOST CASES, THE EXACT CAUSE IS UNKNOWN

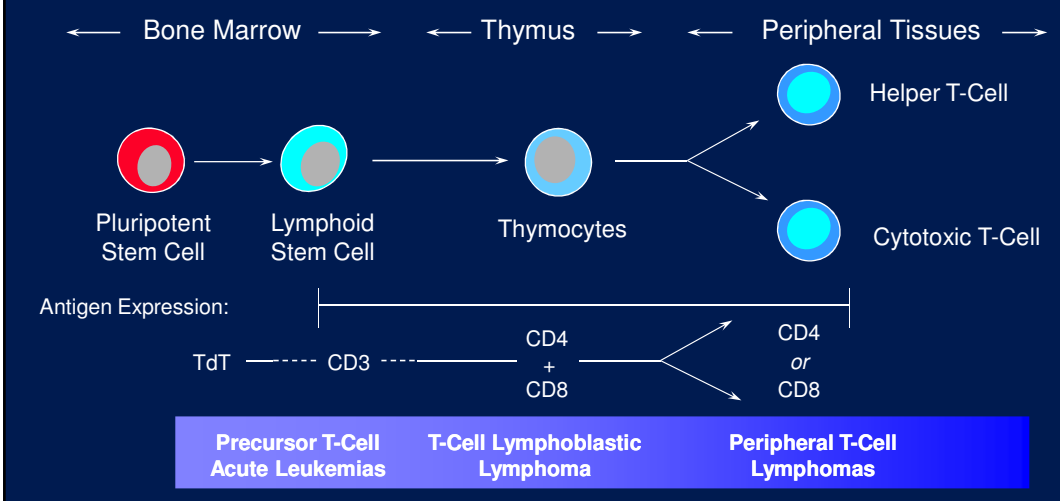
Cellular Origins of Lymphomas & Leukemias



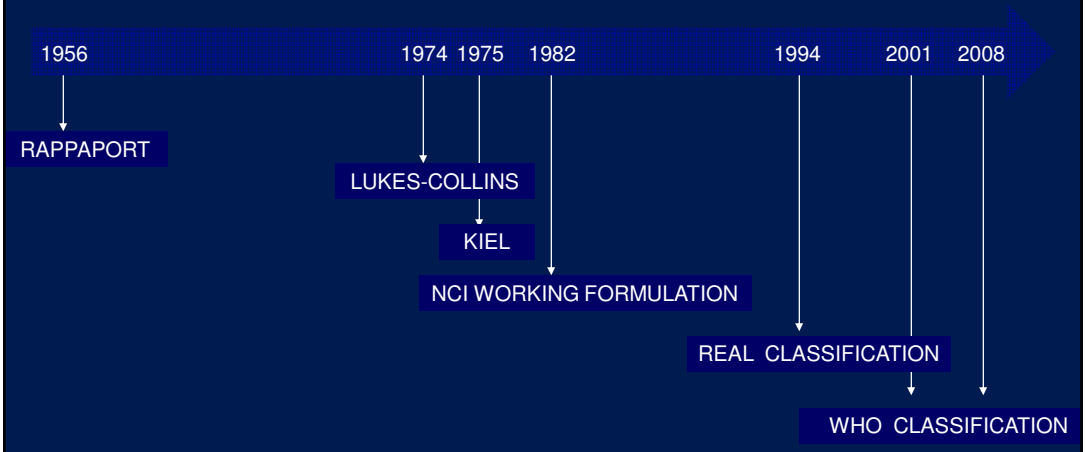
Normal B Cell Life Cycle and Related Lymphoid Malignancy



Normal T-Cell Life Cycle and Related Lymphoid Malignancy



Classification of Lymphomas: the First 50 Years



Diagnosis and Classification of Lymphomas

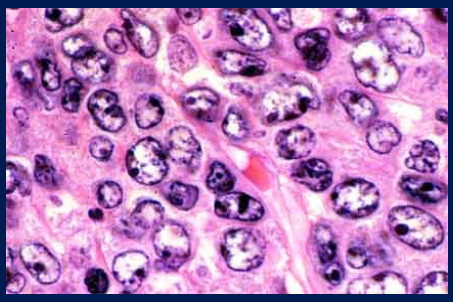
LYMPH NODE OR TISSUE **BIOPSY** FOR EVALUATION OF:

- **HISTOLOGY** (tumor cell size, pattern of tumor cell distribution)
- **IMMUNOPHENOTYPING** (tumor cell-specific proteins)
- **GENOTYPING** (tumor cell-specific genetic changes)

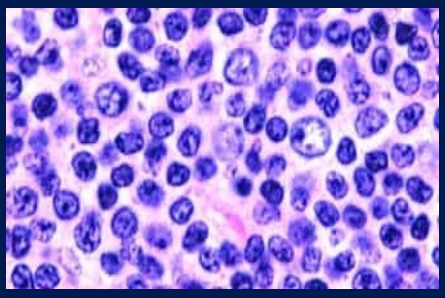
Biopsy (excisional or incisional vs. aspiration)

histology : microscopic appearance of tumor cell size and distribution

diffuse large B-cell lymphoma



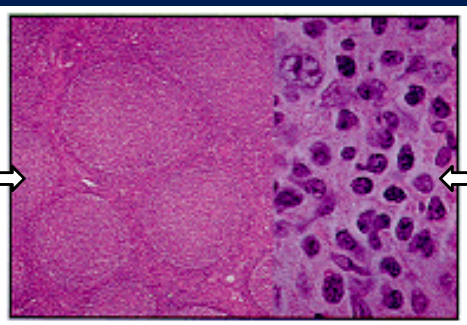
small lymphocytic lymphoma



***IMAGES FROM*: http://pleiad.umdnj.edu/~dweiss/default.html**

Follicular Lymphoma Biopsy

low magnification:
tumor cell distribution



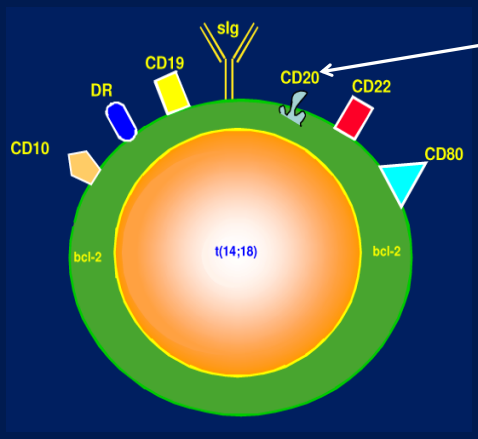
high magnification:
tumor cell size

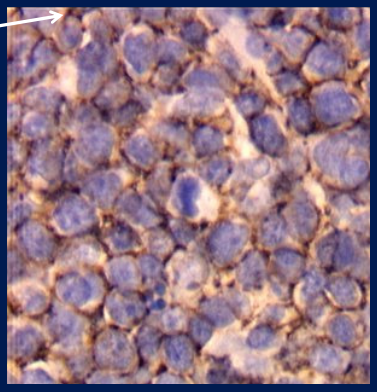
Fig 6. — Follicular lymphoma. Normal architecture is replaced by numerous, fairly uniform, and closely apposed follicles. The follicles show mainly small cleaved cells and a single, large noncleaved cell (hematoxylin-eosin 40x, x 400).

https://www.moffitt.usf.edu/pubs/ccj/v3n2/dept3.html

Immunophenotyping: Follicular Lymphoma

immunophenotyping: staining tumor cell-specific proteins



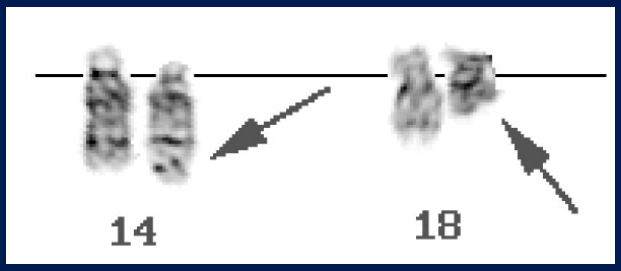


http://path.upmc.edu/cases/case25/images/micro8.jpg

IMMUNOPHENOTYPE: CD5-, CD10+, CD19/20+, CD23-, SIg+

Genotyping: Follicular Lymphoma t(14;18)

genotyping: identifying tumor cell-specific genetic changes

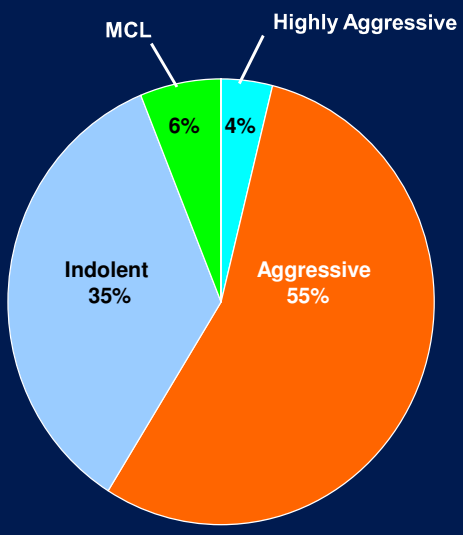


www.pathologyoutlines.com/chromosomes.html

Non-Hodgkin Lymphomas (NHL): Clinical Groups

- "INDOLENT" - untreated survival measured in years
- "AGGRESSIVE" - untreated survival measured in months
- "HIGHLY AGGRESSIVE" - untreated survival measured in weeks

Relative Incidence of NHL Clinical Groups



Clinical Classification of Lymphomas

- Indolent
  - generally slow growing; untreated survival measured in years.
  - common types include: follicular (grades 1/2); small lymphocytic; marginal zone; cutaneous T-cell lymphoma; Waldenstrom's.
- Aggressive
  - grow quickly; untreated survival measured in months.
  - common types include: diffuse large B-cell; peripheral T-cell lymphoma.
- Highly Aggressive
  - extremely rapid growth; untreated survival measured in weeks.
  - common types include: Burkitt's; lymphoblastic.

"Indolent" Lymphomas: WHO Classification

MATURE (PERIPHERAL) B-CELL NEOPLASMS

- B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA / SMALL LYMPHOCYTIC LYMPHOMA
- LYMPHOPLASMACYTIC LYMPHOMA
- SPLENIC MARGINAL ZONE B-CELL LYMPHOMA (+/- VILLOUS LYMPHOCYTES)
- HAIRY CELL LEUKEMIA
- EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA OF MALT TYPE
- NODAL MARGINAL ZONE B-CELL LYMPHOMA (+/- MONOCYTOID B-CELLS)
- FOLLICULAR LYMPHOMA (GRADES 1 AND 2)

MATURE (PERIPHERAL) T-CELL NEOPLASMS

- T-CELL GRANULAR LYMPHOCYTIC LEUKEMIA
- MYCOSIS FUNGOIDES / SEZARY SYNDROME
- ANAPLASTIC LARGE-CELL LYMPHOMA, T/NULL CELL, PRIMARY CUTANEOUS TYPE

Characteristics of "Indolent" Lymphomas

- GENERALLY MALIGNANCIES OF SMALL, MATURE LYMPHOCYTES
- MOST COMMONLY B-CELL TUMORS
- HIGH PROPORTION OF NON-DIVIDING CELLS WITH LOW PROLIFERATION RATE
- LYMPHOID DISEASES WITH HETEROGENEOUS HISTOLOGIES (FOLLICULAR LYMPHOMA MOST COMMON)
- FREQUENT INVOLVEMENT OF BLOOD AND BONE MARROW
- LONG MEDIAN SURVIVAL
- INITIAL SENSITIVITY TO CHEMOTHERAPY AND RADIOTHERAPY
- ADVANCED STAGE AT DIAGNOSIS

"Aggressive / Highly Aggressive" Lymphomas: WHO Classification

MATURE (PERIPHERAL) B-CELL NEOPLASMS

- FOLLICULAR LYMPHOMA (GRADE 3b)
- MANTLE CELL LYMPHOMA
- DIFFUSE LARGE B-CELL LYMPHOMA
  - MEDIASTINAL LARGE B-CELL LYMPHOMA
  - PRIMARY EFFUSION LYMPHOMA
- BURKITT'S LYMPHOMA / BURKITT CELL LEUKEMIA

MATURE (PERIPHERAL) T-CELL NEOPLASMS

- T-CELL PROLYMPHOCYTIC LEUKEMIA
- AGGRESSIVE NK-CELL LEUKEMIA
- ADULT T-CELL LYMPHOMA / LEUKEMIA (HTLV I +)
- EXTRANODAL NK/T-CELL LYMPHOMA NASAL TYPE
- ENTEROPATHY-TYPE T-CELL LYMPHOMA
- HEPATOSPLENIC GAMMA-DELTA T-CELL LYMPHOMA
- SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA
- PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE CHARACTERIZED
- ANGIOIMMUNOBLASTIC T-CELL LYMPHOMA
- ANAPLASTIC LARGE-CELL LYMPHOMA, T/NULL CELL, PRIMARY SYSTEMIC TYPE

Characteristics of "Aggressive" Lymphomas

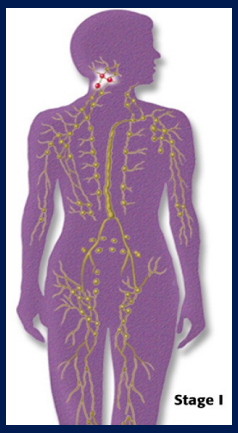
- GENERALLY MALIGNANCIES OF LARGER "TRANSFORMED" LYMPHOCYTES
- MOST COMMONLY B-CELL TUMORS
- HIGH PROPORTION OF DIVIDING CELLS WITH HIGHER PROLIFERATION RATES
- LYMPHOID DISEASES WITH HETEROGENEOUS HISTOLOGIES (DIFFUSE LARGE B-CELL LYMPHOMA MOST COMMON)
- MOST COMMON TYPES POTENTIALLY CURABLE WITH THERAPY
- ABOUT ONE-THIRD EARLY STAGE AT DIAGNOSIS
- MORE FREQUENTLY ASSOCIATED WITH "B" SYMPTOMS

Staging of Lymphomas

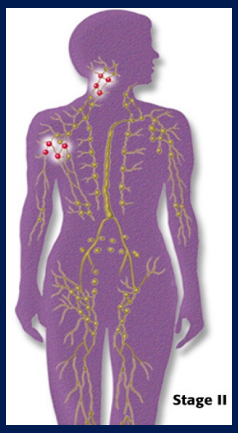
- PHYSICAL EXAM WITH ATTENTION TO LN AREAS, LIVER, SPLEEN
- BLOOD COUNT WITH EVALUATION OF BLOOD SMEAR
- SERUM CHEMISTRIES
- CHEST X-RAY
- CT SCANS OF NECK, CHEST, ABDOMEN AND PELVIS
- ADDITIONAL RADIOLOGIC STUDIES AS INDICATED (*e.g.*, PET SCAN)
- BONE MARROW BIOPSY
- DETERMINATION OF ANN ARBOR STAGE

Staging of Lymphomas

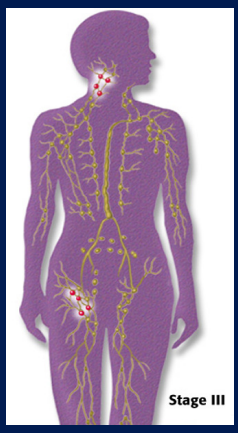
Stage I
single lymph node region / organ



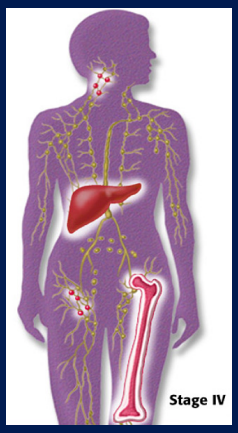
Stage II
2 adjacent lymph node regions



Stage III
≥ 2 lymph node regions in different parts of the body



Stage IV
widespread disease + / - lymph node involvement



Prognosis of non-Hodgkin Lymphomas

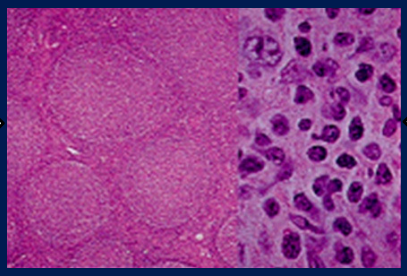
- INDOLENT LYMPHOMAS
  - advanced stage, considered incurable, but long survival.

- AGGRESSIVE LYMPHOMAS
  - frequently curable.

- HIGHLY AGGRESSIVE LYMPHOMAS
  - frequently curable.

Follicular Lymphoma: Biopsy

low magnification (40x): tumor cell distribution



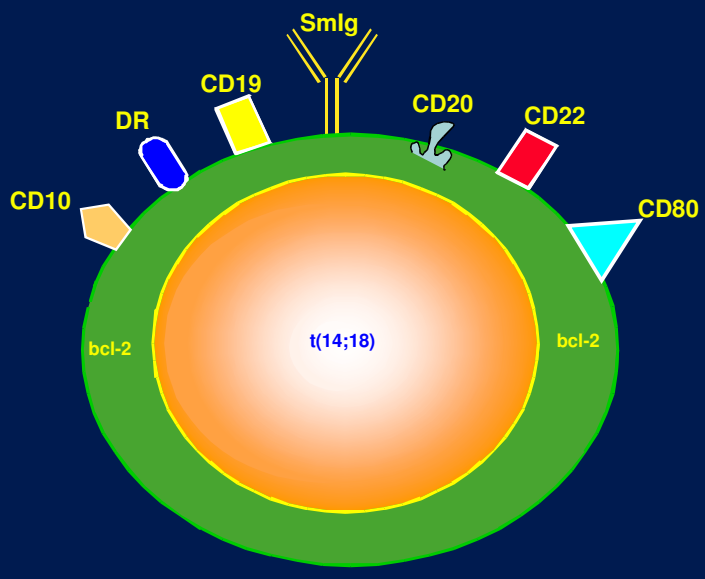
high magnification (400x): tumor cell size

reported pattern	% follicular
follicular	> 75%
follicular + diffuse	25 – 75%
focally follicular	< 25%
diffuse	0%

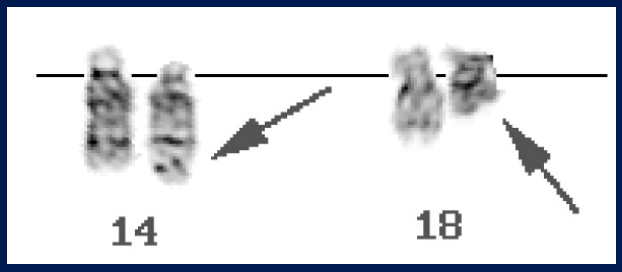
grading	centroblasts / hpf
grade 1-2	0 – 15
grade 3	> 15
- grade 3A	centrocytes present
- grade 3B	sheets of centroblasts

Image from **https://www.moffitt.usf.edu/pubs/ccj/v3n2/dept3.html**

Follicular Lymphoma Cell



Follicular Lymphoma
t(14;18)



www.pathologyoutlines.com/chromosomes.html

Follicular Lymphoma

HISTOLOGY: SMALL CLEAVED AND LARGER NONCLEAVED LYMPHOCYTES ARRANGED IN NODULAR AGGREGATES; THE NUMBER OF LARGE CELLS PRESENT DETERMINES THE TUMOR GRADE (1, 2 or 3).

IMMUNOPHENOTYPE: CD5-, CD10+, CD19/20+, CD23-, SIg+.

CYTOGENETICS: t(14;18).

EPIDEMIOLOGY: 22% OF NHL; MEDIAN AGE 55.

CLINICAL: ADVANCED STAGE AT Dx ($\geq$ 80%); PROGRESSION MORE RAPID IN MIXED AND LARGE CELL TYPES; TRANSFORMATION TO AGGRESSIVE LYMPHOMA IN 25% PATIENTS.

TREATMENT: NO SURVIVAL ADVANTAGE TO EARLY Rx FOR ADVANCED GRADE 1 (or 2) DISEASE. STANDARD FIRST THERAPIES FOR ADVANCED GRADE 1 (or 2) DISEASE INCLUDE RITUXAN, CVP + RITUXAN, R-CHOP, OR R-BENDAMUSTINE; FOR GRADE 3 FOLLICULAR R-CHOP IS A STANDARD FIRST THERAPY.

Lymphoplasmacytic Lymphoma (Waldenstrom's)

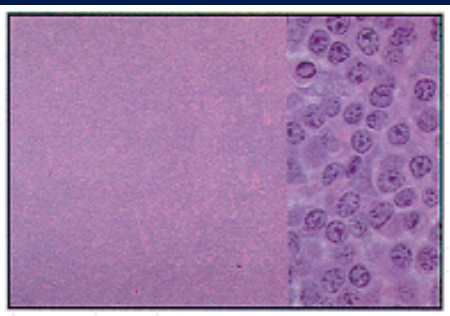
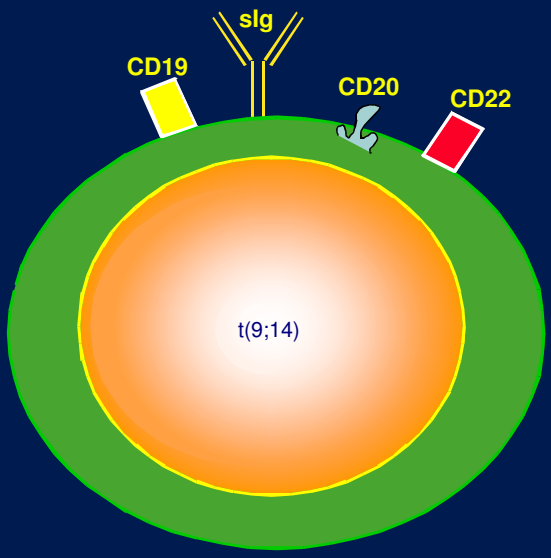


Fig 2. — SLL/PI. Lymph node architecture is effaced by diffuse proliferation of plasmacytoid lymphocytes with moderately abundant cytoplasm. High-power magnification shows uniform plasmacytoid cells and a single Dutcher body (hematoxylin-eosin 40x, x 400).

https://www.moffitt.usf.edu/pubs/ccj/v3n2/dept3.html

Lymphoplasmacytic Lymphoma (Waldenstrom's)



Lymphoplasmacytic Lymphoma (Waldenstrom's)

HISTOLOGY: SMALL BENIGN-APPEARING LYMPHOCYTES WITH PLASMACYTIC DIFFERENTIATION.

IMMUNOPHENOTYPE: CD5+ or -, CD10-, CD19/20+, CD23-, SIg+, CIg+.

CYTOGENETICS: t(9;14)(p13;q32).

EPIDEMIOLOGY: <5% OF NHL; MEDIAN AGE 55 - 65; POSSIBLE ROLE OF Hep C.

CLINICAL: USUALLY ADVANCED STAGE AT DX; PARAPROTEINEMIA (WALDENSTROM'S).

TREATMENT: NO ADVANTAGE TO EARLY Rx. TREAT FOR SYMPTOMS OR REAL / IMPENDING ORGAN DYSFUNCTION. STANDARD FIRST THERAPIES INCLUDE RITUXAN, FLUDARABINE (ALONE OR IN COMBINATION), BENDAMUSTINE (ALONE OR IN COMBINATION WITH RITUXAN) OR CHLORAMBUCIL. IBRUTINIB IS LIKELY TO BE FUTURE STANDARD .

Extranodal Marginal Zone Lymphoma (MALT)

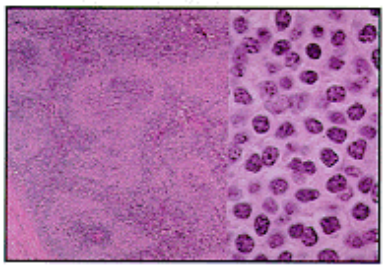
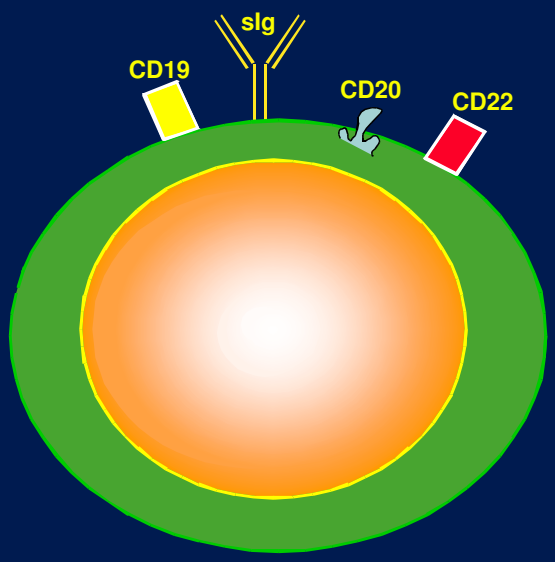


Fig 3. — Marginal-zone lymphoma. Lymph node is infiltrated by monocytoid B cells surrounding germinal centers. This appearance also is referred to as the "inverted follicular" pattern. The monocytoid B cells have abundant, lightly staining cytoplasm and irregular nuclei (hematoxylin-eosin 40x, x 400).

https://www.moffitt.usf.edu/pubs/ccj/v3n2/dept3.html

Marginal Zone Lymphoma (MALT)



Extranodal Marginal Zone Lymphoma (MALT)

HISTOLOGY: ASSO. WITH EPITHELIAL TISSUE (MALT-LYMPHOMA) OR OTHER EXTRANODAL SITES. CELLULAR HETEROGENEITY INC. SMALL LYMPHOCYTES, PLASMA CELLS, MONOCYTOID B-CELLS. LYMPHOEPITHELIAL LESIONS SEEN IN MALT-LYMPHOMAS.

IMMUNOPHENOTYPE: CD5-, CD10-, CD19/20+, CD23+/-, SIg+, CIg+/-.

CYTOGENETICS: TRISOMY 3 IN 60% OF CASES.

EPIDEMIOLOGY: GASTRIC MALT LYMPHOMA IS ASSO. WITH H. PYLORI INFECTION. NONGASTRIC MALT LYMPHOMA IS ASSO. WITH AUTOIMMUNE DISEASE. HEP C IS ASSO. WITH SMZL, NMZLS.

CLINICAL: GASTRIC MALT LYMPHOMA FREQUENTLY LOCALIZED AT DIAGNOSIS. NONGASTRIC MALT LYMPHOMA IS LESS COMMONLY EARLY STAGE AT DIAGNOSIS. MEDIAN AGE AT DIAGNOSIS IS 50 – 60s.

TREATMENT: ANTIBIOTICS FOR EARLY STAGE H. PYLORI ASSO. GASTRIC MALT LYMPHOMA. IN SOME CASES, SURGERY, RADIATION THERAPY AND / OR IMMUNOCHEMOTHERAPY ARE ALSO APPROPRIATE THERAPIES. TREATMENT OF HEP C MAY BE APPROPRIATE FOR SOME PATIENTS.

Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma

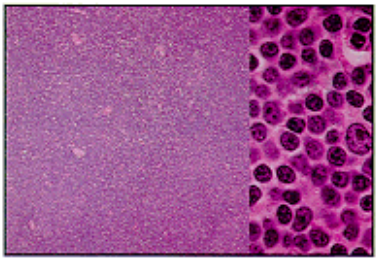
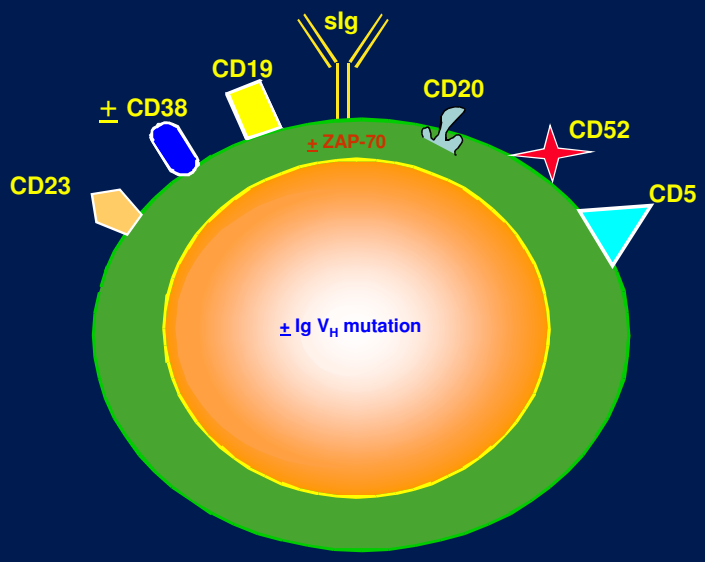


Fig 1. — SLL/CLL. There is diffuse effacement of lymph node architecture, with scattered, pale, staining growth centers, a characteristic pattern of SLL/CLL. No residual germinal centers are present. At higher magnification, uniform infiltration by small, round lymphocytes with scant cytoplasm admixed with larger cells with prominent nucleoli (paraimmunoblasts) is demonstrated (hematoxylin-eosin 40x, x 400).

https://www.moffitt.usf.edu/pubs/ccj/v3n2/dept3.html

Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma



Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma

HISTOLOGY: SMALL ROUND BENIGN-APPEARING LYMPHOCYTE.

IMMUNOPHENOTYPE: CD5+, CD10-, CD19/20+, CD23+, SIg+/-.

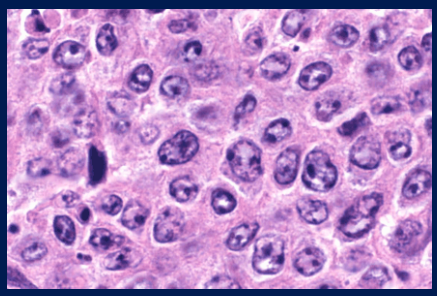
CYTOGENETICS: OCC. TRISOMY 12; del13q; del11q; del17p.

EPIDEMIOLOGY: 5% OF NHL; MEDIAN AGE 60.

CLINICAL: ADVANCED STAGE AT DX (>60 - 80%); FREQ. BLOOD INVL. (CLL).

TREATMENT: NO ADVANTAGE TO EARLY Rx. TREAT FOR SYMPTOMS OR REAL / IMPENDING ORGAN DYSFUNCTION. STANDARD FIRST THERAPIES INCLUDE FLUDARABINE COMBINATIONS USUALLY WITH RITUXAN AND CYTOXAN (FCR OR FR), BENDAMUSTINE +/- RITUXAN, CHLORAMBUCIL. IBRUTINIB IS LIKELY TO BE FUTURE STANDARD .

Diffuse Large B-Cell Lymphoma (DLBCL)

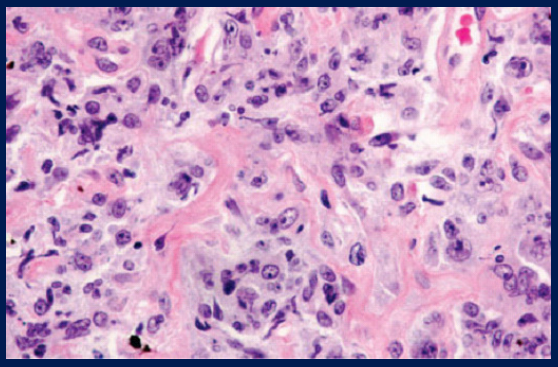


Clinical features:

- most common lymphoma
- median age: 7th decade; broad range
- sex: ♂ > ♀ (slight)
- nodal and extranodal (40%) presentations
- B-cell markers (CD20)
- t(14;18) [25%] ; 3q27 abnl [30%]

http://ashimagebank.hematologylibrary.org/cgi/content/full/2003/0507/100698

Mediastinal Large B-Cell Lymphoma

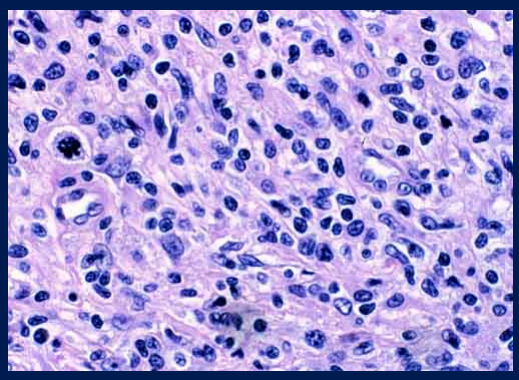


Lichtman's Atlas of Hematology

Clinical features:

- age: 3rd - 5th decade
- sex: ♀ > ♂
- mediastinal presentation
- extranodal metastasis
- B-cell markers (CD20)

Peripheral T-Cell Lymphoma (PTCL)

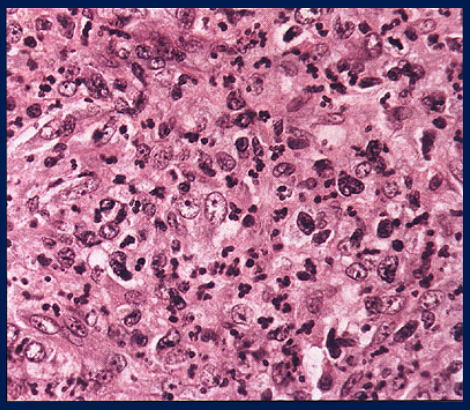


http://pleiad.umdnj.edu/hemepath/T-cell/ptcl3_img.html

Clinical features:

- ~7% of NHL; most common TCL
- age: adults
- sex: ♀ = ♂
- nodal and extranodal
- T-cell markers (CD4 > CD8)
- variants: PTL,nos; AILT; ATLL; ALCL

Anaplastic Large T-Cell Lymphoma (ALCL)



http://www.medscape.com/viewarticle/406829_3

Clinical features:

- ~3% of adult NHL; 10-30% childhood NHL
- variants: ALK+ and ALK-
- age / sex: ALK+ 1st 3 decades, ♂ >> ♀; ALK- older, ♂ = ♀
- nodal and extranodal
- T-cell markers freq. negative (occ. CD2+, CD4+)
- Other markers: CD30; EMA
- t(2;5) in ALK+

Non-Hodgkin Lymphomas: Treatment Overview

- Watch and wait (for indolent lymphomas only)
- Chemotherapy
- Radiation therapy
- Monoclonal antibody therapy
- Combination therapies
- Radioimmunotherapy (RIT)
- Bone marrow and stem cell transplants
- Investigational therapies

Standard Therapeutic Approaches to non-Hodgkin Lymphomas

INDOLENT LYMPHOMAS: *palliative approach in general*

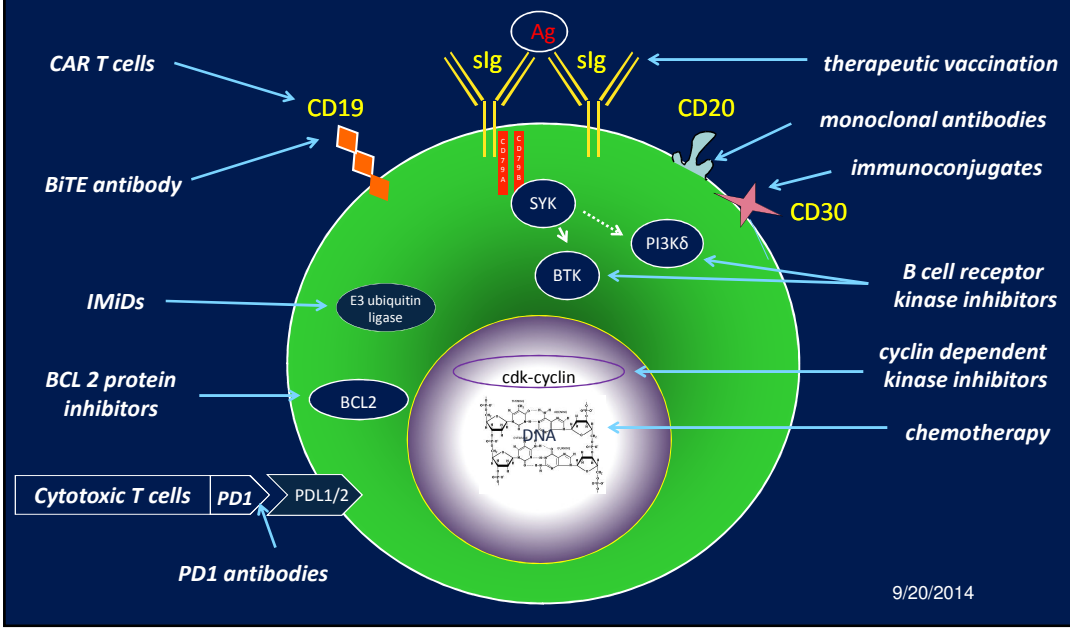
- advanced stage: watch & wait or palliative therapies
- early stage: regional radiation

AGGESSIVE LYMPHOMAS: *curative therapy*

- advanced stage: combination chemotherapy (e.g., CHOP or R-CHOP)
- early stage: combined modality therapy (radiation + R-CHOP)

HIGHLY AGGRESSIVE LYMPHOMAS: *curative therapy*

B cell malignancies: *new therapeutic targets*



9/20/2014

The Future

- Patient- and target- specific therapies
  - Individualized treatment selection
  - Improved prediction of response to therapy
  - Improved prediction of development of resistance and modification of therapy
- Improved drug development

9/20/2014

NHL: Keys to an Accurate Diagnosis

someday is today | LEUKEMIA & LYMPHOMA SOCIETY fighting blood cancers

Question and Answer Session

Dr. Schuster's slides are available for download at
www.LLS.org/programs

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The Leukemia & Lymphoma Society (LLS) offers:

- **Live, Online Chats** that provide a friendly forum to share experiences with others. Living with non-Hodgkin lymphoma chat held on Mondays and Wednesday nights, 8:00-10:00 pm ET, & Caregiver Chat held on Tuesday nights from 8:00-10:00 pm ET.
  - **WEBSITE: www.LLS.org/chat**
- **What to Ask:** For a list of suggested questions to ask about certain topics, download and print any of the following guides.
  - **WEBSITE: www.LLS.org/whattoask**
- **Co-Pay Assistance Program** offers financial assistance to qualified cancer patients to help with treatment-related expenses and insurance premiums.
  - **WEBSITE: www.LLS.org/copay** **TOLL-FREE PHONE: (877) 557-2672**
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL: infocenter@LLS.org** **TOLL-FREE PHONE: (800) 955-4572**