Memorial Sloan Kettering Cancer Center

Overview of Lymphoma

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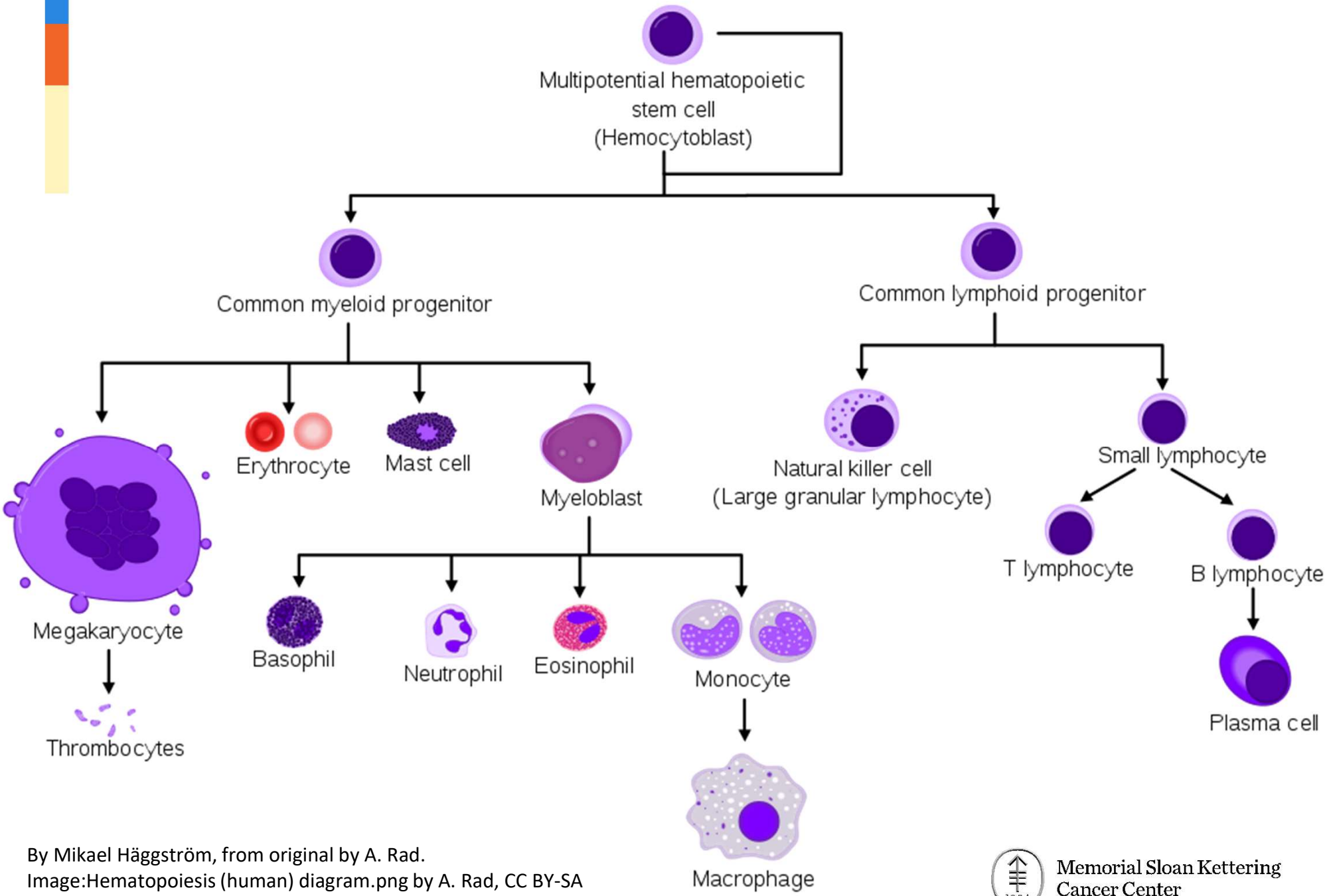
Objectives

- Describe the epidemiology and classification of lymphoma including indolent vs. aggressive, Hodgkin vs. non-Hodgkin
- Describe the clinical features commonly associated with lymphoma, including B symptoms
- Provide an overview of how lymphoma is diagnosed including tissue sampling and laboratory testing
- Provide an overview of lymphoma treatment, and specifically identify treatment and prognosis

What is Lymphoma?

- Cancer derived from B cell progenitors, T cell progenitors, mature B cells, mature T cells, or (rarely) natural killer cells
  - Lymphocytes are cells that circulate in the lymphatic system (lymph nodes, spleen marrow, and thymus) to fight infection
- Non Hodgkin lymphoma (NHL)
  - T cell lymphomas are a subtype of NHL
- Hodgkin lymphoma (HL)

Hematopoiesis



By Mikael Häggström, from original by A. Rad.
Image:Hematopoiesis (human) diagram.png by A. Rad, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=7351905

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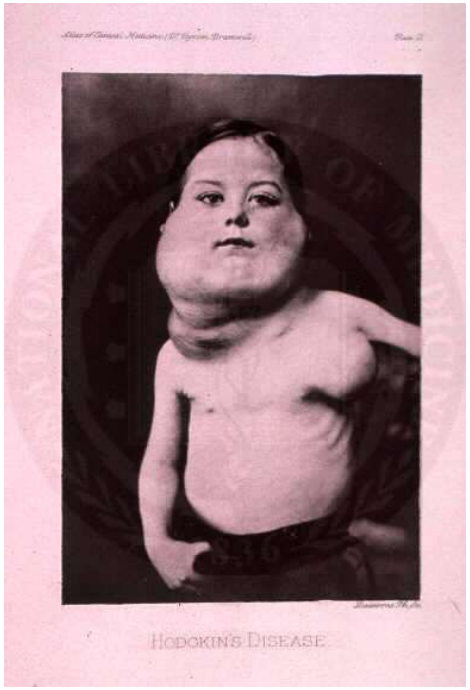
Thomas Hodgkin
(1798-1866)



1832

Hodgkin Lymphoma (HL)

Formerly called Hodgkin's disease (1865).

Group of cancers characterized by a minority of neoplastic Reed-Sternberg (RS) cells in a reactive cellular background variable composed of granulocytes, plasma cells, and lymphocytes.

RS cells are derived from germinal center B cells.

Tends to arise within lymph node areas and to spread in an orderly fashion to contiguous areas of lymph nodes.

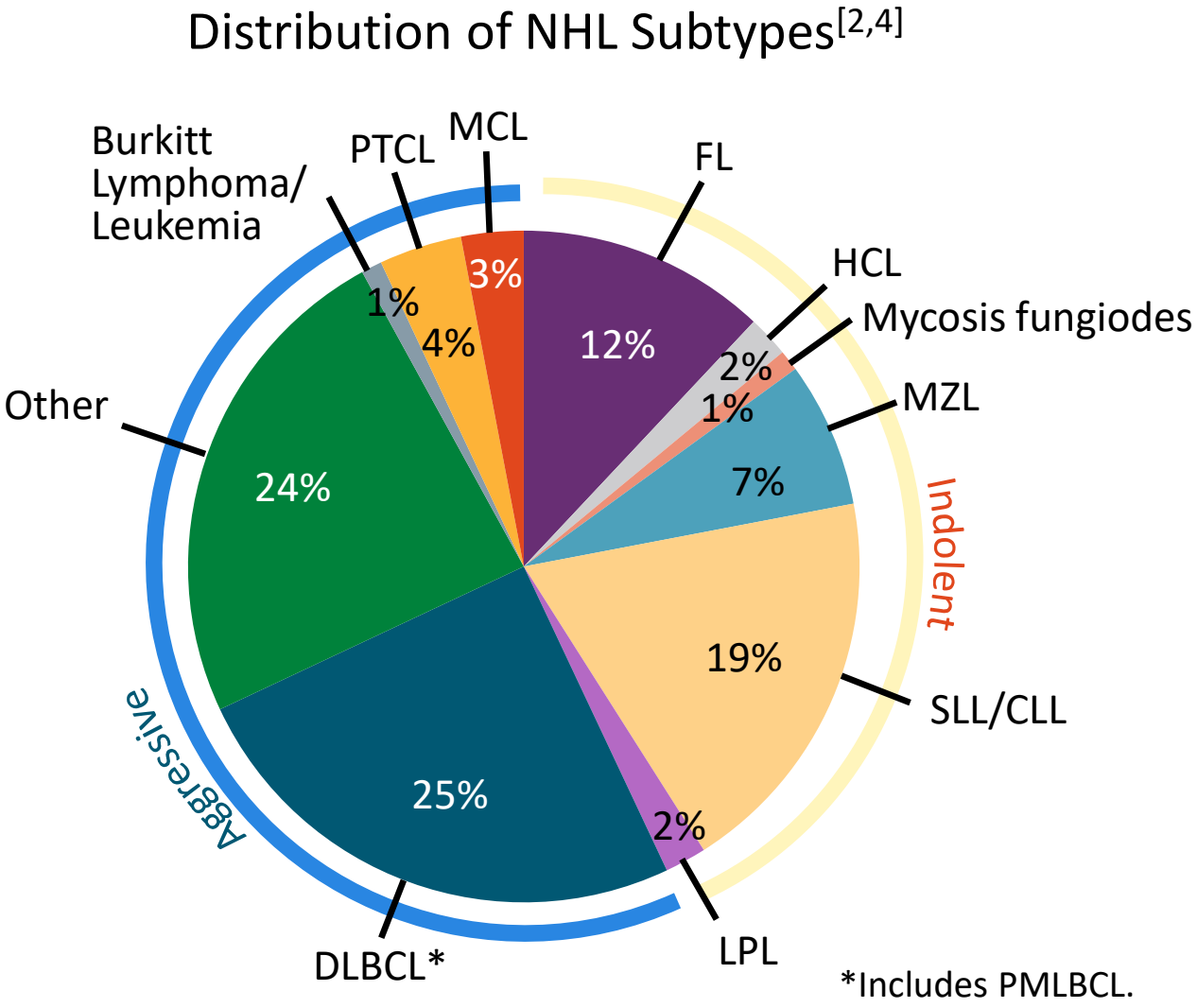
With progressive disease, vascular invasion leads to widespread hematogenous dissemination.

(solid) Hematologic Malignancies

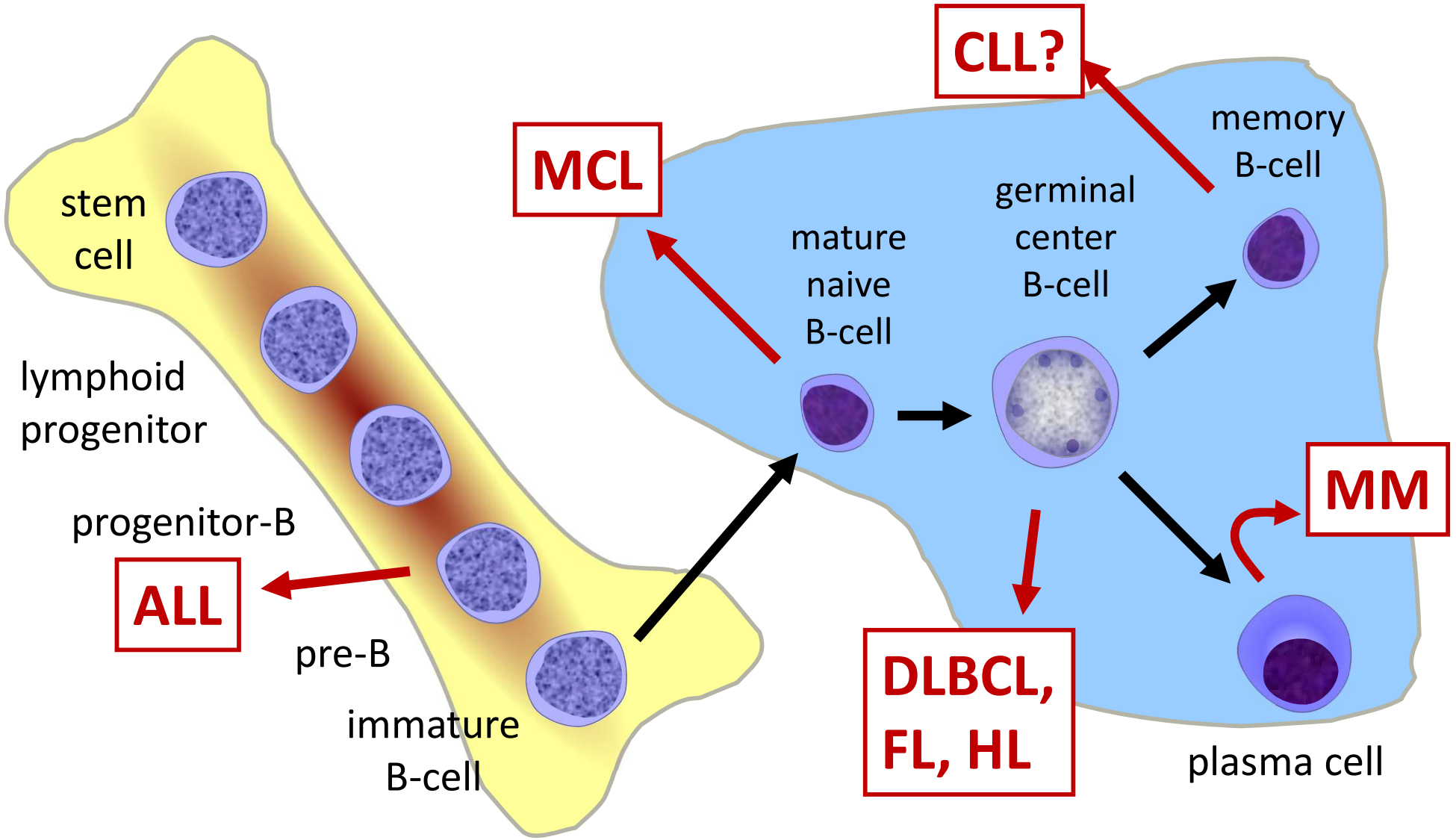
Solid (nodes)	Indolent	Aggressive
Lymphomas	Non-Hodgkin lymphoma (NHL) Small lymphocytic lymphoma Follicular lymphoma Lymphoplasmacytic lymphoma Marginal zone lymphomas Cutaneous T cell lymphomas	Hodgkin lymphoma Non-Hodgkin lymphoma (NHL) Acute lymphoblastic lymphoma Diffuse large B cell lymphoma Mantle cell lymphoma Burkitt lymphoma Anaplastic large cell lymphoma Peripheral T cell lymphomas

INDOLENT	AGGRESSIVE	HIGHLY AGGRESSIVE
Follicular lymphoma	DLBCL	Burkitt
CLL/SLL	PTCL	High grade B cell lymphoma with features b/t DLBCL and Burkitt
Marginal zone lymphoma	Anaplastic large cell	ATLL
Mycosis Fungoides		Hepatosplenic TCL
Mantle cell lymphoma		
Hodgkin lymphoma		

NHL Types


Distribution of NHL Subtypes[2,4]
Burkitt Lymphoma/ Leukemia
PTCL
MCL
FL
HCL
Mycosis fungiodes
MZL
Other
24%
1%
4%
3%
12%
2%
1%
7%
Indolent
19%
SLL/CLL
25%
2%
Aggressive
DLBCL*
LPL
*Includes PMLBCL.

B-cell development and malignant counterparts



The practical way to think of lymphoma (and cancers in general)

Is it curable?

- **Yes**
  - Aggressive lymphomas (intermediate to large cell lymphomas)
    - DLBCL
    - Burkitt lymphoma
    - Hodgkin lymphoma
    - Some T cell lymphomas (peripheral T cell lymphomas)
  - (Early stage indolent lymphomas)

- **No**
  - Indolent lymphomas (small cell lymphomas)
    - Follicular
    - Chronic lymphocytic leukemia (CLL/SLL)
    - Marginal zone, lymphoplasmacytic
    - Some T cell lymphomas (ie. cutaneous T cell)
    - *Mantle cell (non curable, but frequently clinically aggressive)*

Clinical Case #1

A 21 year-old female with no significant past medical history presents to her primary care physician with progressive non-tender left cervical swelling over 4 weeks.

Physical exam is notable for left sided cervical and supraclavicular lymphadenopathy. No splenomegaly or other findings.

PCP gives a trial of Augmentin and Medrol dosepack

Clinical Case #1 (cont)

Patient has transient reduction in her adenopathy on steroids/antibiotics, but neck swelling returns a few weeks later along with generalized pruritus.

PCP sends patient to ENT who completes a fine-needle aspiration

When Do We Suspect Lymphoma?

- Lymphadenopathy *unexplained by other causes*
  - Self-examination
  - Physical examination
  - Imaging studies
- Fevers, chills, night sweats, unexplained weight loss, pruritus, profound fatigue
- Alcohol-induced pain

Diagnosis of Lymphoma

- Initial diagnosis requires a lymph node biopsy
  - Evaluation of architectural features
  - Histologic type
  - Immunophenotyping and cytogenetics
  - Needle biopsy *NOT* adequate for diagnosis
- Core biopsy if not accessible
- Needle biopsy may suffice to document relapse

Utility of Fine Needle Aspiration in the Diagnosis of NHL (n=470)

	WF/REAL/WHO Diagnosis (%)	Lymphoma NOS (%)	"suspicious"/ Non-dx, benign (%)
nitial Diagnosis (n=93)	29	18	53
Recurrent Disease (n=22)	41	27	32

Hehn et al, J Clin Oncol 22:3046, 2004

Clinical Case #1 (cont)

Patient has transient reduction in her adenopathy on steroids/antibiotics, but neck swelling returns a few weeks later along with generalized pruritus.

PCP sends patient to ENT who completes a fine-needle aspiration

Cytology shows atypical lymphocytes ---> excisional biopsy then performed

Clinical Case #1

Duration of adenopathy (progressive over 4 + weeks) at her initial presentation was concerning for a primary malignancy, other etiologies to consider include infections (HIV, histoplasmosis, TB) and autoimmune (SLE, sarcoid etc).

Labs to obtain when lymphoma suspected:

HIV
CBC, CMP, LDH, (ESR)
PT/PTT (if biopsy planned)

Unless urgent clinical intervention is needed (massive adenopathy leading to SVC syndrome, spontaneous TLS, major autoimmune sequela) – refrain from empiric treatment with steroids

Case #1 – Final Diagnosis:

CLASSICAL HODGKIN LYMPHOMA, NODULAR SCLEROSIS SUBTYPE

- **<u>Classical Hodgkin lymphoma (95%) – aggressive, 4 subtypes</u>**
- **- Classic RS cells present in all 4 subtypes**
- - Loss of B cell markers with dysregulated gene expression profiles
- **CD15+, CD30+**
  - **Usually CD20 and CD45 negative**

Hodgkin Lymphoma

- Distinct from Non-Hodgkin lymphoma
  - 4 subtypes
  - Classical Hodgkin has Reed-Sternberg cells
- Approx 10 percent of all lymphomas
- Average age of onset: 34 years
- Highly Curable; OS ~85%

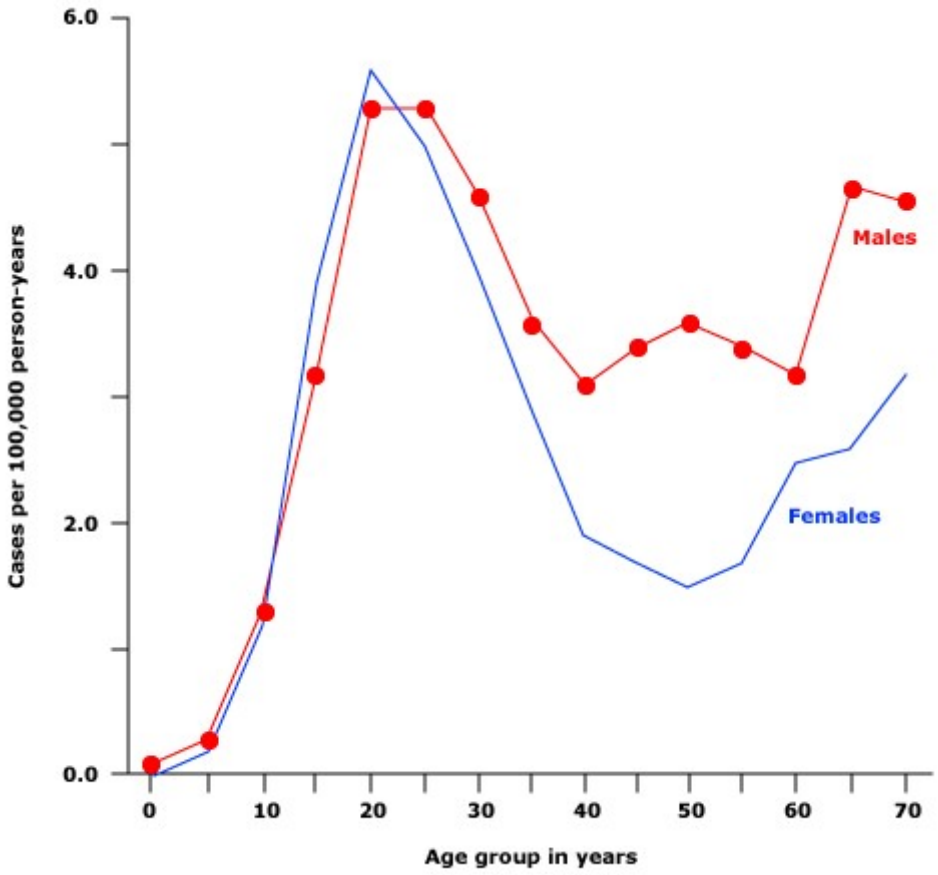
Hodgkin Lymphoma – Epidemiology

Represents 7 percent of childhood cancers and 1 percent of childhood cancer deaths in the United States.

Most common form of cancer in the 15 to 19-year-old age group. Average age is 30.

Bimodal age distribution with one peak in the 20s and 30s, and a second peak over the age of 60

There are approximately 8000 new cases in the U.S. annually.



NEJM PAPER

Hodgkin Lymphoma - Clinical Presentation

- Majority of patients present with **asymptomatic enlarged lymph nodes**.

- Most commonly involved sites are the cervical and supraclavicular nodes.

- A mediastinal mass may be seen on routine chest x-ray.

- Non-specific symptoms such as chest pain, cough, dyspnea are less common.

- **B symptoms** including fever (>100.4), night sweats, weight loss are present in less than 20% of patients with stage I/II disease.

- Differential diagnosis includes non-Hodgkin lymphoma, CLL, other metastatic malignancy, infection, sarcoidosis, reactive.

Hodgkin Lymphoma - Clinical Presentation (continued)

- Generalized pruritus is seen in 10 to 15% of patients.

- Alcohol-induced pain within involved organs (nodes, spleen) occurs in less than 10% of patients but is highly specific for classical HL.

- Paraneoplastic syndromes are rare, but can include neurologic syndromes, nephrotic syndrome, and hypercalcemia.

Hodgkin Lymphoma – Diagnosis*

- **History** should determine the presence or absence, duration, and severity of systemic symptoms which may be associated with Hodgkin lymphoma such as B symptoms, pruritus, and alcohol-induced pain.

- **Physical** exam including complete lymph node survey.

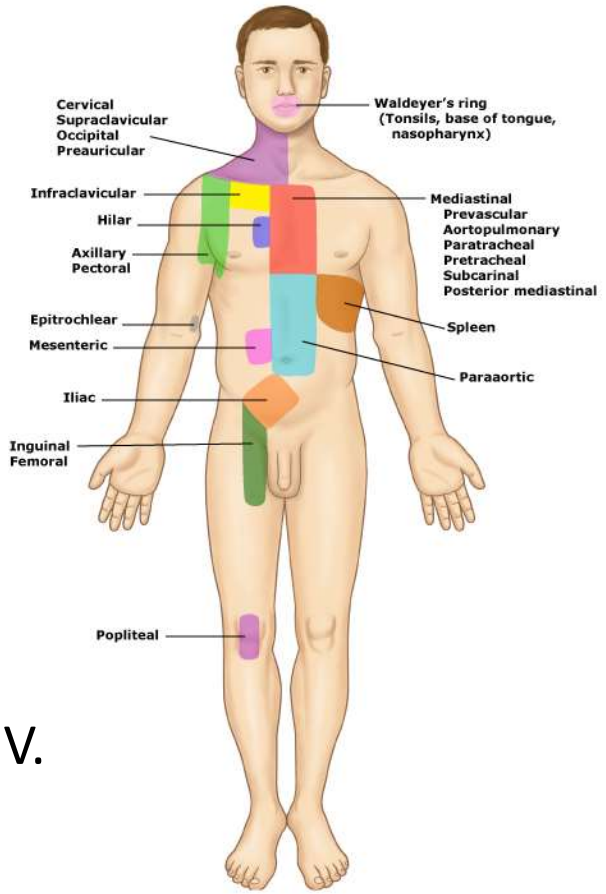
- **Tissue** biopsy, preferably excisional of a superficial node.

- **Bone marrow** biopsy for staging is occassionally done in patients with stage IIB to IV and/or cytopenias.
  Rarely needed now that we have PET/CT

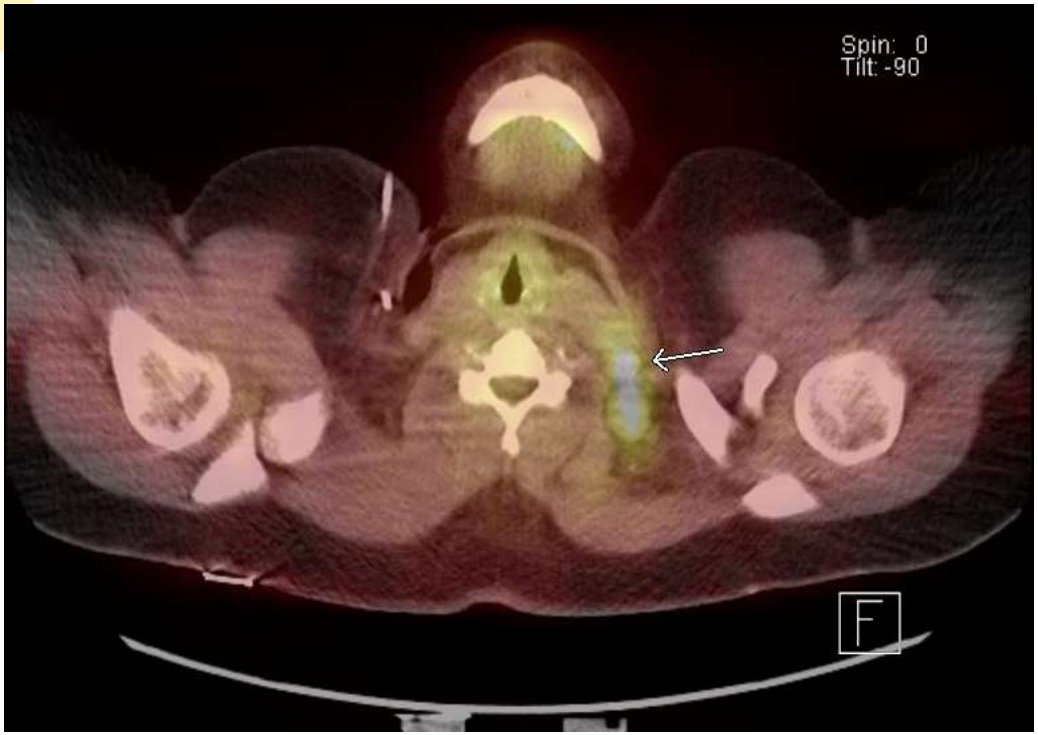
- **Laboratory** evaluation including CBC, ESR, chemistries, LFTs, urinalysis, LDH, albumin, calcium, **pregnancy test**, HIV.

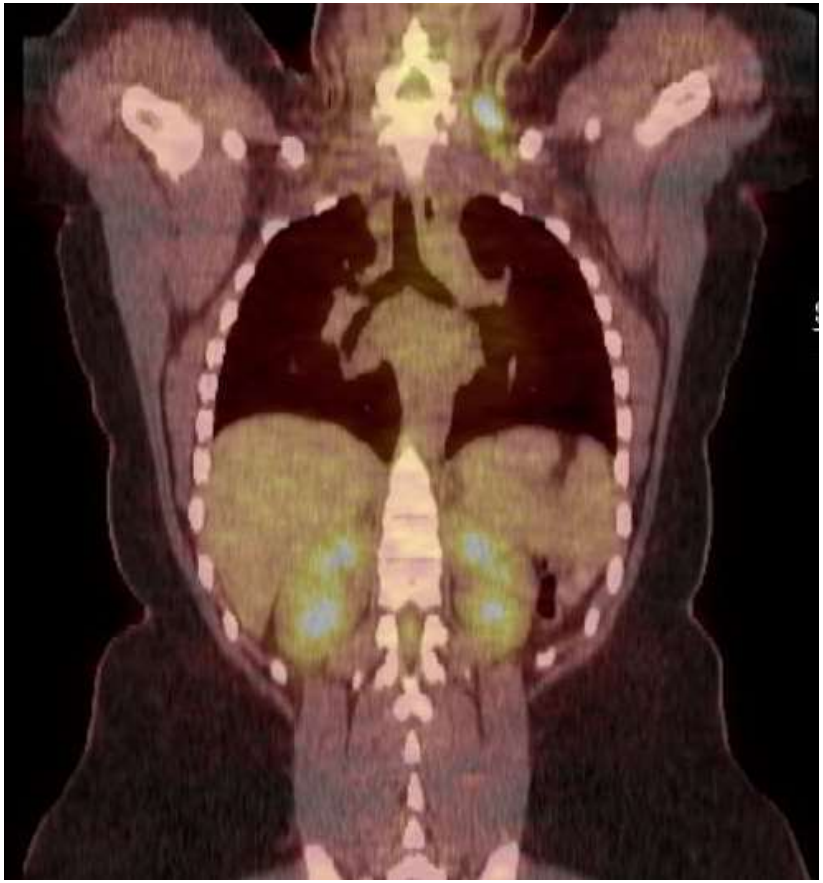
- **Imaging** with integrated PET/CT scan.

- Cardiac function and pulmonary function prior to chemotherapy.



Clinical Case #1

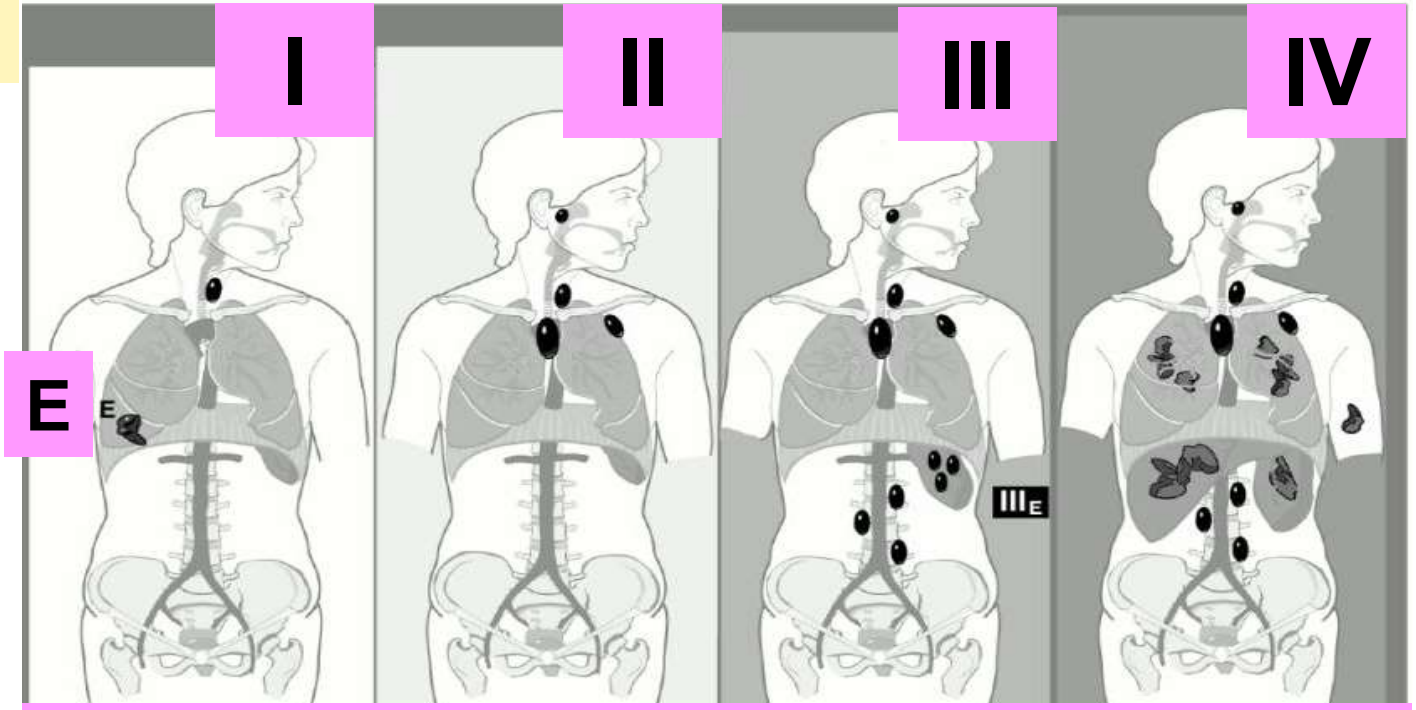




FDG avid disease limited to left cervical and supraclavicular region

Lymphoma staging

Limited stage Advanced stage



Ann-Arbor staging system

A = asymptomatic

B = B symptoms

Hodgkin Lymphoma: Key Points

- HL is a B cell malignancy that is most common in young adults.
  - Requires excisional biopsy and pre-biopsy steroid exposure can delay diagnosis

- Reed-Sternberg cell is the malignant cell in a background of reactive inflammation.

- Two subtypes: CHL (95%) and NLPHL (I treat this as indolent B cell NHL).

- Staging and prognostic features define therapeutic approach.
  Limited stage favorable: 2-4 cycles of ABVD +/- IFRT
  Limited stage unfavorable: 6 cycles of ABVD +/- IFRT
  Advanced stage: 6+ cycles of ABVD or other regimens

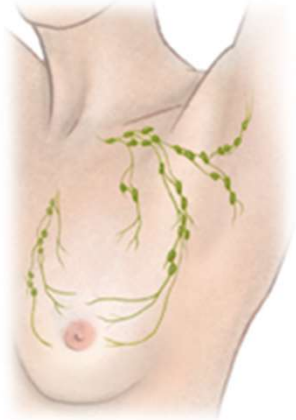
-Curable in ~80+% of patients, with 5 year OS likely to be 90+% with newer agents (PD1 immunotherapy, anti-CD30 antibody drug conjugates)

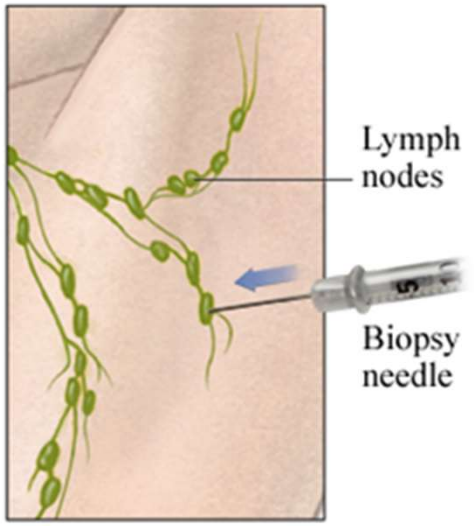
Clinical Presentation

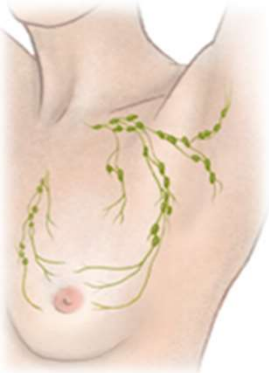
- NHL
  - Aggressive: rapidly growing mass, fever, night sweats, weight loss, elevated LDH, uric acid, pain, fatigue, cytopenias
  - Indolent: slow growing adenopathy, splenomegaly, cytopenias
- HL: painless adenopathy with or without splenomegaly, weight loss, night sweats, pruritus, pain in lymph node with alcohol consumption

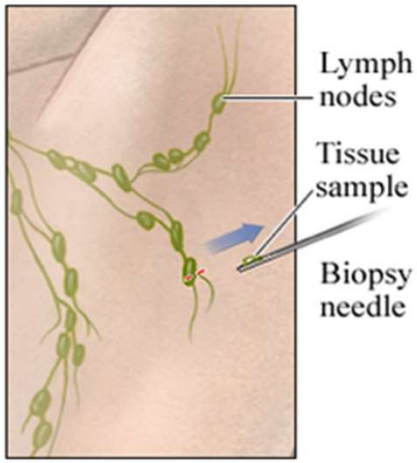
Diagnosis & Work up: Biopsy

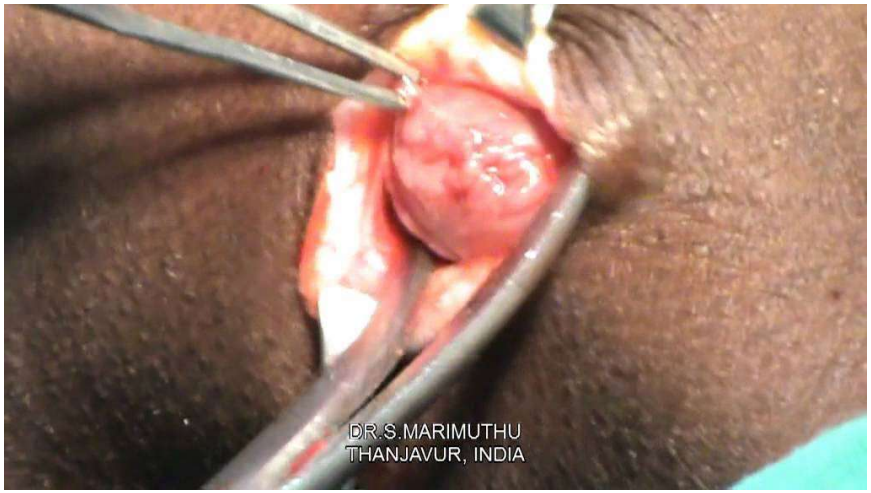
- Biopsy
  - Excisional biopsy
  - Core biopsy
    - FNA not preferred











Diagnosis & Work up: Scans

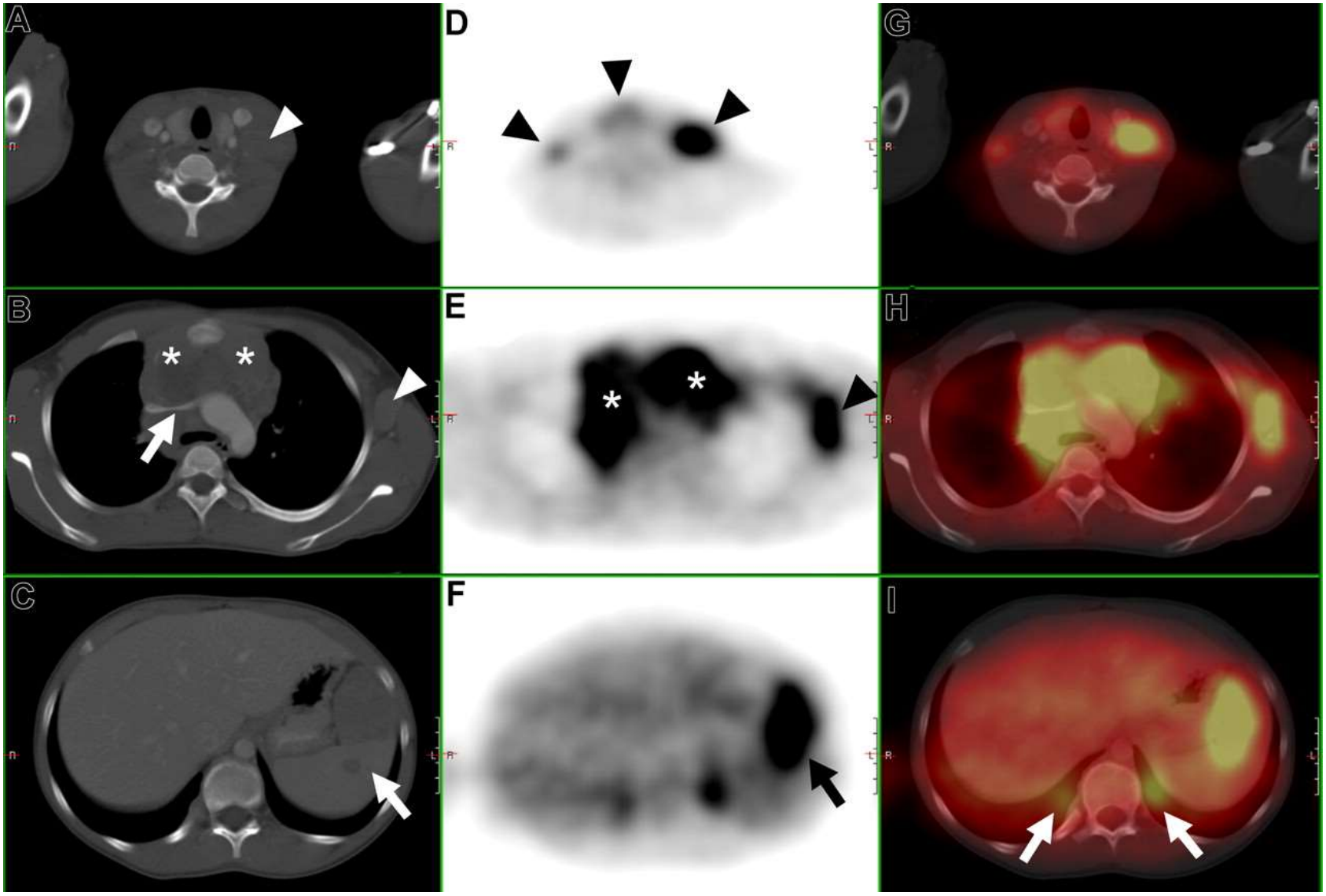
Positron Emission Tomography (PET)

- Radioactive glucose injected, uptake observed
- Highest sensitivity: HL, DLBCL, MCL, FL;
- Lower sensitivity: MZL, PTCL, SLL
- 2-4 hours

Computer Tomography (CT)

- Can visualize soft tissues and lymph nodes
- Accurate bone outline
- IV contrast dye
- No metabolic information
- 10 Minutes

CT, FDG-PET, and FDG-PET/CT fusion



Thomas C. Kwee et al. Blood 2008;111:504-516

blood

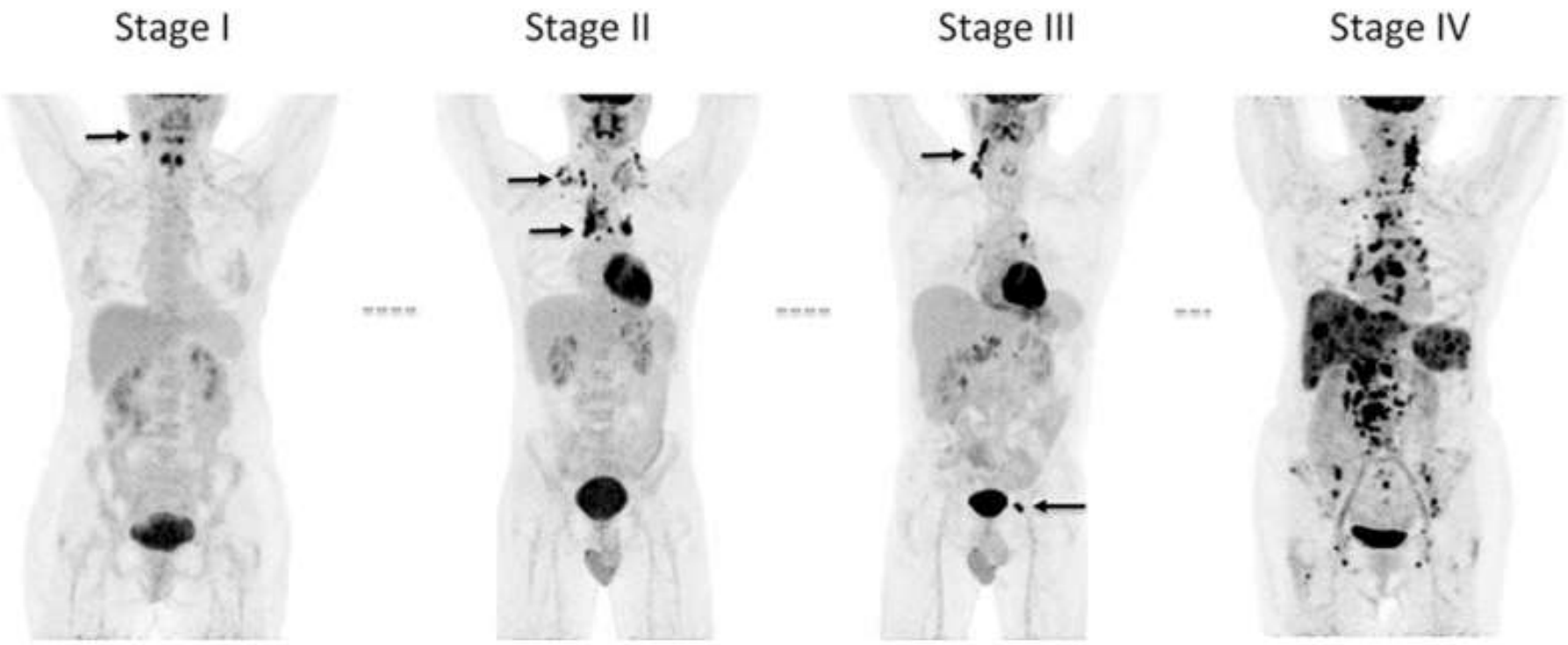
Staging System

Stage	Involvement	Extranodal (E) status
Limited		
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II bulky*	II as above with "bulky" disease	
Advanced		
III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
IV	Additional noncontiguous extralymphatic involvement	Not applicable

- "A": Absence of B symptoms
- "B": B symptoms: weight loss > 10% body weight during prior 6 months, recurrent fevers > 38C during prior month, recurrent drenching night sweats in prior month

*These designations are only used in HL

Staging of lymphoma



Tarec Christoffer El-Galaly, MD, DMSc, Lars Christian Gormsen,MD, PhD, Martin Hutchings, MD, PhD
PET/CT for Staging; Past, Present, and Future. Seminars Nuc Med, vol 48(1):4-16, 2018
https://doi.org/10.1053/j.semnuclmed.2017.09.001

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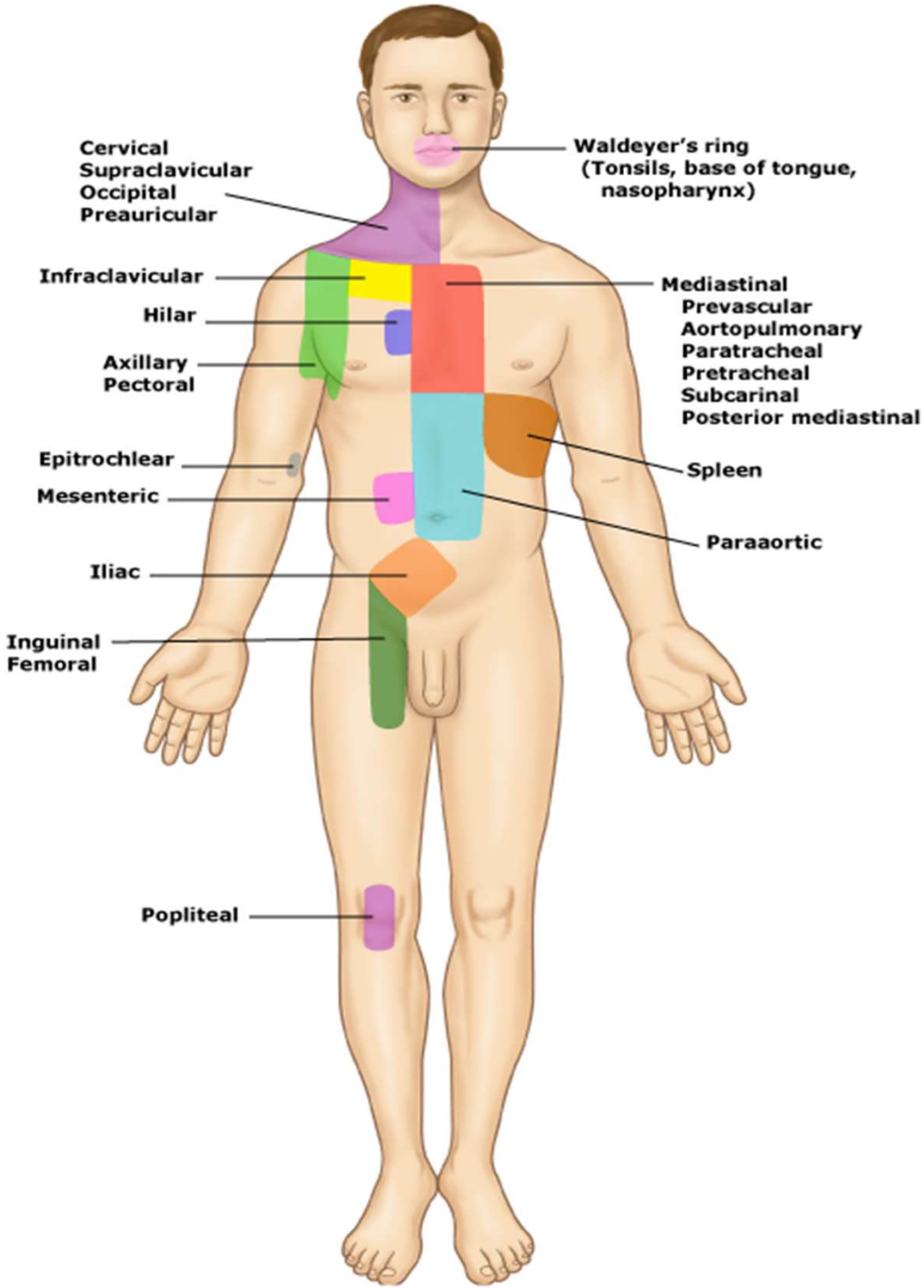
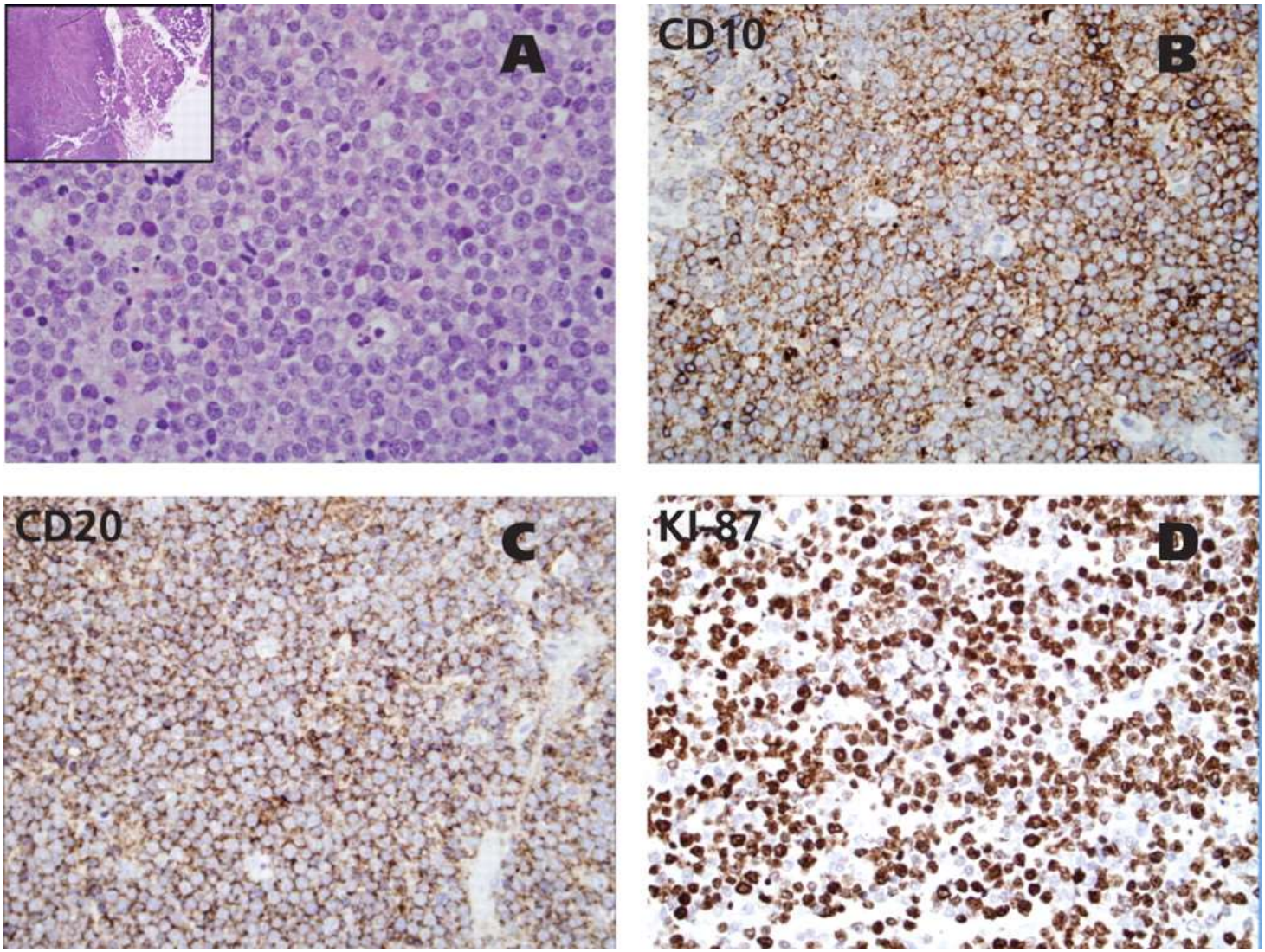
Lymph node regions in lymphoma



Pathology Report

- Histology: what is seen under microscope
  - Morphology and growth pattern
  - Proliferation rate: Ki-67
- Immunophenotype: cell surface markers (stains)
  - Immunohistochemistry (IHC)
- Diagnostic molecular
  - Receptor gene rearrangement and clonality
  - T cell lymphomas
  - IMPACT
- FISH (fluorescence in situ hybridization)
  - Identify structural abnormalities, such as deletions, duplications, translocations
  - "double hit" or "triple hit"

Pathology: DLBCL



Hematopathology report for DLBCL

Specimens Submitted:
1: Right arm mass

DIAGNOSIS:
1. Right arm mass:
- Diffuse large B-cell lymphoma, non-germinal B-cell subtype (Hans' algorithm), see comment.

COMMENT:
FISH for BCL2, BCL6, and MYC gene rearrangements studies will be performed and reported separately.

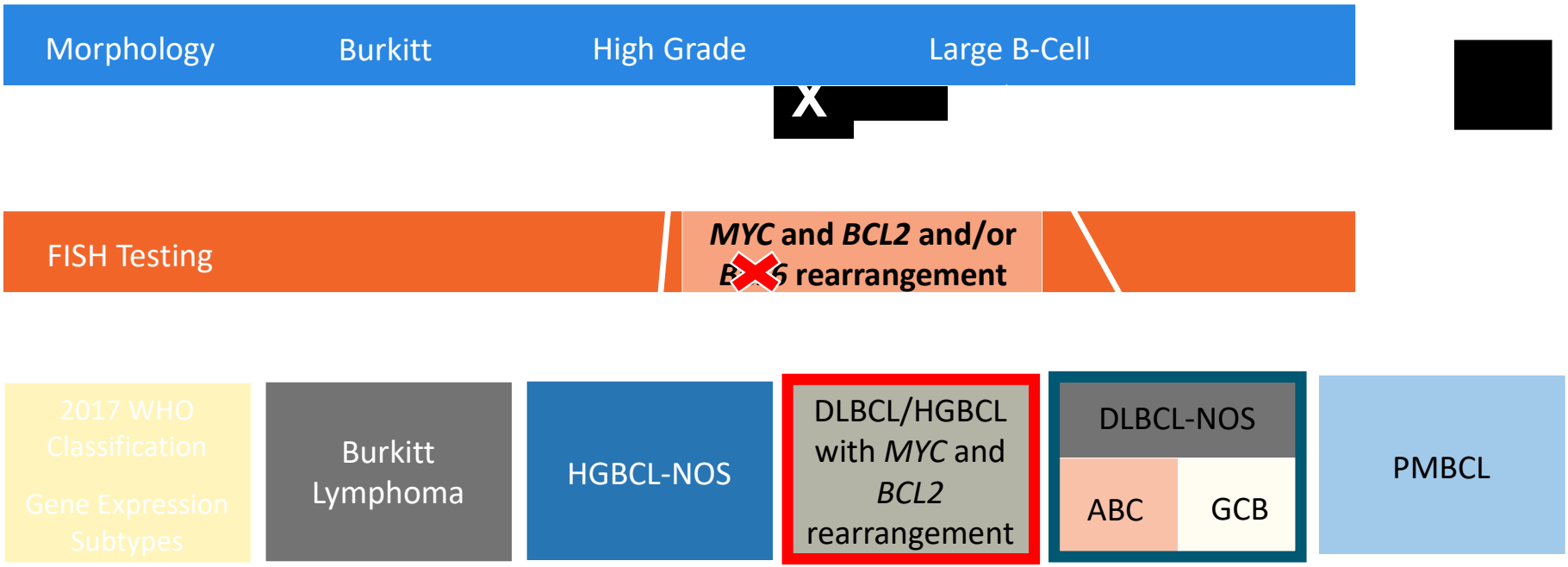
MORPHOLOGY
The histologic sections show a diffuse proliferation of medium to large atypical lymphoid cells with scant cytoplasm, irregular nuclear contours, finely clumped chromatin and distinct nucleoli. There is brisk mitotic and apoptotic activity.

IMMUNOHISTOCHEMISTRY
The neoplastic cells
Express: CD20, BCL2, BCL6, and MUM1, CMYC (~40%)
Do not express: CD3, MUM1, CD23, CD10
Other:
EBV in situ hybridization is negative.
Ki67 proliferation index is ~ 70%.

FLOW CYTOMETRIC ANALYSIS (F18-10563)
Interpretation:
Abnormal B-cell population identified.
No abnormal mature T-cell population detected.

Flow cytometry reveals an abnormal mature B-cell population with abnormal expression of CD19 (slightly bright), CD20 (bright), CD22 (absent), CD38 (bright), increased forward and side scatter suggestive of larger size, lambda light chain restriction, and normal expression of CD45; and without

WHO Classification: Aggressive B-Cell Lymphoma



Swerdlow. WHO Classification of Tumours, Revised 4th Edition. 2017;2. Alaggio. Leukemia. 2022;36:1720.

Diffuse Large B Cell Lymphoma

- Most common NHL – 40% of cases
- median age 60s
- De novo vs transformation
  - Richter's (CLL), Follicular, MZL, Waldenstrom's
- Approx 60% of patients cured
- Germinal center (GCB) v Non-Germinal Center (ABC) v PBML v. Unclassifiable

Treatment Resistance in DLBCL

Tumor Heterogeneity
Genetic and/or epigenetic changes in cancer cells generate spatial and temporal diversity to confer resistance to treatment

Examples of genetic and/or epigenetic alterations in R/R DLBCL

Genetic modifications

Cell cycle regulation
CCND3, CDKN2A, CDKN2B

DNA damage response
TP53

Epigenetic regulation
EZH2, CREBBP, MEF2B, KMT2C, KMT2D

Immune surveillance
B2M, CD58, HLA-A, MS4A1

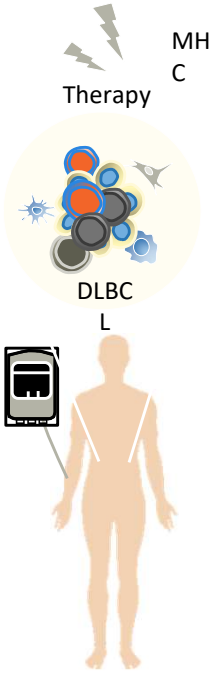
Oncogenes
MYC, PIM1, PRKCQ, GATA3, MLLT10, ABI1

Signaling pathway activation
STAT6, SOCS1, FOXO1, MYD88, CD79B, NFKBIE, NFKBIZ

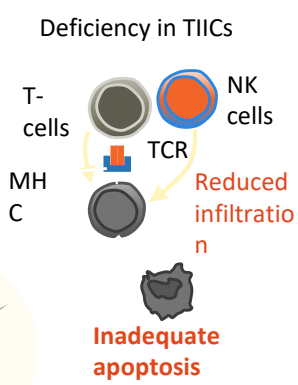
Epigenetic modifications

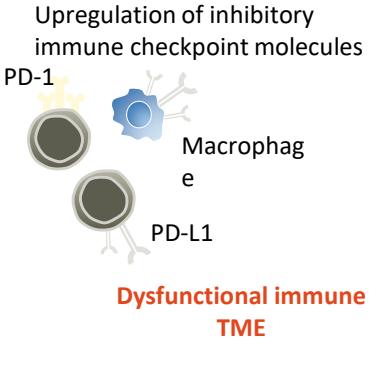
DNA methylation
Histone methylation/acetylation

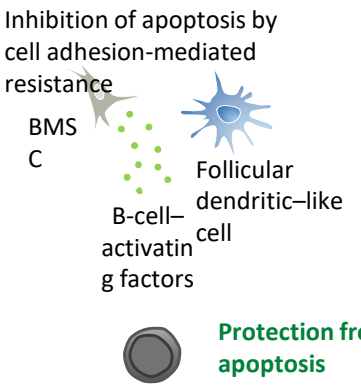
He. Leukemia. 2021;35:2151.



Tumor Microenvironment (TME)
Immune dysfunction and supportive stromal cells promote a protumor environment for treatment resistance



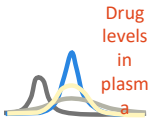


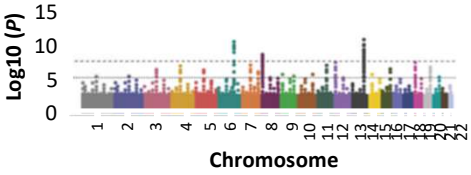


Host variabilities
Interpatient variabilities represented from multiple host-specific factors lead to highly variable responses to treatment

Demographic and physical factors
Age
Body weight
Gender

PK
Absorption
Distribution
Metabolism
Excretion





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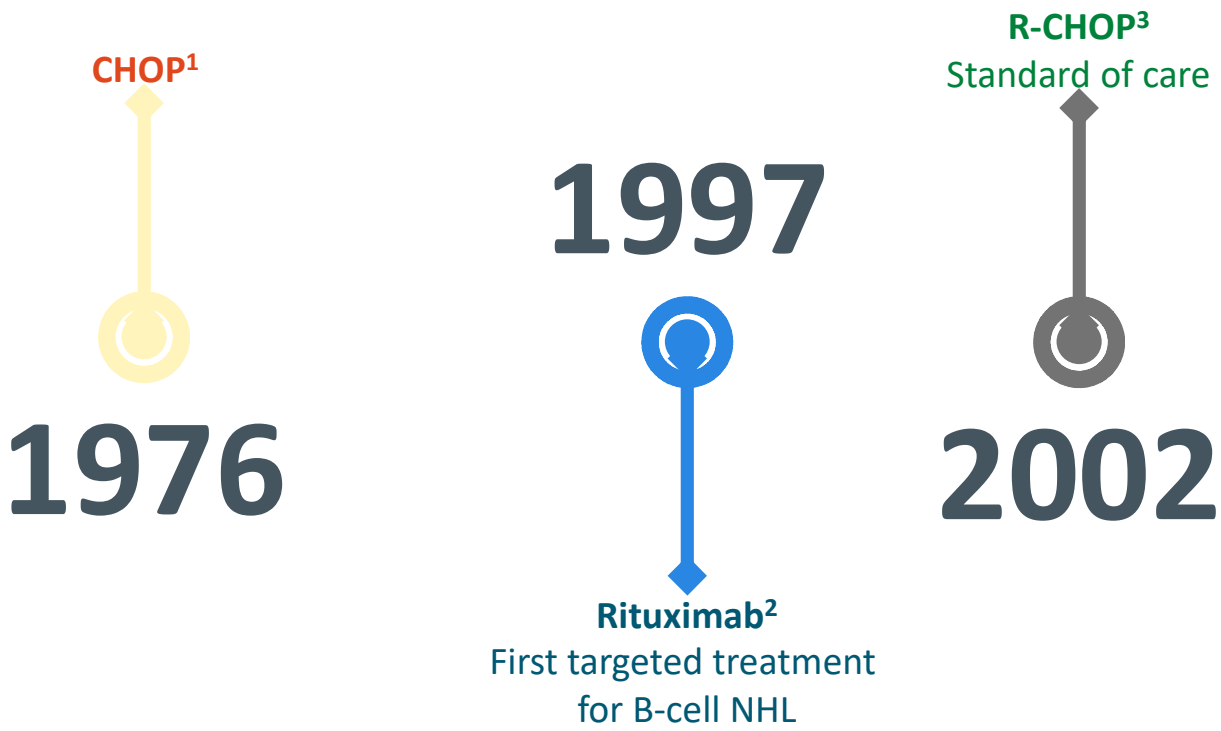
R-CHOP: First-line in DLBCL for 2 Decades



1. McKelvey. Cancer. 1976;38:1484. 2. McLaughlin. JCO. 1998;16:2825. 3. Coiffier. NEJM. 2002;346:235.

DLBCL treatments

- Chemotherapy: combination chemo-immunotherapy
  - R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and prednisone)
  - R-da-EPOCH (Rituximab, Etoposide, Prednisone, Cyclophosphamide, Doxorubicin)
- Second line:
  - RICE, GemOx, RDHAX, RDHAP, clinical trial
- Radiation Consolidation

Follicular Lymphoma

- Second most common NHL
- Follicular(nodular) growth pattern
- Incidence increases with age; median 65
- Patients can live with the disease for years
- T(14;18) overexpression of BCL2 an oncogene
- Grade 1-2, 3a more indolent behaving. Grade 3b more aggressive and treated like DLBCL.
- GELF Criteria

FL treatment

- Observation
- Chemotherapy:
  - G-CHOP or G-CVP
  - O-Benda
  - Rituximab
- Radiation
  - Boom Boom or BOOM
- Ref/rel:
  - G-CHOP, ICE
  - Clinical trial

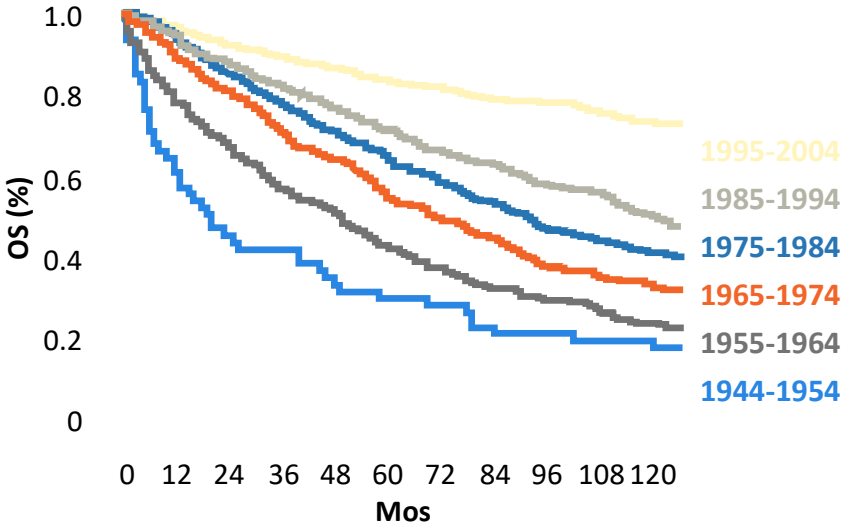
Mantle cell lymphoma

- Often discussed with the indolent NHL, but often has more aggressive behavior
- Typically presents at advanced stage
    - Common sites: nodes, Waldeyer's ring, bone, blood and extranodal sites, such as bone marrow, gastrointestinal tract, breast, pleura, and orbit
- Often has t(11;14) cyclin D1 overexpression

Improved Prognosis for Patients With FL in New Treatment Era

- FL typically regarded as chronic disease with good responses to initial therapy, but with eventual relapses to subsequent therapy[1,2]
- Recent therapeutic advances, most notably rituximab, have improved disease control and long-term clinical outcomes[3-5]
  - 10-yr survival rate: 64% to 92%[3]
  - Median survival is ~ 20 yrs, similar to age matched controls[5-8]
- Current goal of treatment: maintain best QoL by delaying disease progression—will this translate into an OS benefit with longer follow-up?

OS Improvement in Indolent B-Cell Lymphoma from 1944 to 2004: the MDACC Experience[9]



1. WHO. Follicular lymphoma. 2014. 2. ACS. Treating B-cell non-Hodgkin lymphoma. 3. Freedman. Am J Hematol. 2020; 95:316. 4. Kahl. Blood. 2016;127:2055. 5. Provencio. PLoS ONE. 2017;12:e0177204. 6. Maurer. Am J Hematol. 2016;91:1096. 7. Swenson. JCO. 2005; 23:5019. 8. Tan. Blood. 2013;122:981. 9. Neelapu. 60 Years of Survival Outcomes at the MD Anderson Cancer Center. New York, NY: Springer; 2013. p. 241.

Slide credit: clinicaloptions.com

Treatment Considerations for Newly Diagnosed FL

- Disease stage
- Tumor grade
- Tumor burden
- Symptoms
- Patient age and fitness
- Patient goals and priorities

- CR and/or prolonged PFS
  - Prioritizes longer remissions over QoL
  - Usually requires more aggressive treatment that is more toxic in the short term
- Maximize QoL and/or reduce risk for AEs
  - Prioritizes QoL over longer remissions
  - Usually involves gentler treatment with fewer toxicities at the expense of efficacy

Blinman. Ann Oncol. 2012;23:1104. Dreyling. Ann Oncol. 2016;27(suppl 5):v83. Meropol. Cancer. 2008;113:3459.

Slide credit: clinicaloptions.com

GELF Criteria

- A person has high tumor burden if they have ≥ 1 of the following:
  - Any mass ≥ 7 cm in diameter
  - Involvement of ≥ 3 LNs, each ≥ 3 cm in diameter
  - Presence of B symptoms
  - Splenomegaly
  - Compression syndrome (ureteral, orbital, GI)
  - Ascites or pleural effusion
  - Cytopenias (WBC < 1 x 10^9/L or PLTs < 100 x 10^9/L)
  - Leukemia (> 5.0 x 10^9/L circulating malignant cells)
  - (Elevated LDH or β_2-microglobulin)

Solal-Céligny. JCO. 1998;16:2332. Brice. JCO. 1997;15:1110. Dreyling. Ann Oncol. 2016;27(suppl 5):v83.

Slide credit: clinicaloptions.com

Frontline FL: Conclusions

- Outcomes for patients with untreated, advanced FL have improved substantially in the era of rituximab-based strategies
  - Median survival is ~ 20 yrs
- Advances in the first-line treatment of FL continue to prolong PFS
  - Obinutuzumab-based CIT with maintenance decreased risk of PD or death by 24% vs rituximab-based therapy, with increased risk of grade 3/4 cytopenias and IRRs
- Lenalidomide + rituximab is a reasonable option for patients with FL wishing to avoid CT
- Alternate forms of rituximab are now available, including biosimilars and an SQ formulation

Slide credit: clinicaloptions.com

General Approach to Managing Relapsed FL

- Excisional lymph node biopsy to rule out transformation
  - PET/CT scan may guide optimal biopsy site
- Considerations:
  - Presence/absence of symptoms
  - Pace of relapse
  - Time of relapse after initial therapy
  - Type of previous therapy
  - Age, comorbidities, and goals of care

Slide credit: clinicaloptions.com

MCL treatment

- Observation
- Chemotherapy:
  - RCHOP
  - BR
  - Cytarabine
  - High dose therapy/auto stem cell rescue
- Rel/Ref:
  - Ibrutinib
  - Venetoclax (NCCN compendium)
  - Clinical trial

CLL/SLL

- Median age 70
- 25-30% percent of all leukemias in the US
- Can involve predominantly blood, lymph nodes or both
- Often present with painless adenopathy that wax/wanes or incidental lymphocytosis on routine CBC, cytopenias
  - At times associated with autoimmune phenomenon: hemolytic or anemia, immune thrombocytopenia or exaggerated reaction to insect bites
- Cytogenetics evaluated to help prognosticate:
  - ex: 17p deletion, CD38 positivity, unmutated IgHV, del11q, trisomy 12, del 13q

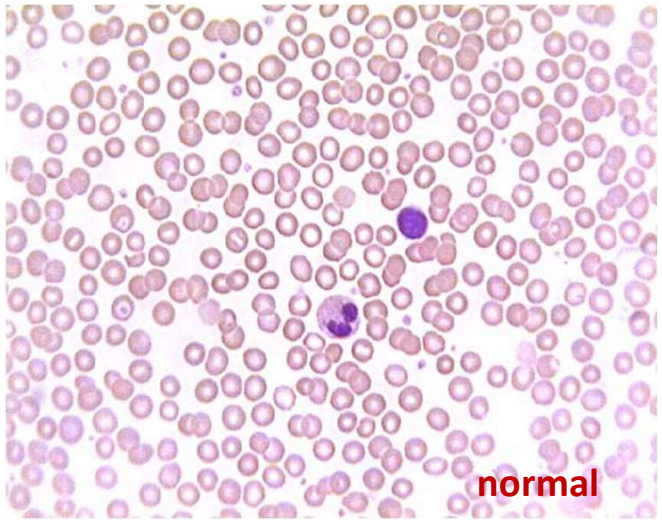
Clinical Case #2

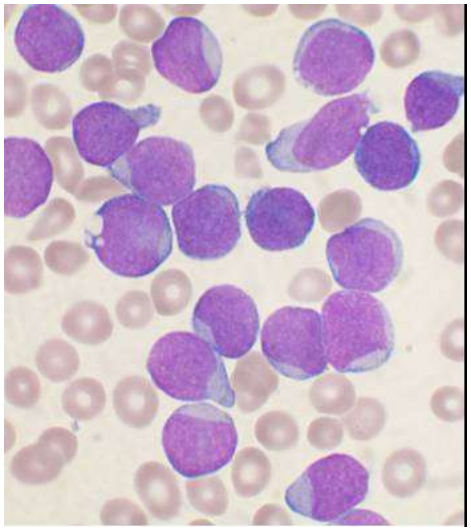
81 year-old male with h/o hypertension and hyperlipidemia presents to his primary care physician to reestablish care. He offers no complaints.

Physical exam is notable for palpable spleen. Routine laboratory studies reveal a WBC of **121,000** with a differential of 5% granulocytes, 94% lymphocytes, and 1% monocytes. Hgb 12 and platelets were 280,000.

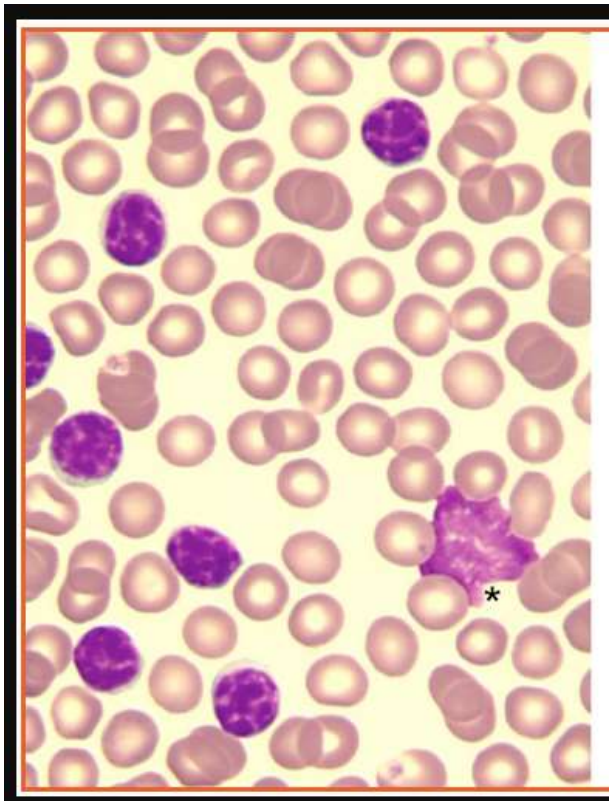
Patient sent to ED over concerns of new leukemia.

Lymphocytosis



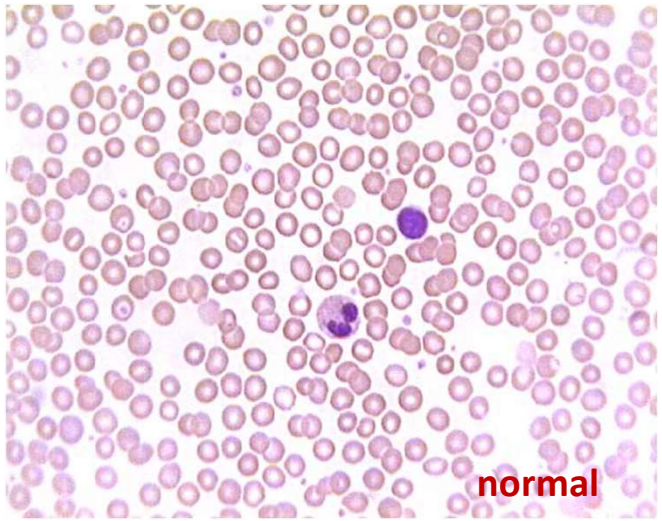


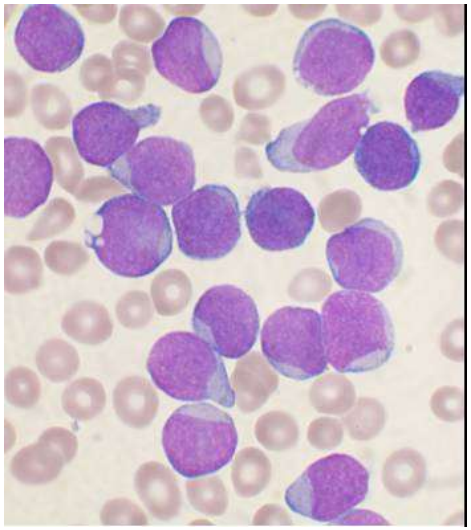
Marked increase in large, atypical leukocytes (AML/ALL)



Marked increase small lymphocytes
- CLL
- Hairy cell leukemia
- T cell leukemia

Lymphocytosis





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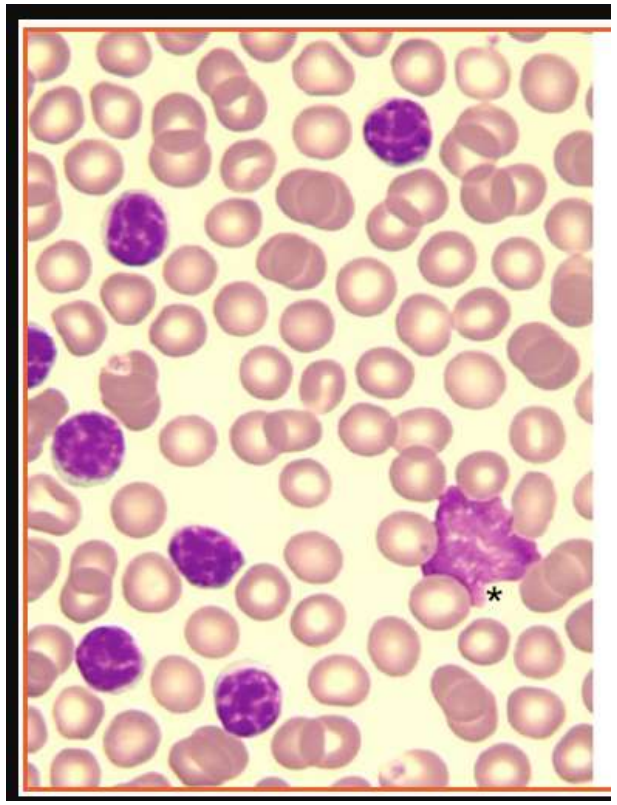


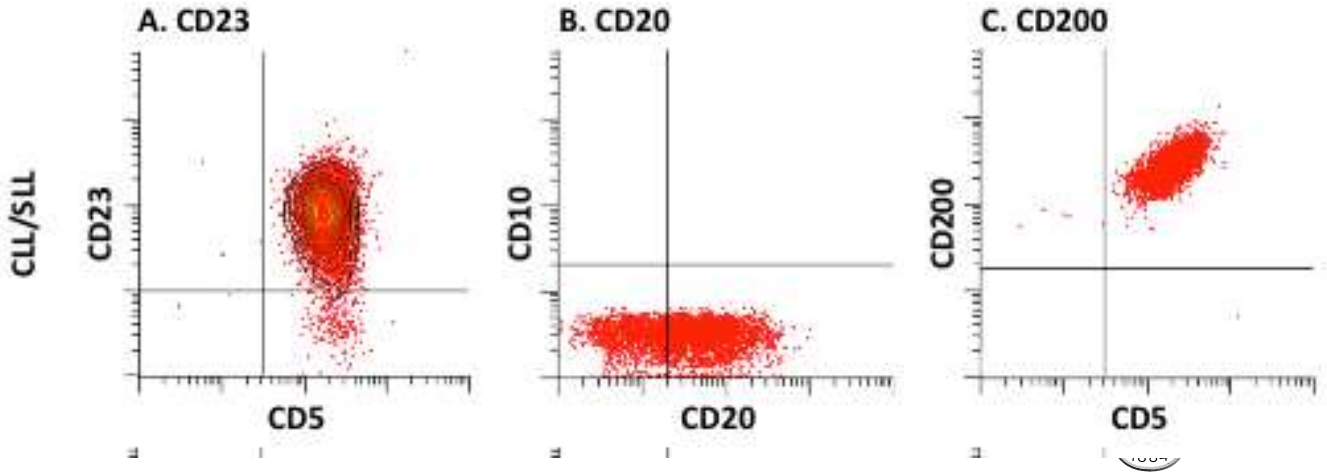
Marked increase small lymphocytes
- CLL
- Hairy cell leukemia
- T cell leukemia

Clinical Case #2

Peripheral blood smear with marked number of small lymphocytes

Labs in the ER otherwise reassuring (preserved renal function, normal LDH, no coagulopathy (PTT/PT/fibrinogen), no evidence of TLS with normal K, Phos, Ca, and uric acid)

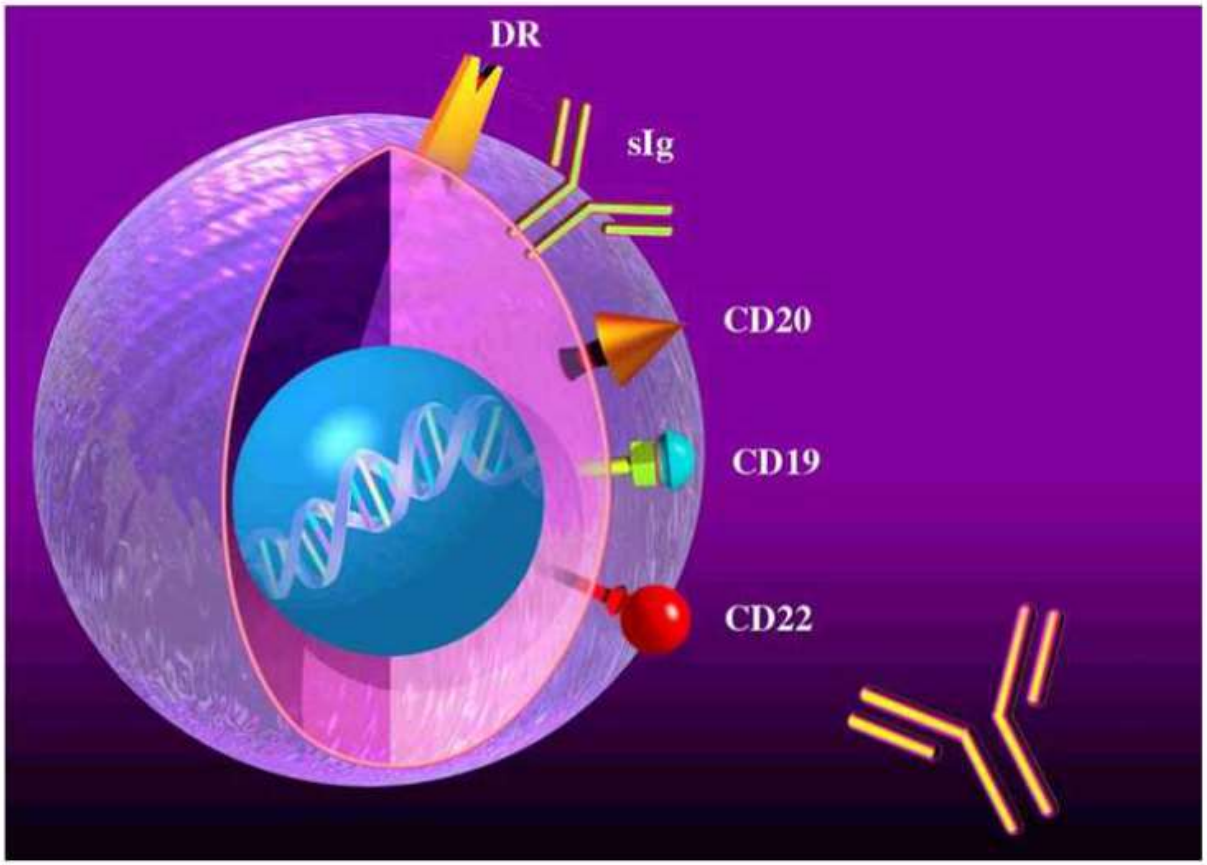
Peripheral blood sent for flow cytometry and patient sent home with outpatient follow up in clinic



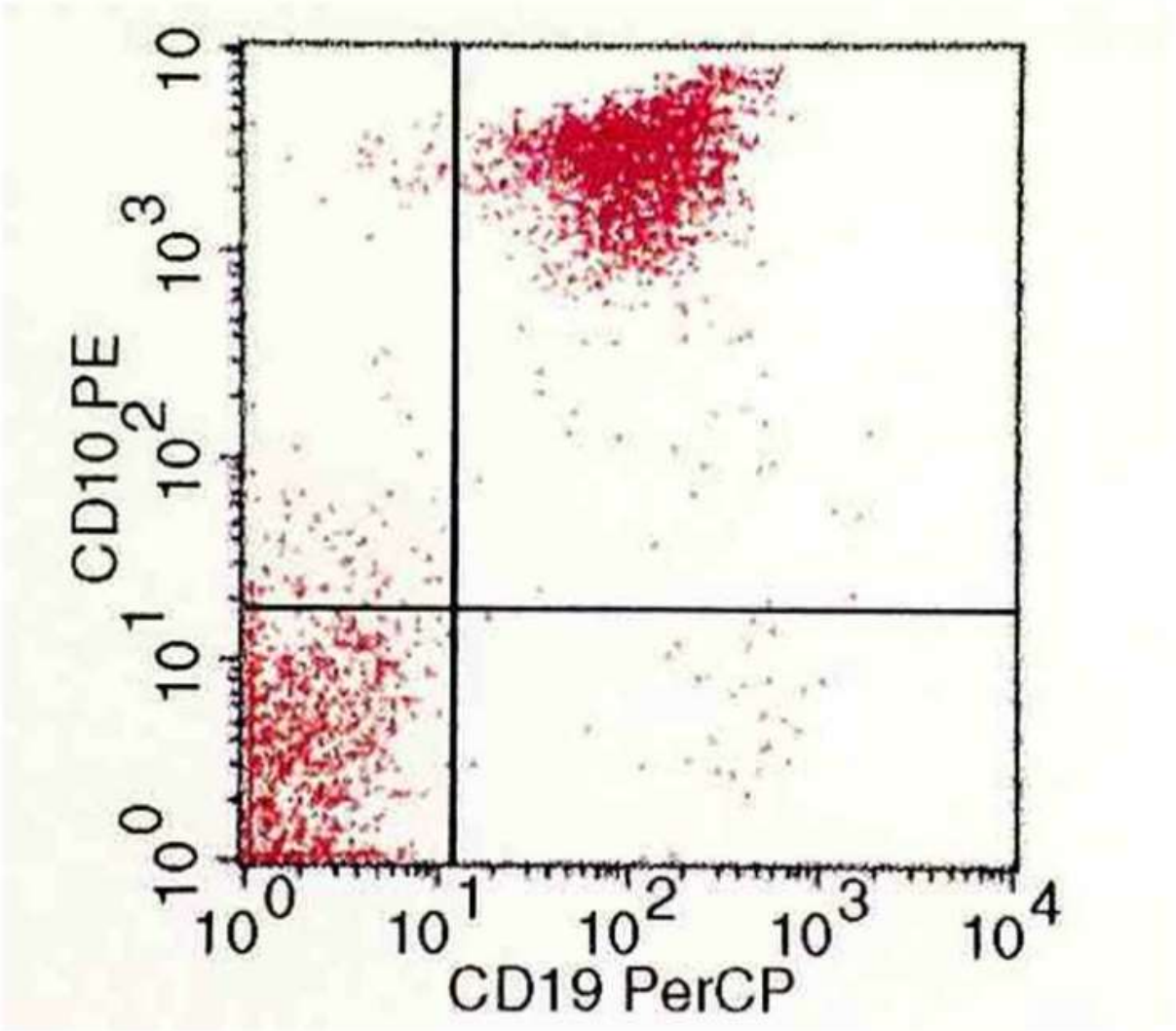
Kettering

Flow Cytometry

Takes cells in a suspension and checks for proteins on the surface



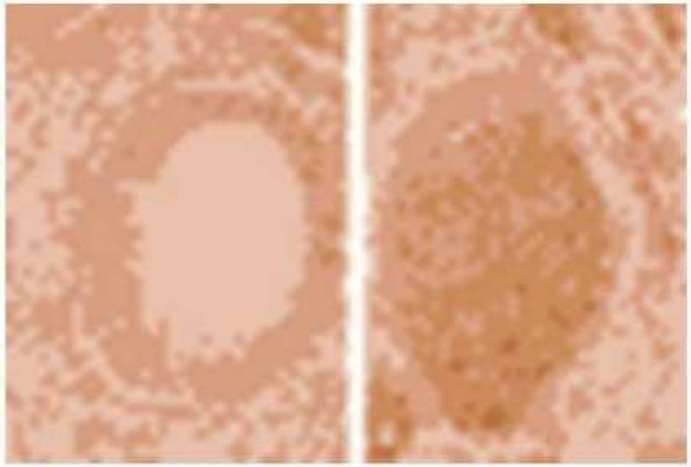
Flow cytometry: example



Follicular lymphoma: CD10 positive, CD19 positive

Immunohistochemistry (IHC)

- Similar to flow cytometry but is done on TISSUE SECTIONS
- Can be used to test for prognostic markers



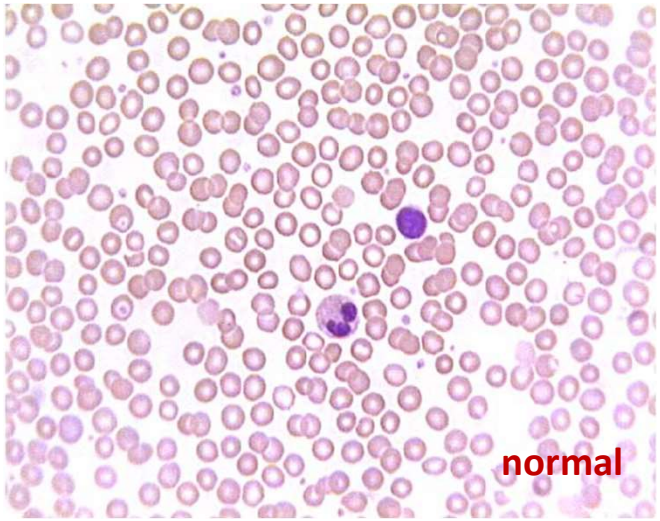
Bcl2 staining in normal and malignant follicle

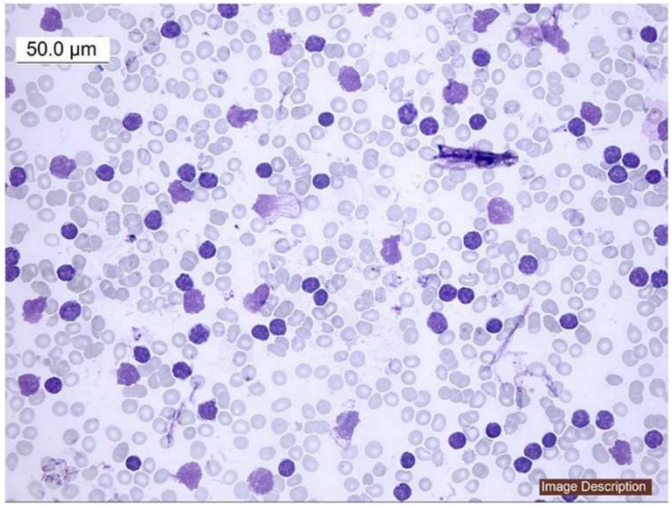
Chronic Lymphocytic Leukemia (CLL)

Common phenotypes of B-cell cancers

Diagnosis	CD5	CD10	CD19	CD20	CD23	CD79b	FMC-7	CD25	CD11c	CD103
CLL/SLL	+	-	+	+(w)	+	-	-	-/+	+/-	-
Mantle cell lymphoma	+	-	+	+	-	+	+	-	-	-
Follicular Lymphoma	-	+	+	+	-/+	+/-	+/-	-	-	-
Marginal zone lymphoma	-	-	+	+	-	+/-	+/-	-/+	+	-
Hairy cell leukemia	-	-	+	+	-	+/-	+/-	+/-	+	+

Lymphocytosis – Differential Diagnosis





Infection

- Viral
  - EBV
  - HIV (primary infection)
  - HHV6
  - HTLV1
- Bacterial
  - *Bordetella pertussis*
  - *Bartonella henslae*
  - *Babesia microti*

Malignancy

- CLL
- Hairy cell leukemia
- T cell leukemia
- Acute lymphoblastic leukemia

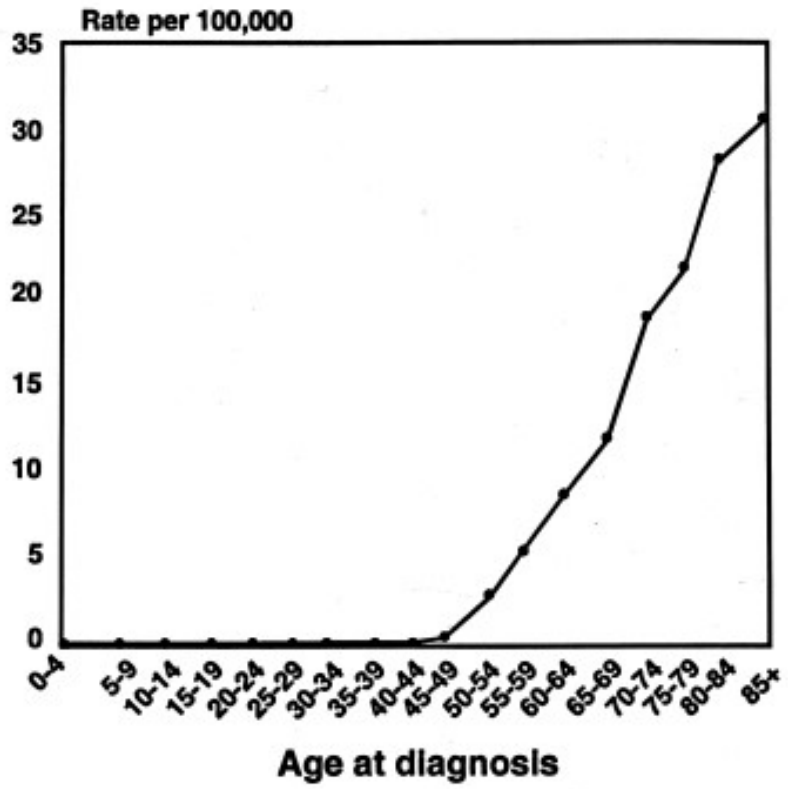
Chronic Lymphocytic Leukemia (CLL)

- Clonal proliferation of **mature CD5+ CD10- CD19+ CD23+ B cells**

- CLL is **heterogeneous** - many patients will have an indolent clinical course that does not require intervention for many years while others may progress rapidly from the time of diagnosis.

- **Small lymphocytic lymphoma (SLL)** is the same disease but only involves the lymph nodes and spleen. There is no or few circulating cells in SLL.

CLL- Epidemiology



- Most common form of leukemia in the Western world

- Approximately 30% of all leukemias.

- Incidence: 2.7 per 100,000 in the USA.

- 15,000 diagnosed and 4,500 deaths in the U.S.

- More than 90% of cases occur in patients >50 years.

- Higher incidence in men (M:F=2.8).

- Rarely familial.

- Median survival, 10 years.

CLL – Clinical Presentation

- Most patients (~25-50%) are asymptomatic at diagnosis.

- Approximately 5-10% will present with B symptoms (unintentional weight loss, unexplained fever, and night sweats).

- Less than 10% of patients will present with complications of CLL including infection, anemia, or thrombocytopenia.

- The indolent nature of the disease is such that it may go undiagnosed for many years until it begins to progress.

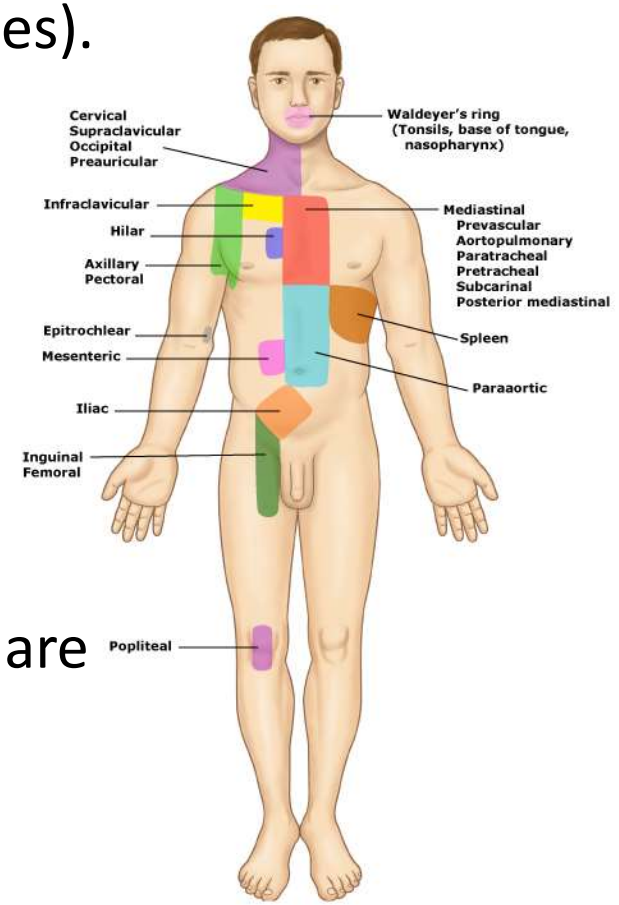
Looking at our patient's CBC from 2012-2014 – while his WBC was normal, his differential had increasing lymphocyte predominance

CLL – Diagnosis

- Physical exam may reveal enlarged, firm, non-tender **lymph nodes and/or splenomegaly** (~25-55% of cases). Any organ may be involved.

- **Laboratory evaluation** including CBC, peripheral smear, chemistries, LFTs, lactate dehydrogenase (LDH), flow cytometry (immunophenotyping).

- In patients with confirmed CLL by **immunophenotyping**, additional prognostic studies are typically obtained including cytogenetics, FISH, and IgVH mutational status



Monoclonal B cell Lymphocytosis (MBL)

- The absolute blood lymphocyte threshold for diagnosing CLL is 5000 lymphocytes/µL.

- Patients with <5000 CLL cells/µL and no lymphadenopathy, organomegaly, cytopenias, or disease-related symptoms have a monoclonal B cell lymphocytosis (MBL).

- MBL can be detected using high sensitivity flow cytometry in approximately 5 percent of patients over the age of 60 with normal blood counts.

- This precursor state progresses to CLL at a rate of 1-2%/year.

- Patients are followed at yearly intervals with repeat flow cytometry of blood lymphocytes performed according to the physician's clinical judgment.

Clinical Staging Systems for CLL*

Stage			
Value	*Rai*	*Binet*	*Median survival*
Lymphocytosis (>5,000/uL)	0	-	12.5 years
Lymphocytosis plus nodal involvement	I	A <3 node groups	8.5-9 years
Lymphocytosis plus organomegaly	II	B >3 node groups	5-6 years
Anemia (Hgb <11)	III	C Hgb <11 PLT <100	1.5-2 years
Plts <100	IV		

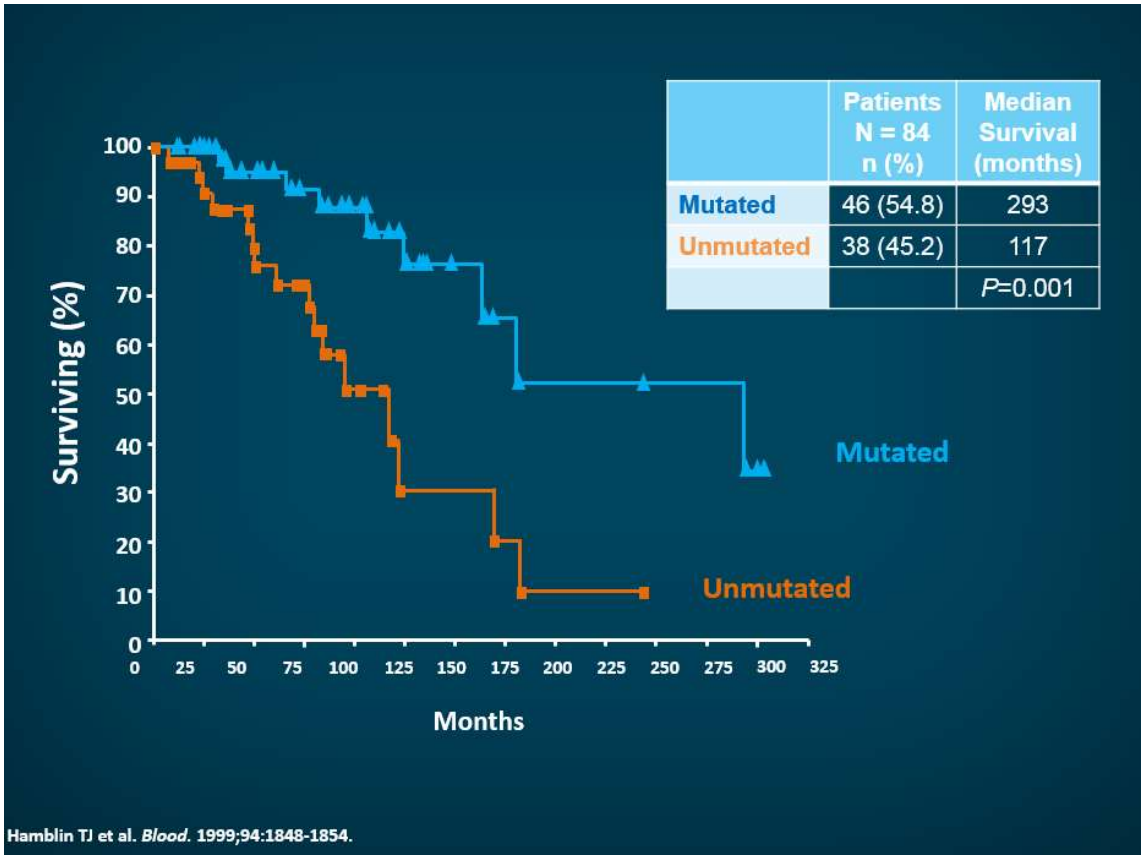
Genetic Abnormalities in CLL

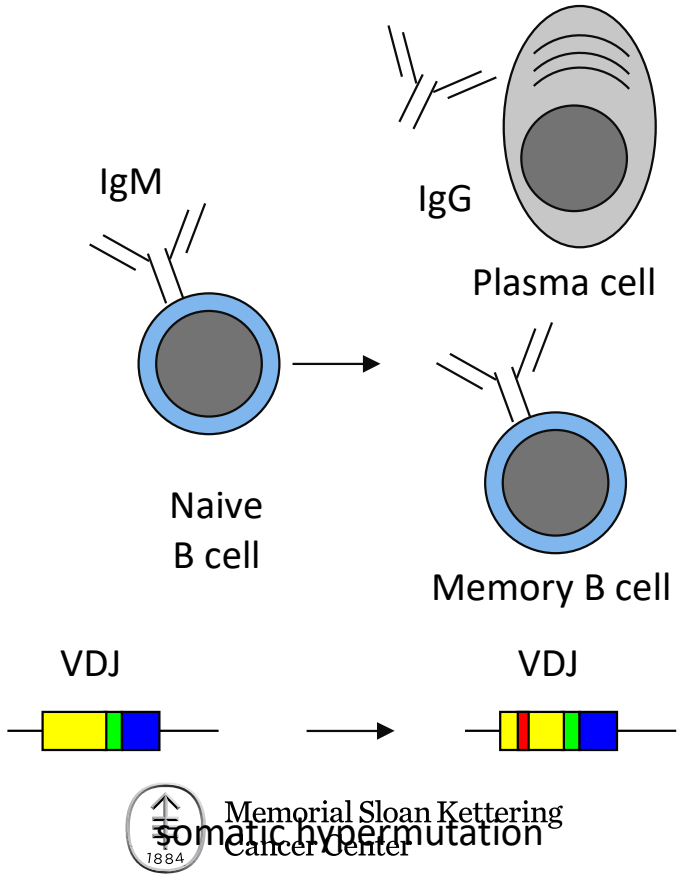
Genetic abnormality	*Incidence (%)*	*Median survival (months)*	*Clinical correlation*
deletion 13q	55-62	133-292	Typical morphology Mutated IgVH genes Stable disease
trisomy 12	16-30	114-122	Atypical morphology Progressive disease
deletion 11q (ATM)	18	79-117	Bulky LNs Unmutated IgVH genes Progressive disease Early relapse post auto SCT
deletion 17p (p53)	7	32-47	Atypical morphology Unmutated IgVH genes Advanced disease Drug resistance

Diagnostic and Prognostic Markers in CLL

IgVH mutational status – Somatic hypermutation is a normal B cell process that introduced point mutations into the immunoglobulin variable region to result in antibody affinity maturation.

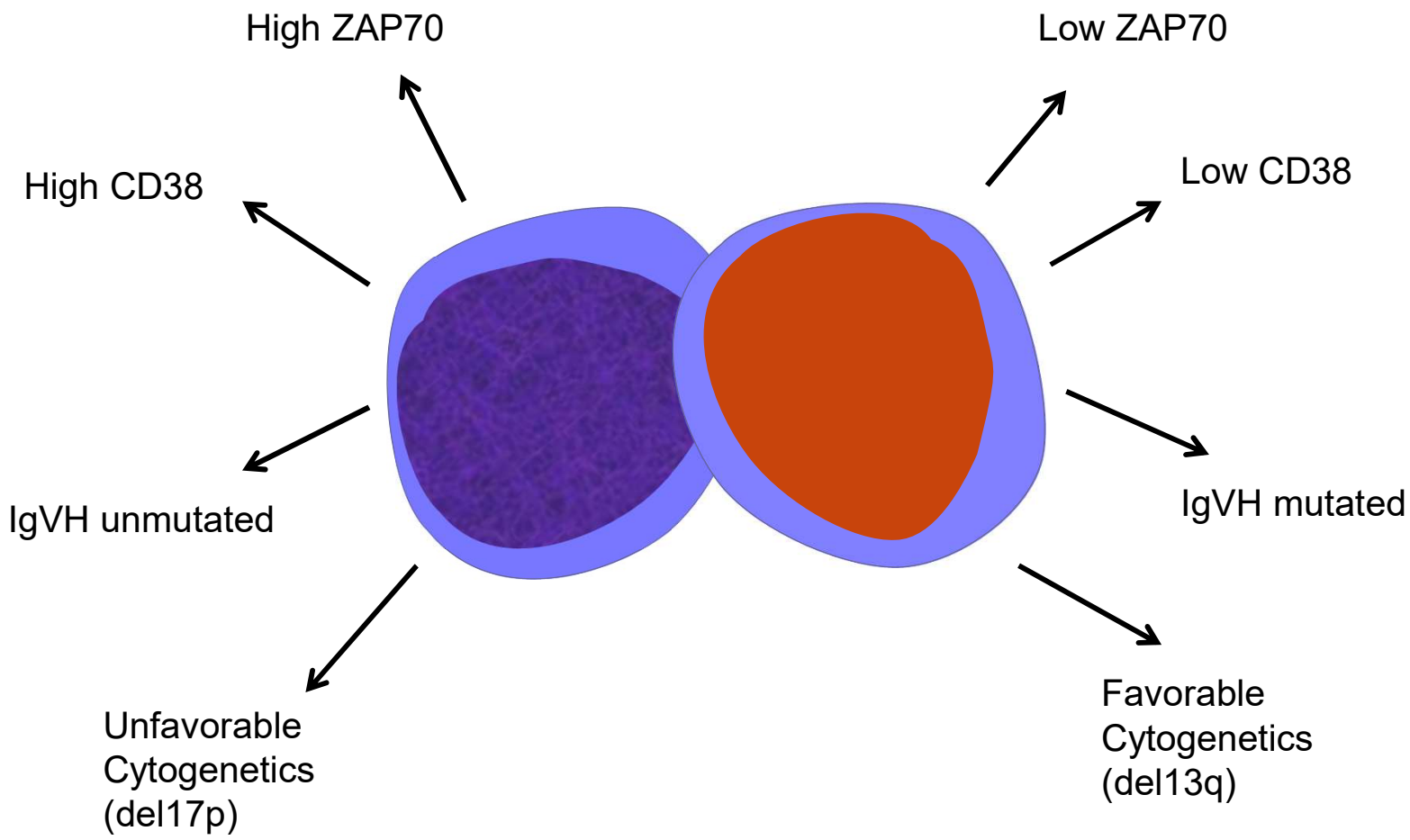
Unmutated status = more immature = more aggressive





Median survival, 8-10 years

Median survival, >25 years



CLL – Complications*

- Older patients diagnosed with ‘low risk’ CLL (deletion 13q, mutated IgVH, CD38-, ZAP-70-) will often die of causes unrelated to their CLL.

- The B cells do not function properly in CLL.

- Immune phenomena such as immune thrombocytopenia and autoimmune hemolytic anemia. Treated with steroids +/- rituximab.

- Hypogammaglobulinemia puts patients at risk for infection. Treated with intravenous immunoglobulin (IVIg).

- Anemia and thrombocytopenia related to bone marrow involvement.

- Transformation to high-grade non-Hodgkin lymphoma

Richter's Transformation

- Evolution of CLL into a high-grade lymphoma, most commonly diffuse large B cell lymphoma.

- Incidence is 3-7% and approaches 15% in patients who have received 3 or more prior treatments.

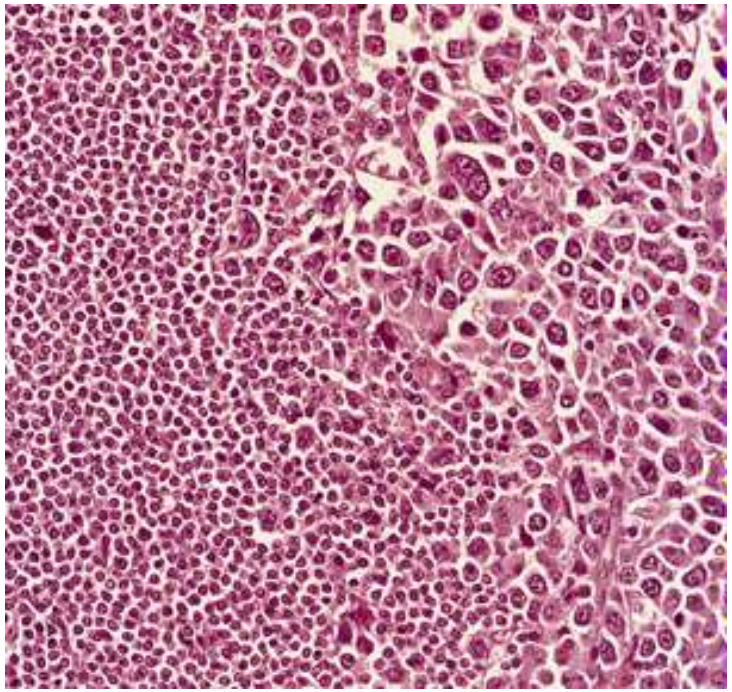
-Median time to transformation is 2-4 years.

- Clinical features: adenopathy, rising LDH, cytopenias, B symptoms.

- Risk factors are poorly defined and may include rising LDH and advanced stage

- Treated with combination chemotherapy used for aggressive lymphomas.

- Median survival is 5-8 months.



CLL ⟶ DLBCL

CLL (and indolent NHL) - Indications for Treatment

CLL and advanced stage indolent NHLs are not curable with standard immunochemotherapy – treatment typically reserved for those patients with symptomatic disease:

- Constitutional symptoms (B symptoms, fatigue)
- Threatened end-organ function
- Progressive anemia (typically hgb <10)
- Progressive thrombocytopenia (plt <100k)
- Transformation to aggressive large cell lymphoma
- Bulky disease (massive splenomegaly or adenopathy)

CLL – Management*

Type of disease	*Treatment*
Early-stage favorable (Rai stage 0 or 1)	Watchful waiting (3-6 month follow-up) No advantage to early intervention
Symptomatic Rai stage II or stage III or IV Fit/young patients	6 cycles of chemo: BR = bendamustine + rituximab (anti-CD20) FCR = fludarabine + cyclophosphamide + rituximab
Elderly patients with multiple comorbidities or poor performance status	Ibrutinib (BTK inhibitor) Chlorambucil + obinutuzumab
Deletion 17p – resistant to fludarabine and DNA alkylating agents	Ibrutinib (BTK inhibitor) Clinical trials
Relapsed refractory disease	High dose combination chemo regimens B cell receptor signaling Role of stem cell transplant is unclear

Clinical Case, continued

81 year-old male with h/o hypertension and hyperlipidemia presents to his primary care physician to reestablish care. He offers no complaints.

Physical exam is notable for palpable spleen. Routine laboratory studies reveal a WBC of **121,000** with a differential of 5% granulocytes, 94% lymphocytes, and 1% monocytes. Hgb 12 and platelets were 280.

Flow cytometry of the patient's peripheral blood demonstrates a population of CD5+, CD10-, CD19+, CD23+ **B cells**.

Cytogenetics demonstrates multiple abnormalities, including deletion 17p

Rai Stage II (splenomegaly on exam) with high risk cytogenetics

Clinical Case, continued

Close active surveillance was recommended and the patient remained asymptomatic with preserved counts

Over 6 months – worsening lymphocytosis (130 -> 200) and anemia (hgb 9).

Ibrutinib recently started due to del17p status

CLL (indolent NHL in general): Key Points

- CLL is a disease of mature but functionally incompetent CD5+ CD10- CD19+ CD23+ B cells

- Incidence rises sharply after the age of 60

- Asymptomatic patients are managed with active surveillance and decision to treat with lymphoma-directed therapy is based on symptomatic or progressive disease.

- Currently incurable, but new agents are generally well tolerated and show promise in offering durable responses to patients with previously high risk disease

    - Rare SLL patient presenting with limited stage disease may be cured with radiation (similar for early stage nodal indolent NHL)

Chronic Lymphocytic Leukemia: Key Points

- CLL is a disease of mature but functionally incompetent CD19+ CD5+ CD 23+ B cells.

- Incidence rises sharply after the age of 50.

- The natural history of CLL is extremely variable and unpredictable. Some patients will live a normal lifespan and other will die from complications of their disease within 2 years.

- There are numerous prognostic markers including cytogenetics, IgVH mutational status, CD38 and ZAP-70 expression.

- Early stage patients are managed with 'watchful waiting' and decision to treat with chemotherapy is based on symptomatic or progressive disease.

- Currently incurable, but new agents show promise.

The practical way to think of lymphoma (and cancers in general)

Is it curable?

- Yes
  - Aggressive lymphomas (large cell lymphomas)
    - DLBCL
    - Burkitt lymphoma
    - Hodgkin lymphoma
    - Some T cell lymphomas (ie. anaplastic large cell)

- No
  - Indolent lymphomas (small cell lymphomas)
    - Follicular
    - CLL
    - Marginal zone, lymphoplasmacytic
    - Some T cell lymphomas (ie. cutaneous T cell)
    - *Mantle cell (non curable, but frequently clinically aggressive)*

A practical way to think of lymphoma

Category		Survival of untreated patients	Curability	To treat or not to treat
Non-Hodgkin lymphoma	Indolent - follicular - CLL/SLL	Years	Generally not curable	**Defer treatment**
	Aggressive - mantle cell - multiple myeloma	Months	Curable in some	Treat
	Very aggressive -diffuse large B cell -Burkitt	Weeks	Curable in some	Treat
Hodgkin lymphoma	All types	Variable – months to years	Curable in most	Treat

CLL/SLL Treatment

- Observation
- Chemotherapy:
  - FCR
  - BR
  - Ibrutinib(17p del)
  - Idelalisib
  - Venetoclax
  - Clinical trial

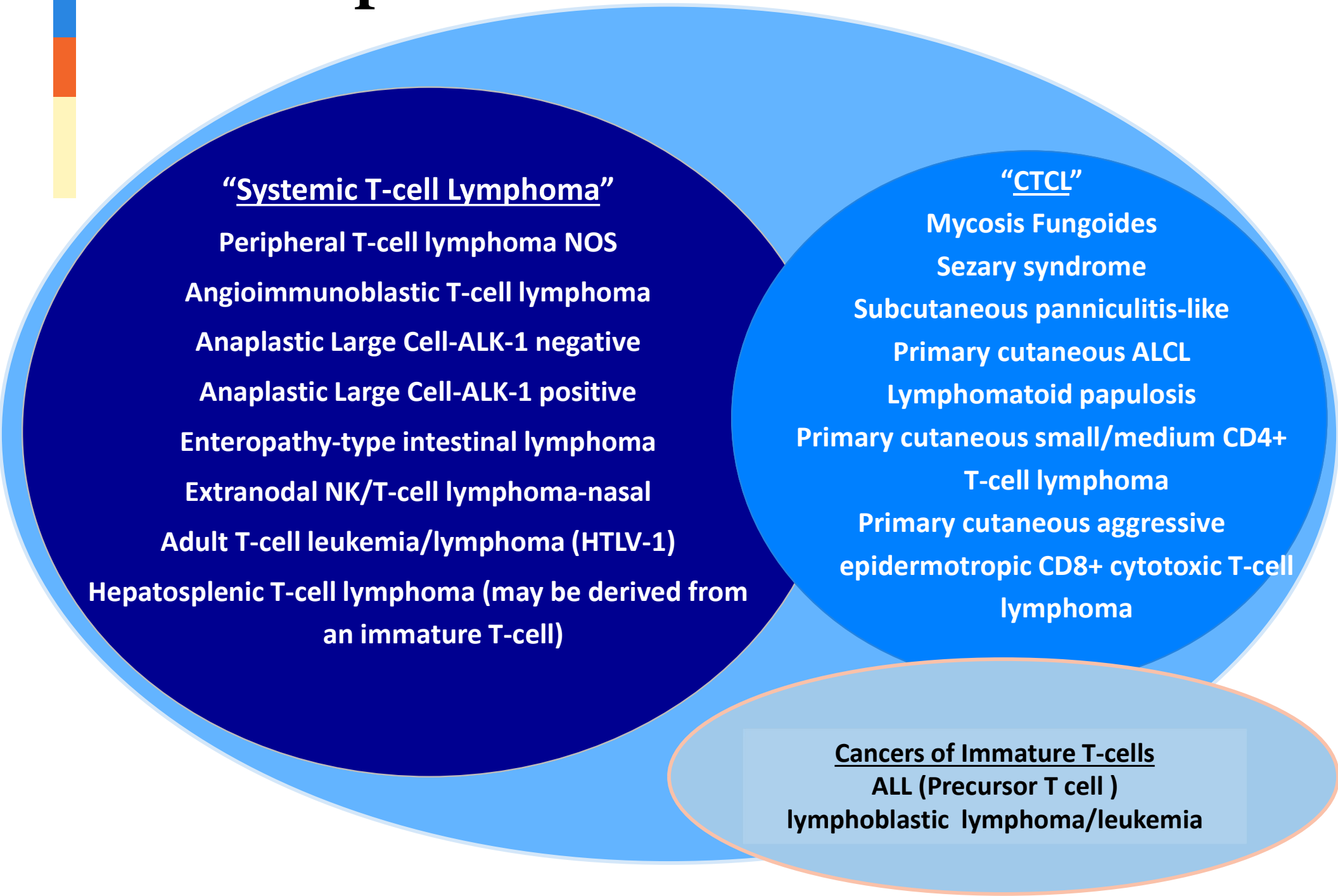
Marginal zone

- Consists of 3 diseases: Extranodal(MALT), Nodal and Splenic
- Some subtypes are a consequence of chronic infection/inflammation
  - H. pylori, Borrelia burgdorferi, Hepatitis C, Chlamydia psittaci, Campylobacter jejuni
  - Autoimmune d/o: Sjogren's, Hashimoto thyroiditis

MZL treatment

- Observation
- Radiation
- Systemic therapy
  - Rituximab
  - Ibrutinib
  - Clinical trial

T-Cell neoplasms



T-cell Lymphoma

- 10-15% of all NHL cases
- Systemic T cell neoplasms
  - Disease involved in lymph nodes, extranodal organs and/or skin
  - Typically aggressive in nature
- Cutaneous T cell lymphoma (CTCL)
  - Disease confined to the skin only
  - Typically indolent in nature

T cell lymphoma treatments

Systemic treatment

- Biologic response modifiers
- HDAC inhibitors
- Extracorporeal photopheresis (ECP)
- Methotrexate
- Steroids
- Targeted therapy
- Chemotherapy
- Allo transplant?

Topical treatment

- Steroids
- Topical chemotherapy
- Local radiation
- Topical retinoids
- Phototherapy (UVB/PUVA)
- Topical immune response modifiers (imiquimod, resiquimod)
- Phototherapy (UVB/PUVA)
- Total skin electron beam therapy (TSEBT)

Relapsed/Refractory disease

- Relapsed: disease recurs after an initial complete remission
- Refractory: disease less than 50% decrease in size with treatment.
- Progressive disease: new lesion or >50% increase in a previous lesion on treatment
- Treatment
  - Salvage chemotherapy followed by auto or allo transplant
  - Clinical trial

Chemotherapy Regimen Side Effects

- RCHOP
  - Fatigue
  - Fever/febrile neutropenia
  - Infusion reaction
  - Nausea/vomiting
  - Tumor lysis(TLS)
  - Neuropathy
  - Constipation
  - Hair loss
  - Cardiotoxicity
- ICE
  - Neurotoxicity
  - Nausea/vomiting
  - Nephrotoxicity
  - Myelosuppression
  - Hemorrhagic cystitis
- R-Benda
  - Fatigue
  - Myelosuppression
  - Rash
  - Nausea/vomiting
- Lenalidomide
  - Thromboembolic events
  - Fatigue
  - Rash
  - Diarrhea
  - Thrombocytopenia/neutropenia

Chemotherapy Regimen Side Effects

- ABVD
  - Neutropenia
  - Nausea/vomiting
  - Constipation
  - Alopecia/hair thinning
  - Pulm toxicity
  - Cardiotoxicity
- Ibrutinib
  - Fatigue
  - Rash
  - Diarrhea
  - Thrombocytopenia
  - Afib
  - Bleeding
- Brentuximab
  - Edema
  - Peripheral neuropathy
  - Rash
  - Diarrhea
  - Neutropenia
  - Pneumontis
- http://ssddpweb1:9068/intranet/shared/pharmacy/guidelines/index.htm

Emerging Immunotherapies and treatment Paradigms