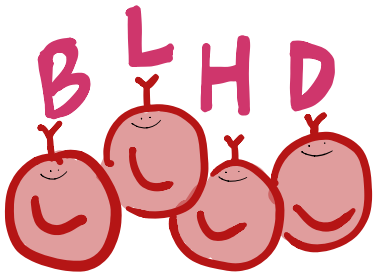


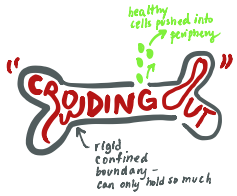
BLHD WEEK 5

malignant HEMATOLOGY
FIRSTAID p.417-422

This Week:
- AT Intro to Malignancies
- AT Multiple Myeloma
- AT Lymphomas
- AT CLL
- AT ALL
- AT Immunotherapies

malignant HEMATOLOGY

issues in uncontrolled proliferation (esp of immature clone)
inappropriate survival



malignant system OVER POWERS normal system

symptoms of poorly functioning hematologic system

ddx DIFFERENTIAL

ABNORMAL BLOOD COUNTS due to
- PRODUCTION PROBLEM: not enough normal cells forming (cells that are lazy)
- DESTRUCTION PROBLEM: immune attack in the periphery
- SEQUESTRATION PROBLEM: spleen issues (crowding out d/t excess malig cells)

+ CLINICAL TOOLS

- TdT → T: CD2 CD3 CD4 CD5 CD6 CD7 CD8 (NEVER CD10)
- TdT → B (pre-B cell): CD10 CD19 CD20 CD22
- MPO → myeloid precursor: CD13 CD33 CD34 CD117
- ? accumulation of this protein leads to what classic finding on histology?

blood flow CYTOMETRY
analysis of cell surface markers
fluorescent antibody tags marker of interest
separation of markers
T+ cell population aka lymphoblasts
fluorescent antibody tags

KARYOTYPE
analysis of chromosomal abnormalities
dividing cells necessary

FISH
presence of known/expected chromosomal abnormalities

MUTATION ANALYSIS
presence of known/expected mutations

PCR

PERIPHERAL blood smear

FINE NEEDLE ASPIRATION

BONE MARROW BIOPSY (GOLD STANDARD) → BE ABLE TO IDENTIFY FROM PHOTOS!

LYMPH NODE BIOPSY

SPEP
MM

+ CLINICAL SX

RBC counts

anemia
SHORTNESS OF BREATH
FATIGUE
DIZZINESS

erythrocytosis
STASIS/VISCOSITY d/t BLOCKAGE
PLETHORA, CONFUSION
"reddish complexion"

thrombocytopenia
MUCOSAL BLEEDING (GUMS/EPISTAXIS)
PETECHIAE/PURPURA

neutropenia
MOUTH SORES
INFECTIONS (RECURRENT)

ORGAN INFILTRATION moves from blood → TISSUES
BONE PAIN
SPLENOMEGALY
GUM HYPERPLASIA

ABNORMAL IMMUNOGLOBULIN
→ RISK FOR INFECTION (loss of antibody diversity)
HYPOGAMMAGLOBULINEMIA

"constitutional" B symptoms
fever
night sweats
weight loss (unintentional)

FIXED FIRM LN

CANCER
excess cell division

LYMPHADENOPATHY

THEME: homogeneity ≅ monotony monoclonality ≅ CANCER
AS WITH ALL THINGS LACK OF DIVERSITY IS PROBLEMATIC!

MULTIPLE MYELOMA

a monoclonal gammopathy

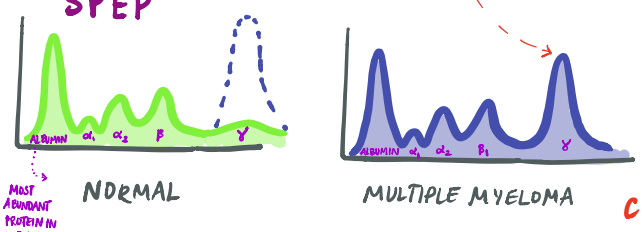
abnormal plasma cell clone → excess immunoglobulins in serum + urine → organ damage, systemic complications d/t buildup

IgG 55% or IgA 25%

monoclonal M spike

SPEP

γ spike



MOST ABUNDANT PROTEIN IN BODY

NORMAL

MULTIPLE MYELOMA

monoclonal gammopathy of undetermined significance (MGUS)

← ASYMPTOMATIC BUT HAS M-SPIKE ON SPEP

can progress

smoldering multiple myeloma (SMM)

can progress

multiple myeloma (MM)

Classic MM SX

- Bence Jones proteinuria — LIGHT CHAINS IN URINE
- Roleaux formation — "STACKED COINS"
- C — hypercalcemia
- R — renal involvement — LIGHT CHAINS ACCUMULATE, CLOG TUBULES
- A — anemia — COATING — normal cell production impaired
- B — "punched out" Lytic Bone lesions — SKULL "moth eaten" VERTEBRAE

susceptible to infections d/t lack of antibody diversity

HYPOGAMMAGLOBULINEMIA

hyperviscosity

t(4;14)
t(14;16)
17p- deletion

Other monoclonal gammopathies

AL amyloidosis (LIGHT CHAIN)

underlying abnormal clone → excess production → free light chains (unstable) → deposition in tissues → ORGAN DAMAGE

AMYLOID (β-pleated sheets)

- heart
- kidney
- periorbital purpura
- macroglossia
- nail dystrophy

dx apple green birefringence when stained w/ CONGO RED & under polarized light

Waldenstrom's macroglobulinemia

(IgM)

no C.R.A.B sx

hyperviscosity syndrome
- blurred vision
- Raynaud's

POEMS

- polyneuropathy
- organomegaly
- endocrinopathy
- monoclonal protein
- skin changes

solitary plasmacytoma

NEURO FIBROMATOSIS — DOWN SYNDROME — ATAXIA TELANGIECTASIA

ALL

ACUTE LYMPHOBLASTIC Leukemia

immature

in the blood

affects kids (adults w/ ALL → bad prognosis)

>20% lymphoblasts in bone marrow + blood

associated w/ DOWN SYNDROME (TRISOMY 21) (XXX) usually onset after 5 Y.O

CLASSIFICATION: based on surface markers

Tdt+ LYMPHOBLAST MARKER should be absent in mature lymphocytes

- T-ALL — CD2 CD3 CD4 CD5 CD6 CD7 CD8 (NEVER CD10)
  - ✓ teens can present w/ mediastinal mass - "acute lymphoblastic LYMPHOMA"
  - SVC-like syndrome
- B-ALL (MORE COMMON) — PRE-B CELL — CD10 CD19 CD20 CD22

PROGNOSIS: based on cytogenetic analysis

t(12;21) more favorable prognosis seen in kids

t(9;22) (Philadelphia chromosome) less favorable prognosis seen in adults (can use IMATINIB) — OHSU

CHRONIC LYMPHOCYTIC Leukemia

CRUSHED LYMPHOCYTES

"SMUDGE CELL" ON HISTOLOGY

mature

in the blood

aka SLL small lymphocytic leukemia

MOST COMMON ADULT LEUKEMIA in WESTERN "WORLD"

elderly adults (72 Y.O)

(>5K in blood)/uL = lymphocytosis

not curable w/ std chemotherapy

high risk of infxn (bact) as cause of mortality

CD5+, CD19+, CD20+, low levels of surface Ig w/ κ or λ restriction

SX: Lymphadenopathy

splenomegaly, hepatomegaly

ecchymosis, petechiae, AIHA

HYPOGAMMAGLOBULINEMIA

cytopenias → infection

RICHTER transformation → can progress to DLBCL (AGGRESSIVE)

- → abrupt clinical deterioration
- → elevated LDH
- → hypercalcemia
- → LAD progressive

cells on P.B.S larger, more cytoplasm

α RNP

SJOGREN'S SYDROME

..... unilateral growth of one of the bilaterally enlarged parotid glands late in disease course

means has progressed into → B cell lymphoma

CD18- L.A.D deficiency (integrin β-2)

EBV tropism of B cells

CD21-

CD14- monocyte/ lineage macrophage

Lymphomas

ORIGINATE in Lymph nodes, also likely in spleen, extralymphatic tissue

FIXED
FIRM
LN (1 or more)
>2 cm
CONCERNING!

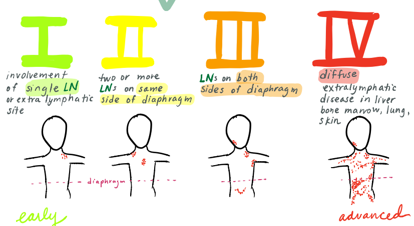
"constitutional" B symptoms
- fever
- night sweats
- weight loss (unintentional)

CANCER

dx: excisional biopsy of LN
- IHC
- flow CYTOMETRY } identify CD markers
- FISH } identify chromosomal translocations

prognosis determined by ANN ARBOR STAGING → PET/CT
this also guides/informs treatment strategy

- A = no B symptoms
- B = B symptoms present!
- E = extra nodal continuous extension
- X = bulky mass >10 cm, >1/3 transverse thorax diameter



? A man comes into clinic w/ complaints of fever, 15-lb weight loss, fatigue. He also wakes up drenched in sweat. Upon exam you observe LAD of cervical and axillary lymph nodes, 4cm each. No other LAD observed on PET/CT.

What is his Ann Arbor staging score?

A. II A
B. I B
C. II A
D. II B

T

mature NK cells

MYCOSIS FUNGIODES
- ✓ mature CD4+ in skin
- ✓ rash
- ✓ pautrier microabcess
- ✓ kids
- ✓ hypopigmented macules (rare)

ATLL
reverse transcriptase — found in Japan, Caribbean — HTLV virus
- ✓ mature CD4+ in skin
- ✓ rash (red scaly, pruritic, well demarcated)
- ✓ punched out lytic bone lesions, HSM, hyper Ca2+
- ✓ generalized lymphadenopathy

? What other malignant hematolic condition has this feature? what distinguishes ATLL from it?

B

CD20+

HAIRY CELL LEUKEMIA
TRAP+ — CD103+, CD11+, CD25+ (not much juice)
- adult males
- mature B cell proliferation, typically no lymphadenopathy
- marrow fibrosis
- "DRY TAP" on bone marrow d/t fibrosis
- splenomegaly, pancytopenia
- BRAF mutation

tx: cladribine — ? what is mechanism? what 3° immunodeficiency would cause cladribine induce?

CLL
CD5+ CD23+ — RICHTER transformation → can progress to DLBCL — AGGRESSIVE cells on PBS larger, more cytoplasm

C(rushed) L(il') L(ymphocytes)

"SMUDGE CELL" ON HISTOLOGY

CHRONIC LYMPHOCYTIC Leukemia — in the blood
MOST COMMON ADULT LEUKEMIA — elderly adults
malignant mature B cell proliferation
tx: alemtuzumab (CD52)

~HIV autoimmune

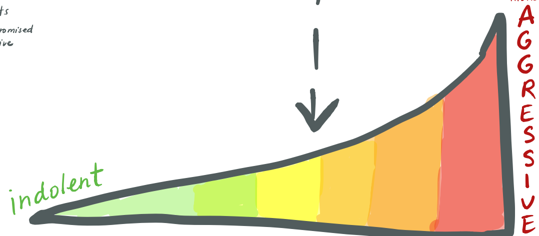
40% → HODGKINS (Epstein-Barr virus)
60% → NHL

CHL
CD15+ CD30+
owl eye nuclei = Reed-Sternberg cells
mostly inflammatory cells comprise tumor, release cytokine storm, causing sx
alcohol-induced pain
tx: ABVD

- NS CHL: ✓ young females ✓ mediastinal, neck LYMPH NODES ✓ fibrosis (sclerotic) around LNs ✓ lacunar cells — lots of space surrounding R. Sternberg cells
- MC CHL: ✓ adults ✓ IL-5 eosinophilia ✓ immuno compromised
- LR CHL: ✓ best prognosis
- LD CHL: ✓ elderly ✓ HIV+ patients ✓ immuno compromised ✓ most aggressive

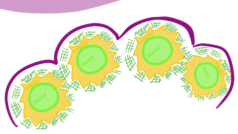
NLPHL
nodular lymphocytic predominance Hodgkin's lymphoma

NHL

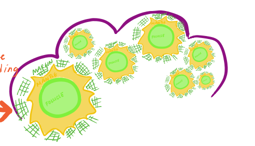


- t(11;18) MZL — marginal zone lymphoma — ∴ chronic inflammation (e.g. Sjogren's) chronic gastritis → MALT lymphoma
- t(14;18) FL — follicular lymphoma — painless "waxing & waning" lymphadenopathy — IgH, Bcl2 (inhibits apoptosis by stabilizing mito membrane) — tx: rituximab α CD20 — not curative
- t(11;14) MCL — mantle cell lymphoma — CD5+ — tx: bortezomib, carfilzomib — IgH, CCND1 (cyclin D1, cell cycle promoter)
- DLBCL — diffuse large B cell lymphoma — Bcl-2, Bcl-6 alterations — HIV+ — most common NHL in adults CD20+ — tx: R-CHOP
- t(8;14) Burkitt's lymphoma — Epstein-Barr virus — ON HISTOLOGY "starry sky appearance" (macrophages) — IgH, c-myc (oncogene/prolif)
  - endemic form: jaw lesion (AFRICA)
  - sporadic form: pelvic or abdomen
  - immunodeficiency-associated: HIV+, solid organ transplant

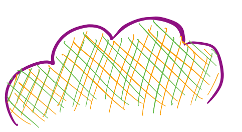
ARCHITECTURE of Lymph Nodes



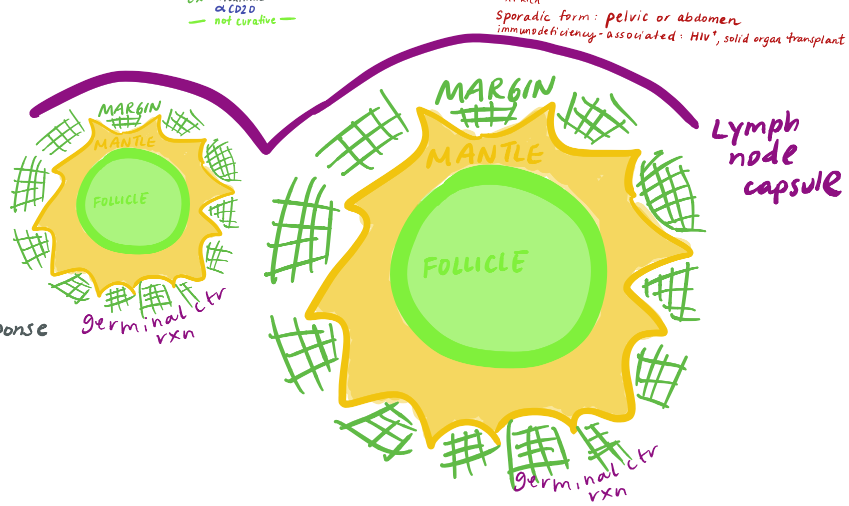
NORMAL LN
follicles all the same size



REACTIVE LN
variably sized follicles/germinal centers d/t antigen recognition + response



DLBCL (lymphoma, NHL)
very homogenous, diffuse sheet → no gradient
homogeneity ≅ monoclonality ≅ CANCER



BE THE MATCH
national registry

BONE MARROW TRANSPLANT

what's the point?

ctrl + alt + delete > RESTART

GOLD STANDARD

Bone marrow (no age limit) = an accessible source of HEMATOPOETIC STEM CELLS

other sources:

- ✓ peripheral blood stem cells
  - G-CSF stimulation 4-5 days before harvest (bone pain side effect)
  - donor must be >12 y.o
- ✓ umbilical cord blood
  - limited by amount
  - more permissive donor matching

INDICATIONS for B.M.T ····> MUST BE SEVERE!

malignancies
- blood: ALL, AML, MDS, CML
- HIGH RISK solid: Relapsed lymphoma, neuroblastoma, sarcoma, brain tumors

severe aplastic anemia
blood congenital disorders
primary immunodeficiencies
inborn errors of metabolism
autoimmune d/o affecting blood
hemoglobinopathies

TYPES of TRANSPLANT

- $$$ 360,000 — autologous — SELF — cryopreserved harvested weeks earlier
- syngeneic — IDENTICAL TWIN
- $$$$$ 800,000 — allogeneic — OTHER (even if family member) — harvested same day used fresh
  - likely will hear auto & allo shorthand...

GRAFT vs HOST DISEASE (GvHD)

MOA: Tissue damage activates HOST APCs which in turn activate donor T cells
skin, gut, liver most commonly affected
acute + chronic forms
excessive incr. cellular + inflammatory mediators
(cytolysis, cytokines)

SX: skin issues
- rash
- dryness
- discoloration
- scleroderma

tx: immunosuppress!!
sirolimus, cyclosporine, etc

IDENTIFY DONOR → PRE-TRANSPLANT EVALUATION → CONDITIONING → DAY0 TRANSPLANT → EARLY PHASE → DAY100 → LATE PHASE

IDENTIFY DONOR: 2 wk - 6 months
PRE-TRANSPLANT EVALUATION: 2 wk - 3 wk
CONDITIONING: 5 - 10 days

- * if malignancy, eliminate residual cancer cells
- * clear out space in marrow to receive new stem cells
- * immunosuppression of recipient T cells (ablation) that can reject new graft
  - RISK of INFXN!

EARLY PHASE
- TOXICITY ↓↓
- RISK OF INFXN
- GRAFT vs HOST DISEASE
- RELAPSE

LATE PHASE

BMT complications

BMT CONDITIONING

Myeloablative REGIMENS
- CYCLOPHOSPHAMIDE + TOTAL BODY IRRADIATION
- CYCLOPHOSPHAMIDE + BUSULFAN

less/non Myeloablative REGIMENS
- BUSULFAN + FLUDARABINE
- MELPHALAN +/- FLUDARABINE
- FLUDARABINE + low dose TOTAL BODY IRRADIATION

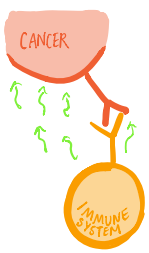
drugs / tx

	MOA	ADR
CYCLOPHOSPHAMIDE	Nitrogen mustard, DNA alkylating	hemorrhagic cystitis (tx: co-admin of mesna), amenorrhea, sterility, pulmonary fibrosis, cardiotoxicity
BUSULFAN	alkyl sulfonate, DNA alkylating	amenorrhea, sterility, pulmonary fibrosis, skin hyperpigmentation, hepatotoxicity, seizures
FLUDARABINE	purine analog, inhibits DNA synthesis	blurry vision, lung failure, pneumonitis, paresthesia
MELPHALAN	Nitrogen mustard, DNA alkylating	hypotension, rash/itching, anaphylaxis, seizures
IRRADIATION TOTAL BODY	kills all rapidly dividing cell at all active phases (no effect on G0)	n/v/d, skin burn/discolored, nerve issues, damaging lower organ toxicity

generally, all regimens cause:
- pancytopenia
- alopecia (hair stem cells)
- nausea/vomiting/diarrhea
- mucositis
- fatigue

IMMUNO THERAPY

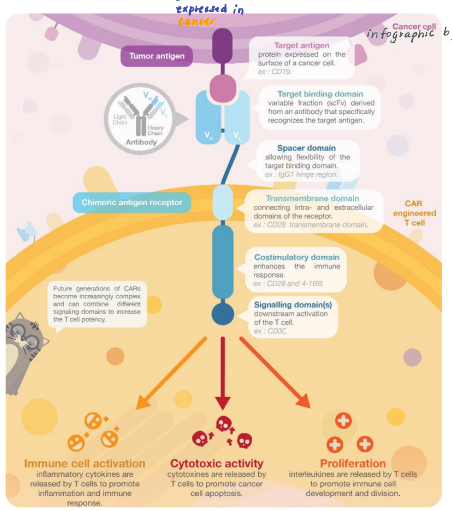
WORK IN PROGRESS!



- gene therapy
- CHIMERIC ANTIGEN RECEPTOR CART therapy

adoptive transfer of autologous T cells genetically modified (CRISPR, likely) to express α CD19 CART into patients

tx: tisagenlecleucel — ADR: cytokine release syndrome - fever, hypotension, poor lung oxygenation
tx: axicabtagene ciloleucel



infographic by Etienne Raimondeau, PhD