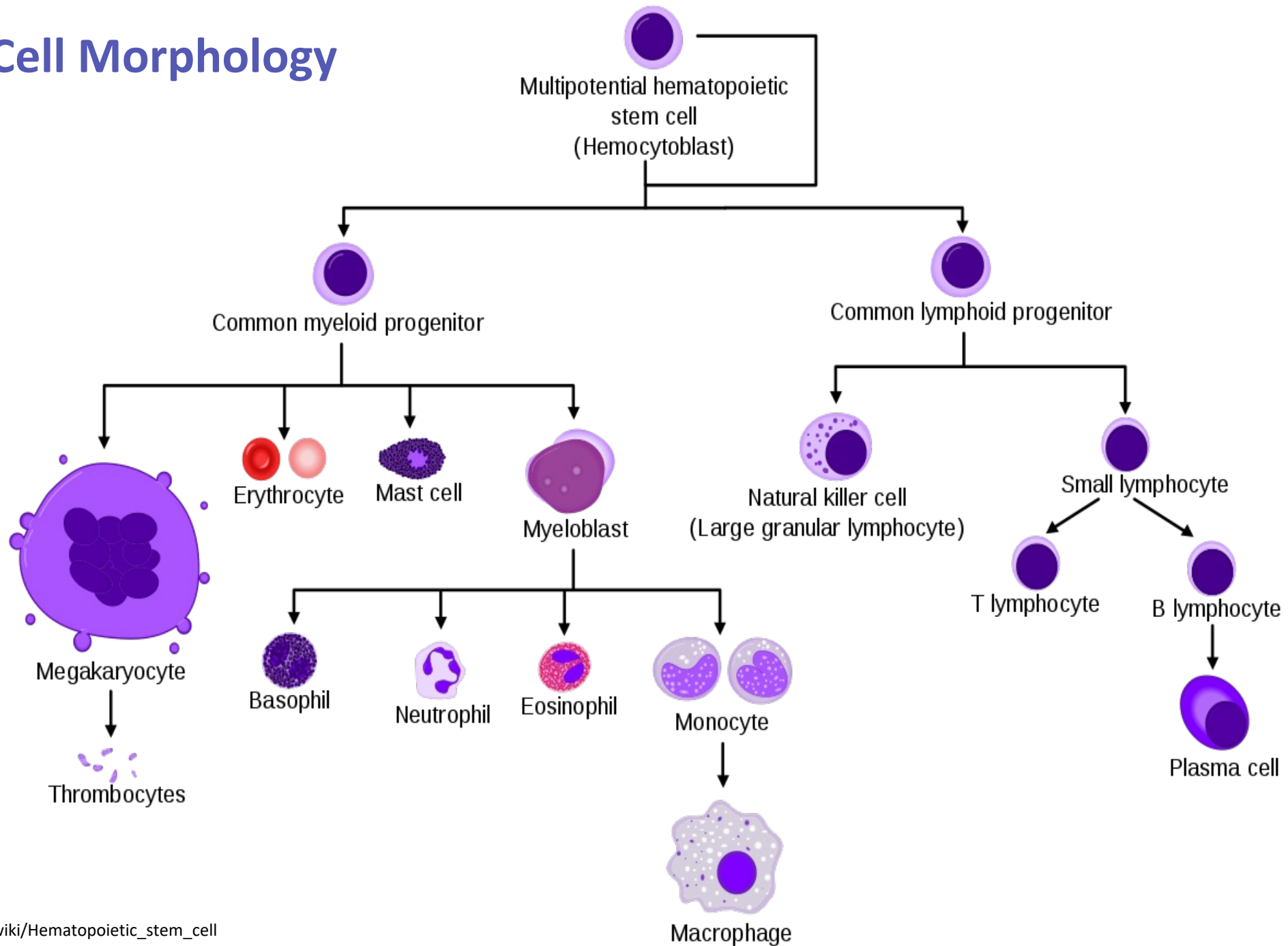


CHRONIC LYMPHOCYTIC LEUKEMIA
Introductory Lecture

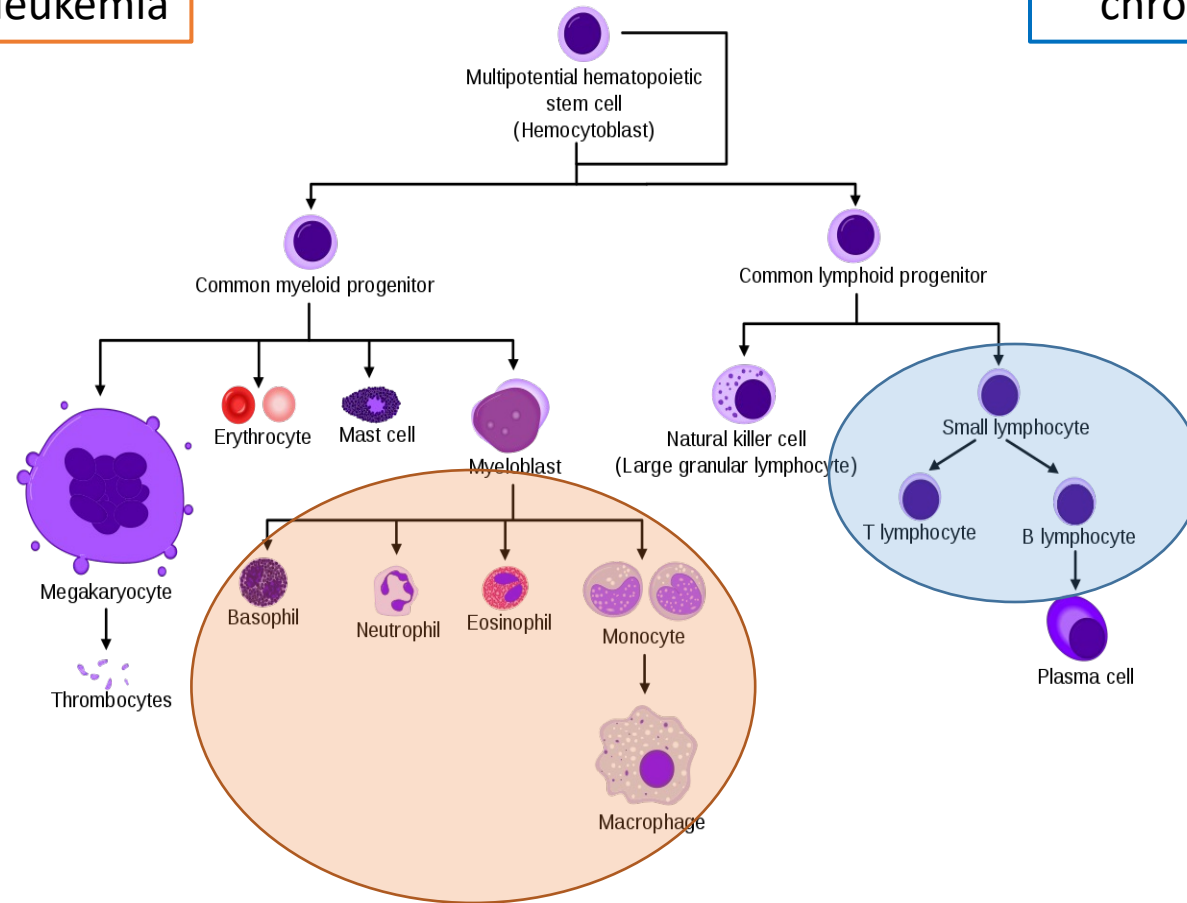
Blood Cell Morphology



Types of Chronic Leukemia

chronic **myelogenous** leukemia

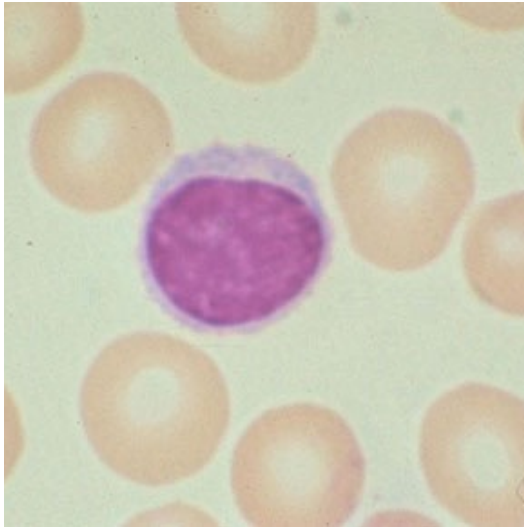
chronic **lymphocytic** leukemia



PERIPHERAL BLOOD SMEARS

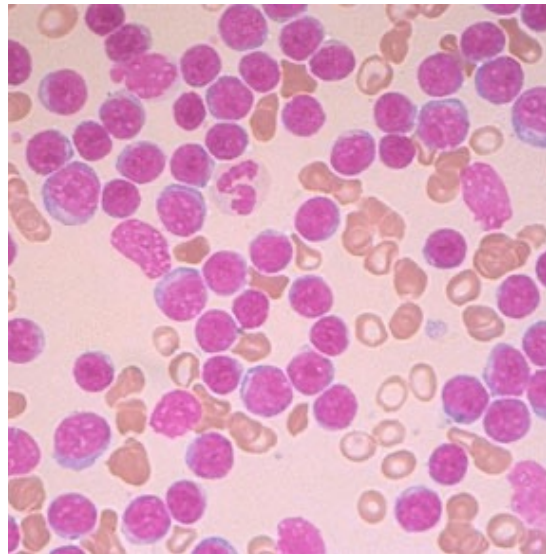
Mature Lymphoid Cells

Mature Lymphocyte

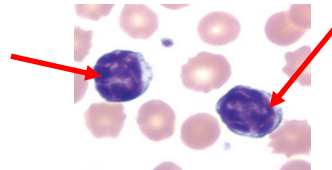


- Size slightly bigger than surrounding RBCs
- Large round/oval nucleus
- Slightly eccentric nucleus
- Thin rim blue cytoplasm

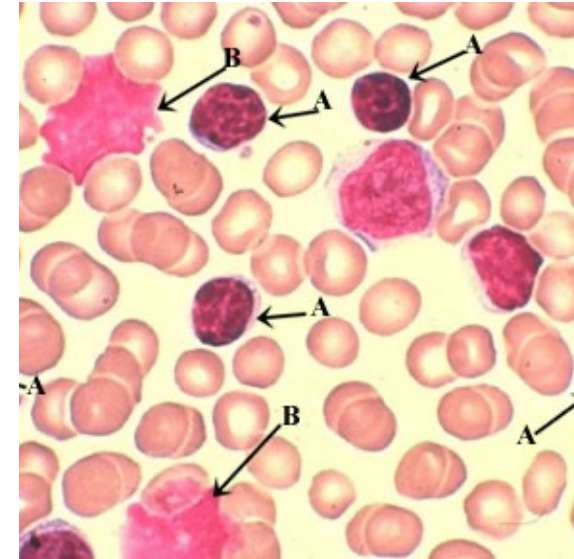
CLL



- Increased number of mature, small lymphocytes
- "soccer ball" chromatin nuclear pattern



Smudge Cells



- (A) mature lymphocytes
- (B) "smudge cells" = nucleus of a disrupted lymphocyte. Smudge cells are smear prep artifacts from friable lymphocytes

Chronic Lymphocytic Leukemia

CLL Pathology & Presentation

Risk Factors

Older age (avg 70s)

Race (White)

Gender (Male)

Family History

Chemical Exposure

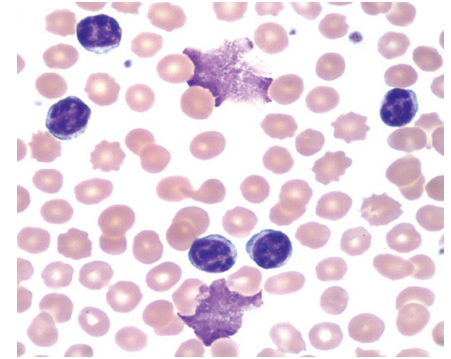


| COMPLICATION | SYMPTOM/LAB FINDING |
|--|---|
| Leukocytosis | Peripheral mature lymphocytosis Smudge cells Fatigue LAD, HSM |
| Anemia Myelophthistic | Fatigue Pallor SOB Peripheral teardrop RBCs |
| Thrombocytopenia Myelophthistic | Petechiae Mucocutaneous bleeding |
| Autoimmune Hemolytic Anemia | + Hemolysis labs + DAT/Coombs Test |
| Hypogammaglobulinemia | Recurrent sinopulmonary infections |
| Richter's Transformation Transformation to lymphoma | Hypercalcemia Rising LDH LAD B-symptoms Pancytopenia |
| Red Cell Aplasia | Anemia |

CLL Diagnosis

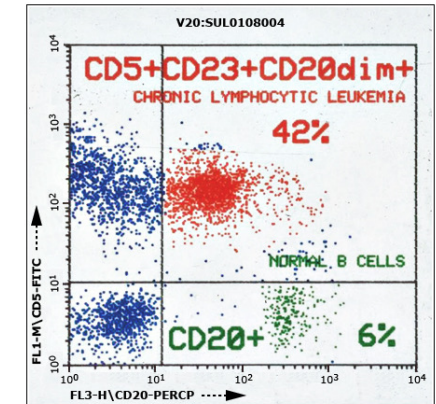
Peripheral Smear

Mature lymphocytes, “soccer ball” nuclear pattern, smudge cells



Flow Cytometry

Monoclonal B cell population
CD5+, CD23+ (CD23 can be negative in atypical CLL)
CD19+, CD20 dim (B-cell markers)
Single immunoglobulin light chain: kappa or lambda
* Don't need bone marrow for diagnosis



Cytogenetics

Del(11q), del(13q), del(17p), trisomy 12

CLL Diagnosis: SLL vs. CLL

SLL = small lymphocytic leukemia

**Monoclonal B-lymphocytes
< 5,000 cells/ul**

CLL = chronic lymphocytic leukemia

**Monoclonal B-lymphocytes
> 5,000 cells/ul**

*** In flow cytometry or lymph node biopsy**

CLL Staging

| Rai Staging System | | OS (years) |
|------------------------------|------------------------------------|----------------|
| Low 0 | Lymphocytosis | > 10 |
| Intermediate I-II | LAD HSM | 7 |
| High Risk III-IV | Anemia Thrombocytopenia | 2 |

| Binet Staging System | | OS (years) |
|----------------------|--|---------------|
| A | < 3 nodal sites Hb >10, plt >100 | > 7 |
| B | > 3 nodal sites Hb >10, plt >100 | < 5 |
| C | Cytopenias Hb <10, plt <100 | < 2 |

CLL Treatment: When to Treat

Asymptomatic



don't treat

Leukocytosis

Symptomatic



treat

Cytopenias

Organ damage

B symptoms

AIHA or ITP

Rapid lymphocyte doubling time

CLL Diagnosis: Risk Stratification

Good Risk

Deletion 13q

IgVH

Prognosis: > 10 yrs

Intermediate Risk

Trisomy 12

Normal cytogenetics

Prognosis: > 8 yrs

Poor Risk

Deletion 11q (ATM)

Deletion 17p (TP53)

ZAP70

CD38+

Prognosis: 2-6 yrs

CLL Pharmacology: Mechanisms of Action

| MECHANISM OF ACTION | DRUGS |
|------------------------|--|
| CD20 Antibodies | Rituximab Obinutuzumab Ofatumumab |
| BTK Inhibitors | Ibrutinib Acalabrutinib Zanubrutinib |
| BCL2 Inhibitor | Venetoclax |
| PI3K Inhibitors | Idelalisib Duvelisib |
| Chemotherapy | Fludarabine Bendamustine Chlorambucil |

CLL Treatment: Pharmacology

no del17

Ibrutinib

Acalabrutinib + Obinutuzumab

Venetoclax + Obinutuzumab

Fludarabine +/- Cyclophosphamide
+ Rituximab (FCR)

Bendamustine + Rituximab (BR)

Pentostatin + Cyclophosphamide +
Rituximab (PCR)

* FCR preferred in IGHV+

Del17/TP53

Ibrutinib

Acalabrutinib + Obinutuzumab

Venetoclax + Obinutuzumab

* Del17p does NOT respond
well to chemotherapy

Old/Poor PS

Ibrutinib

Acalabrutinib + Obinutuzumab

Venetoclax + Obinutuzumab

Chlorambucil + Obinutuzumab

CLL Pharmacology: Notable Side Effects

Ibrutinib

side effects

Afib

Anti-platelet effect

Peripheral lymphocytosis

Diarrhea

Rash

*** Acalabrutinib has lower risk of afib**

CLL Complications Management

| COMPLICATION | MANAGEMENT |
|------------------------------------|--|
| Leukocytosis | <ul style="list-style-type: none">• No need to treat if asymptomatic otherwise• Rare to get leukostasis with small mature cells• Lymphocyte doubling time can be indication for treatment |
| Anemia | <ul style="list-style-type: none">• Transfusions• Growth factor support (EPO) |
| Thrombocytopenia | <ul style="list-style-type: none">• Transfusions• Growth factor support |
| Autoimmune Hemolytic Anemia | <ul style="list-style-type: none">• Start systemic treatment• Consider steroids |
| Hypogammaglobulinemia | <ul style="list-style-type: none">• Monthly IVIG if IgG < 500 mg/dL |
| Richter's Transformation | <ul style="list-style-type: none">• Treat as lymphoma |

CLL Review Handout

CLL Diagnosis

Peripheral Smear

Mature lymphocytes, "soccer-ball" nucleus, smudge cells

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CLL = chronic lymphocytic leukemia

Monoclonal B-lymphocytes
> 5,000 cells/mcl

CLL Risk

Good Risk

Intermediate Risk

Poor Risk

Deletion 13q

Trisomy 12

Deletion 11q

IgVH

Deletion 17p
(TP53)

CLL Staging

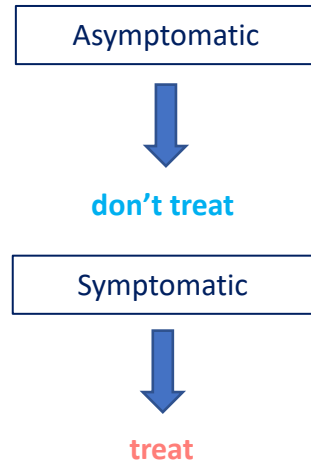
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CLL Symptoms

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no del17

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Old/Poor PS

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Acalabrutinib + Obinutuzumab

Venetoclax + Obinutuzumab

Chlorambucil + Obinutuzumab

CLL Drug Side Effects & Complications

Ibrutinib

Afib
Anti-platelet effect
Peripheral lymphocytosis
Diarrhea
Rash

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