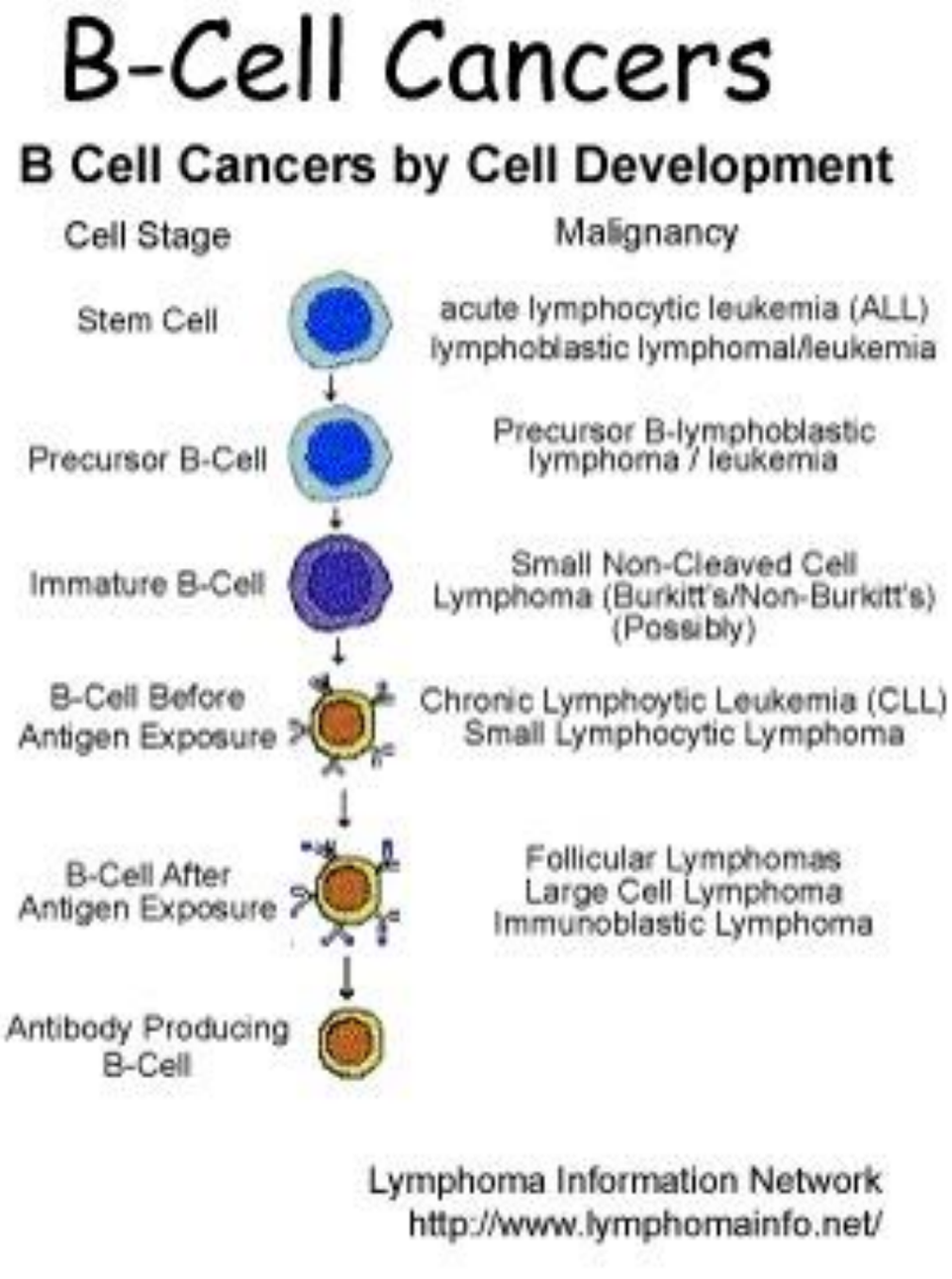
Lymphoma, Leukemia and Multiple Myeloma

Non Hodgkin's Lymphoma (NHL)

- Definition: Neoplasm of lymphoid origin
- B cell (80%)/T cell
- lymph nodes, solid tumor, blood, bone marrow, skin
- Many types: Burkitts, DLBC, hairy cell leukemia, cutaneous T cell
- Type is based on clonal proliferation of cells in a certain developmental stage



NHL

- **Incidence**
- All ages but risk increases with age
- M>F
- 5th most commonly diagnosed cancer
- Increasing in incidence

- **RISK FACTORS**
- Family Hx
- Immunosuppression immunodeficiency
- Prior radiation
- Some chemo/medication (methotrexate)
- Connective tissue disease
- Most patients have no known cause

NHL
Clinical Manifestations

Systemic

- B symptoms: wt loss, night sweats, fever
- Fatigue
- Anorexia
- Cytopenias/bone marrow infiltration

Local

- Lymphadenopathy
- Splenomegaly
- Sx dependent ion site of infiltration: CNS, spinal cord compression, ascities, plural effusion, etc

Symptom presentation can vary widely

Asymptomatic to severely ill

Develop over weeks, months or years

Lymphadenopathy

- Concerning lymphadenopathy consists of palpable nodes that are Firm, Fixed and Painless
- "Painless." can be painful depending on size and location
- Indolent lymphomas often have waxing and waning lymphadenopathy
- Benign nodes are mobile/non fixed, soft, painful
- Differential: normal variant, infection, malignancy

NHL
Diagnosis

Excisional lymph node biopsy!!
Pathology review

If non diagnostic....rebiopsy

FNA is not good enough!

NHL Staging

Stage	Definition
I	present in 1 lymph node
II	Present in several lymph nodes either all above or all below the diaphram
III	In lymph nodes both above and below the diaphram
IV	In lymph nodes across all areas and spread to at least one organ

NHL

- There are many types of NHL
- They are grouped into categories of indolent, aggressive and very aggressive and treatment is influenced by the category
- Prognosis is based on the type of lymphoma and the international prognostic scoring system for NHL

Category	Prognosis if untreated	Curability	To treat or not to treat
Indolent	Years	Not curable	Only treat if symptomatic
Aggressive	Months	Some curable	Treat
Very aggressive	Weeks	Some curable	Treat

Follicular Lymphoma

Follicular Lymphoma General Characteristics

- Second most common NHL
- Indolent B cell lymphoma
- Often asymptomatic
- Most stage 4 at diagnosis
- **Considered non curable but can have remission**
- Average prognosis 10 years depending on Cytogenetics
- May transform into DLBCL
- **<u>Pathology Characteristics</u>**
- T(14;18), bcl2 overexpression
- Closely packed follicles with cleaved cells. Lacks "light and dark" areas of typical follicle

Follicular Lymphoma Treatment

- If stage 1/2: radiation, +/- chemo depending on the individual case
- If stage 3/4, **treat only if symptomatic**
- Standard first line therapy is combination chemo called R-CHOP
- Post treatment CT or PET compared to baseline to assess response

Diffuse Large B Cell Lymphoma (DLBCL)

DLBCL
General Characteristics

- most common b cell lymphoma
- Is a type of NHL
- aggressive, most stage 3/4 at diagnosis
- 70% remission, 50% cure rate
- Should be treated
- **Pathology characteristics:**
- 2-5x normal size lymphocyte
- Diffuse growth pattern

DLBC Treatment

- **Should be treated**

- Standard first line chemo RCHOP x 6-8 cycles (rituximab, cyclophosphamide, doxorubicin, oncovin, prednisone)

- Intrathecal methotrexate x 4 cycles if CNS involvement

- Radiation can be considered for localized control or early stage

- PET CT post 3 cycles and post 6-8 cycles of chemo to asses response compared to baseline.

Hodgkins Lymphoma (HL)

HL
General Characteristics

- Discovered by Dr. Thomas Hodgkin in 1830s
- Cancer of Precursor B cell
- Distinctive clonal **Reed-Sternberg cells** (large and multilobed)
- 85% cure
- Typically occurs in teenagers or young adults
- Several subtypes

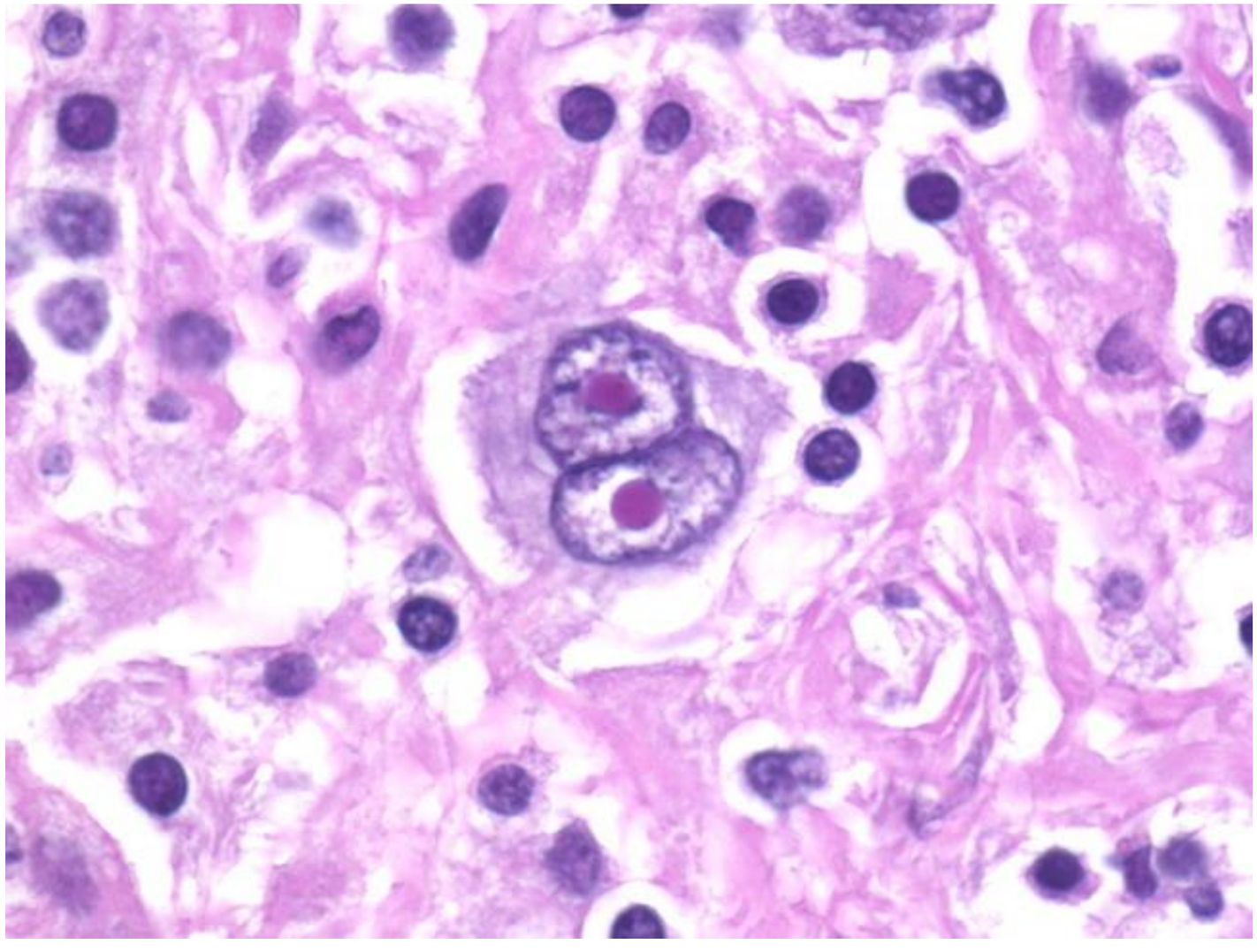


Image from web pathology
http://www.webpathology.com/image.asp?n=5&Case=388

Type	Features	Frequency
Modular sclerosing (classical)	Bands of fibrosis Reed-Sternberg cells	Most common type 60-80% F>M
Mixed cellularity (classical)	Many different cells	Older adults 10-15%
Lymphocyte rich (classical)	Reactive lymphocytes Reed-Sternberg cells	Uncommon Older adults
Lymphocyte depleted (classical)	Reed-Sternberg cell and variants	Rare
Lymphocyte predominance	Slower growing Few Reed-Sternberg variant cells (+CD20)	Uncommon

Signs and symptoms

- Similar to NHL
- Painless lymphadenopathy
- Usually starts supradiaphragmatic and spreads contigously
- B symptoms
- Cytopenias
- Organomegally

Diagnosis and Staging

- Diagnosis based on Excisional lymph node biopsy

Stage	Definition
I	present in 1 lymph node
II	Present in several lymph nodes either all above or all below the diaphram
III	In lymph nodes both above and below the diaphram
IV	In lymph nodes across all areas and spread to at least one organ

Treatment

- Combination Chemotherapy: ABVDx 4 cycles (adriamycin, bleomycin, vinblastine, dacarbazine)
- Recurrent dz: treated with bone marrow transplant

All Lymphomas
Summary of Management

Type	Indolent NHL	Aggressive NHL	Hodgkin's lymphoma
Early stage	RT	R-CHOP +RT	ABVD +RT
Advanced stage	No sx: observation Sx: chemo alone Chemo +R R alone	R-CHOP	ABVD
Relapsed	Different chemo	Autologous transplant or Different chemo	Autologous transplant

Leukemia

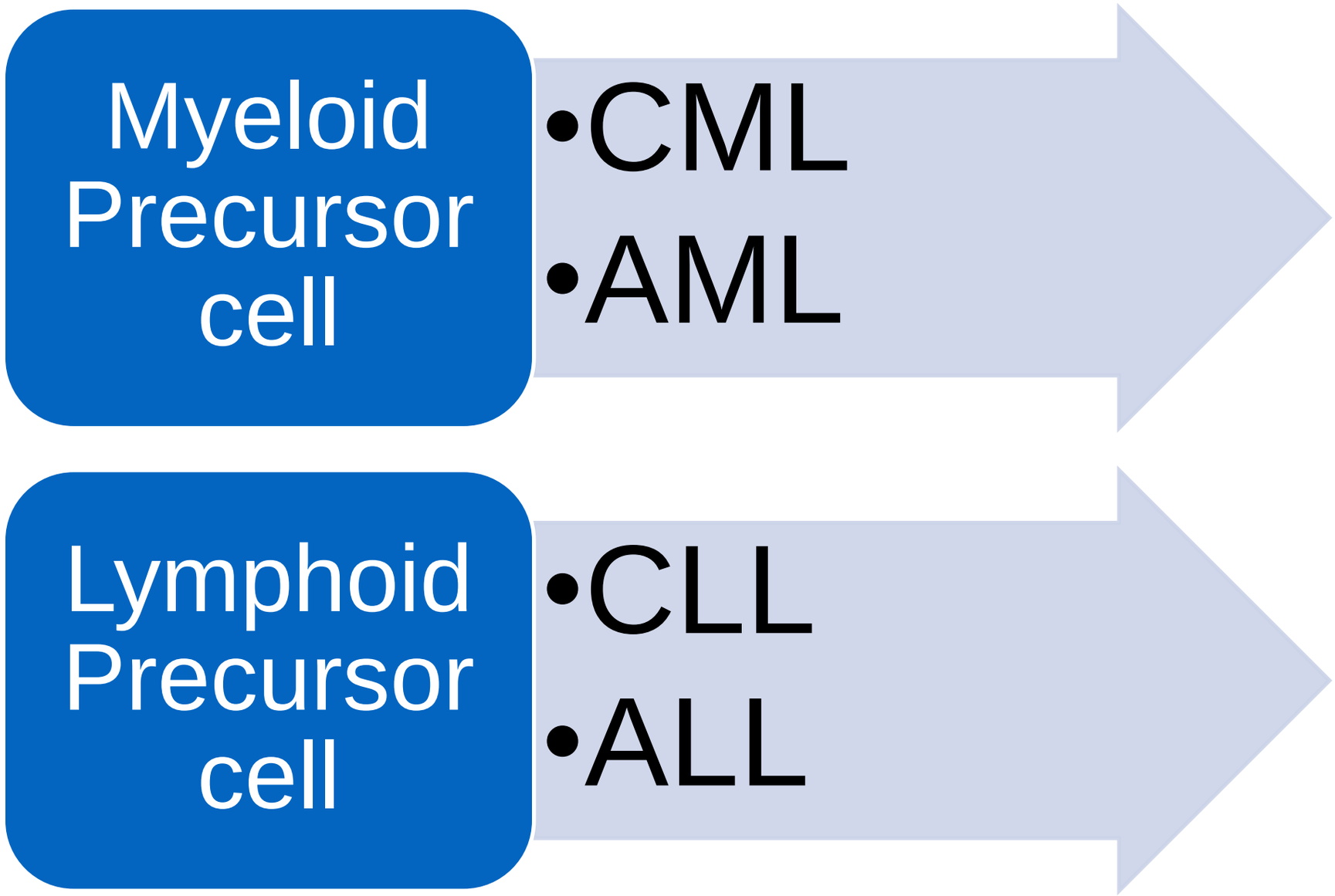
Leukemia

- Leukemia is a malignant disease with unregulated proliferation of one cell type.
- accumulation of blasts in marrow

Chronic: onset can be slower and is usually less aggressive, and the cells involved are usually more mature cells

Acute: onset is rapid, the disease is very aggressive, and the cells involved are poorly differentiated with many blasts.

4 Basic Types



	Acute	Chronic
Age	ALL: kids AML: adults	Adults
Clinical onset	Sudden	Insidious
Course if untreated	<6 months	3-6 yrs
Leukemic cells	Immature blasts>20%	More mature cells
Anemia	Prominent	Mild
Thrombocytopenia	Prominent	Mild
WBC	Variable	Increased
Lymphadenopathy	Mild	Prominent
Splenomegaly	Mild	Prominent

Acute leukemia

<u>Sympoms resulting from</u>:

- Bone marrow failure
- Tissue infiltration
- Leukostasis
- B symptoms

<u>Labs</u>:

- WBC usually elevated but can be normal or low
- Blasts in peripheral blood
- Normocytic anemia
- Thrombocytopenia
- Neutropenia

Diagnosis

- BMbx: necessary for dx. Must have >20% blasts

- AML: Auer rods, cytoplasmic granules

- ALL: no Auer rods or granules.

- Auer rods: elongated needles seen in the cytoplasm of leukemic blasts cells

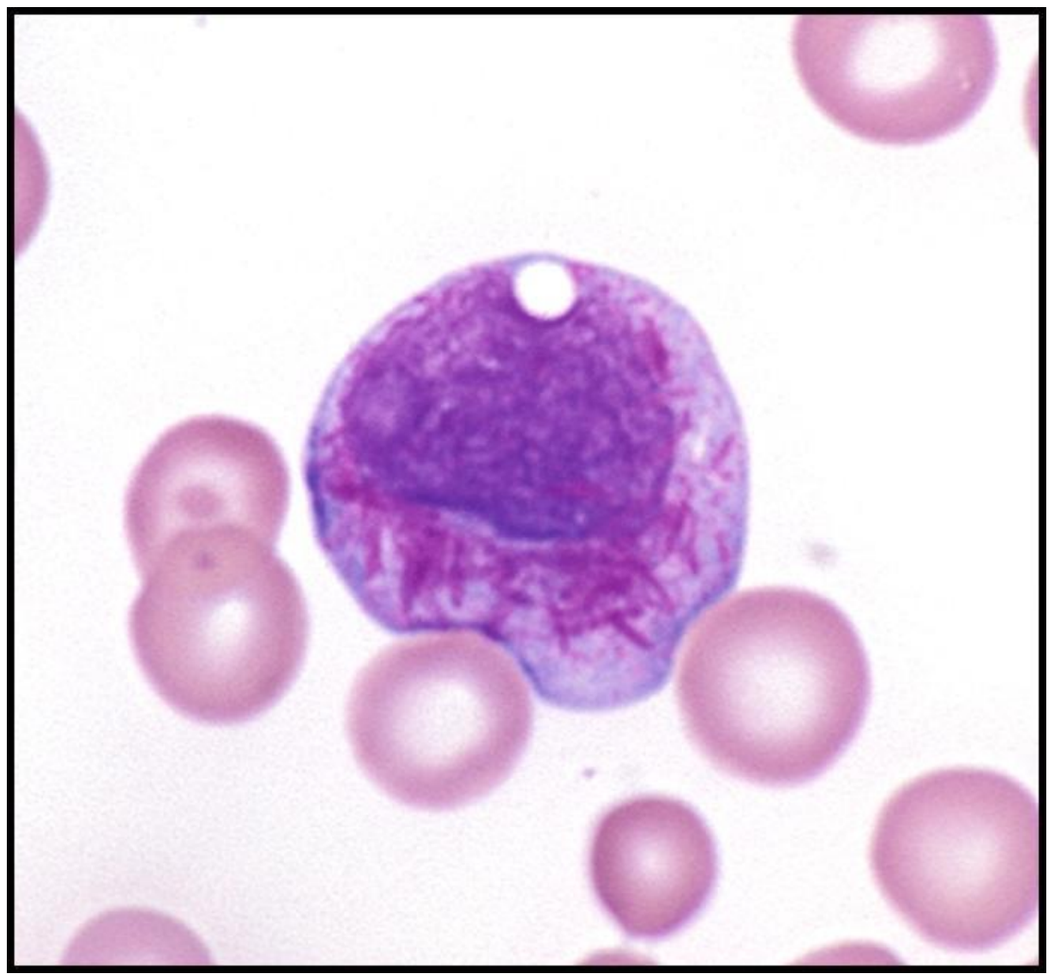


Image Source https://www.pathologystudent.com/?p=2208

Treatment

- Combination of chemo, Radiation therapy and Stem cell transplant (SCT)
- SCT: source of stem cells can be blood, bone marrow, umbilical cord blood
- Autologous, allogenic, Syngenic

SCT

- Autologous stem cell transplants are preferred when possible as allogeneic stem cell transplants have a higher risk
- Only those under age 65 will be considered in Canada
- Patient first receives chemotherapy to reduce the number of circulating cancer cells
- Stem cells are then harvested from the patient via bone marrow or peripheral blood
- The patient then undergoes high dose chemotherapy to cell death to the bone marrow.
- The patient then receives the transplanted stem cells

CML

- Clonal stem cell malignancy
- >95% have Philadelphia chromosome (ph)
- T(9,22)
- translocation results in the transfer of the Abelson (ABL) on chromosome 9 oncogene to an area of chromosome 22 termed the breakpoint cluster region (BCR).
- results in a fused BCR/ABL gene and in the production of an abnormal tyrosine kinase protein that causes the disordered myelopoiesis

CML Treatment
Gleevec/imatinib

- Tyrosine kinase inhibitor
- Inhibits abl/bcr from phosphorylating proteins and initiating the singnaling cascade for growth leading to apoptosis
- This is targeted therapy, thus SE are minimal. Most common itchy rash, fluid retention
- Due to gleevec, prognosis is close to normal life expectancy. Used to be 3-6 yrs.

CLL

- Myeloproliferative disorder
- Clonal stem cell malignancy affecting lymphocytes
- Can be classified as a lymphoma or leukemia
- Dx: Flow cytometry showing CLL phenotype OR
- Dx: BMbx showing CLL and cytogenetics
- Staging uses the Rai system, not the TNM system

CLL Staging

Rai Stage	Definition	Risk Category
0	Lymphocytosis	Low Risk
I	Lymphocytosis and enlarged lymph nodes	Intermediate Risk
II	Lymphocytosis, splenomegal, lymph nodes enlarged	Intermediate Risk
III	Lymphocytosis and anemia. May have splenomegaly and enlarged nodes	High Risk
IV	Lymphocytosis, thrombocytopenia and enlarged nodes and spleen	High Risk

Treatment

- Chemotherapy is used for treatment
- There are different types of chemotherapy combinations and regiments based on the stage and performance status of the patient.

Multiple Myeloma

MM
General Characteristics

- 2nd most common hematalogic malignancy
- M>F
- Canadian relative 5 year survival rate is 43% according to the Canadian cancer society
- Peak age 65-70 years

MM
Definition

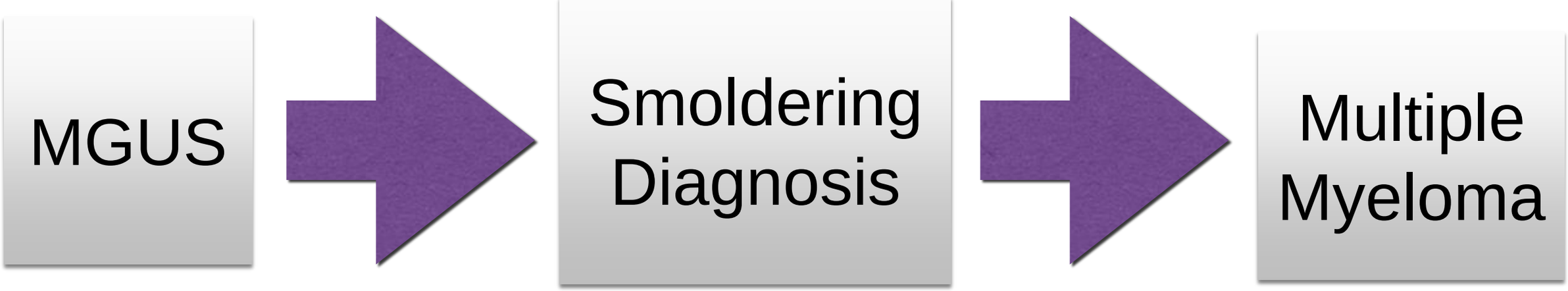
- Multiple myeloma is a malignancy of plasma cells. Abnormal plasma cells accumulate in bone marrow and produce paraproteins and abnormal immunoglobulins.

- Paraprotein M is a common level in MM that can be measured in blood and urine. Serum free light chains measure abnormal immunoglobulins in the blood. These levels are used to aid diagnosis and assess severity and progression of disease.

- The precancerous condition is called monoclonal gammopathy of unknown significance or MGUS. This can turn into MM.

- Smoldering myeloma is an indolent form of MM that has no symptoms. This may turn into active MM

Development of MM



Clinical features

- Bone pain
- Recurrent infections
- Weight loss
- Fatigue
- Fractures
- Hyperviscosity/blood clots
- Neurological symptoms/ hypercalcemia
- Neuropathy

Lab findings

- Anemia, leukopenia, thrombocytopenia
- Renal failure: hypercalcemia, increased Cr, increased uric acid
- Proteinurea and casts
- Elevated B2 microglobulin
- Lytic bone lesions

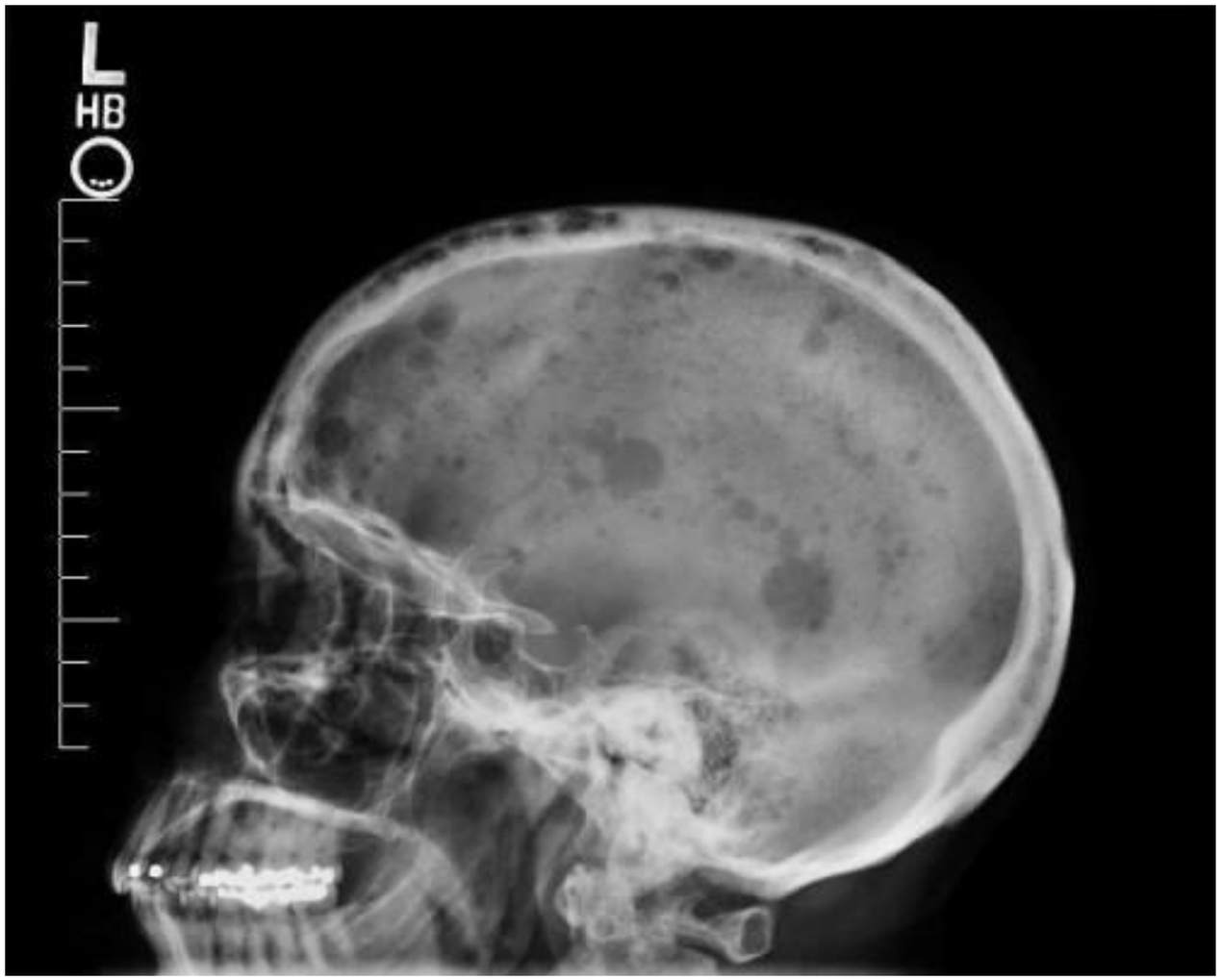


Image Source http://www.myelomapennstate.net/Contents/08a-BoneDis-Eval.htm

Lab Findings

- SPEP/light chains:elevated M protein

Serums protein elecrotphoresis measures immunoglobulin levels

- Bence-Jones protein in urine

Serum light chains measures fragmented and incomplete immunoglobulins that formed light chains only

- IgA, IgG most common. Can be found in blood or urine

Diagnosis	Serum monoclonal protein	Bone marrow	End organ disease	Treatment
MGUS	3g/100ml	<10% plasma cells	None	Observation
Smoldering Myeloma	>3g/100ml	>10% plasma cells	None	Observation
Multiple myeloma	>3g/100ml	>10% plasma cells	Lytic bone lesions, hypercalcemia, renal insufficiency, anemia	Chemo or stem cell transplant

Treatment

- MGUS and Smoldering Myeloma: observation
- Research in Smoldering myeloma is rapidly changing and treatment may become common place
- MM starts with IV bisphosphonate and chemo. If the response to chemo is promising, patients who qualify will undergo autologous stem cell transplant (ASCT). For those who do not qualify, they will receive maintenance chemo
- If MM relapses after ASCT, a second transplant is sometimes considered

Chemo Meds
Bortezomib/Velcade

- Proteasome inhibitor
- binds to the catalytic site of the 26S proteasome
- prevents degradation of pro-apoptotic factors, allowing for programmed cell death in neoplastic cells
- complete clinical responses have been obtained in patients with otherwise refractory or rapidly advancing disease.

Side effects: peripheral neuropathy, GI, increased risk of shingles

Chemo Meds Lenolidamide/Revlimid

- Inhibits angiogenesis
- complete clinical responses have been obtained in patients with otherwise refractory or rapidly advancing disease.
- Side effects: Myelosupression often dose limiting effect, DVT, PE, hepatotoxicity, teratogenic

ASCT

- Autologous stem cell transplants are preferred as allogeneic stem cell transplants have a higher risk and are not standard of care
- Only those under age 65 will be considered in Canada
- Patient first receives chemotherapy to reduce the number of circulating cancer cells
- Stem cells are then harvested from the patient via bone marrow or peripheral blood
- The patient then undergoes high dose chemotherapy to cell death to the bone marrow.
- The patient then receives the transplanted stem cells
- This is not considered a cure but can produce remission
- Occasionally second transplants are done
- Median survival rate for those who achieve complete remission post ASCT is ~7 years