Leukemia and Lymphoma:
ACP Seattle Internal Medicine Review

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Case #1A

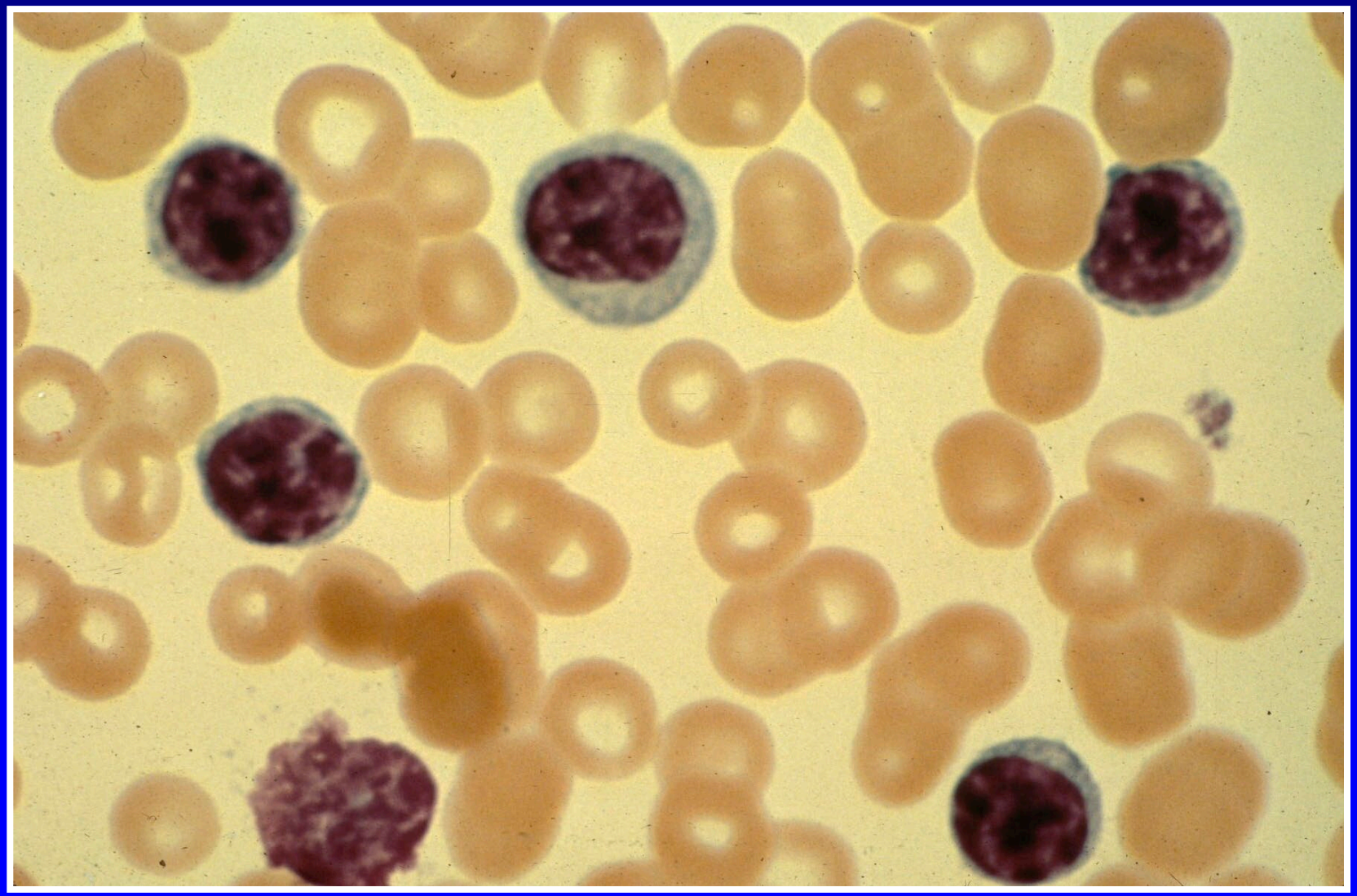
- A 75 year-old man presents because of “swollen glands” in his neck for 2 years. Exam confirms diffuse rubbery adenopathy, 2 cm in diameter, and no hepatosplenomegaly
- His CBC shows WBC 65,000/μL, Hct 35%, platelets 112,000/μL
- The most likely diagnosis is:

    1. Acute myeloid leukemia
    2. Acute lymphoblastic leukemia
    3. Chronic myeloid leukemia
    4. Chronic lymphocytic leukemia
    5. Lymphoma

Chronic Lymphocytic Leukemia

- Most common form of leukemia
- Median age at diagnosis - 72 years
- “B” symptoms - night sweats, fever, weight loss
- Exam - diffuse rubbery adenopathy
- Labs - high WBC, with lots of small mature-appearing lymphocytes, “smudge cells”

CLL Smear



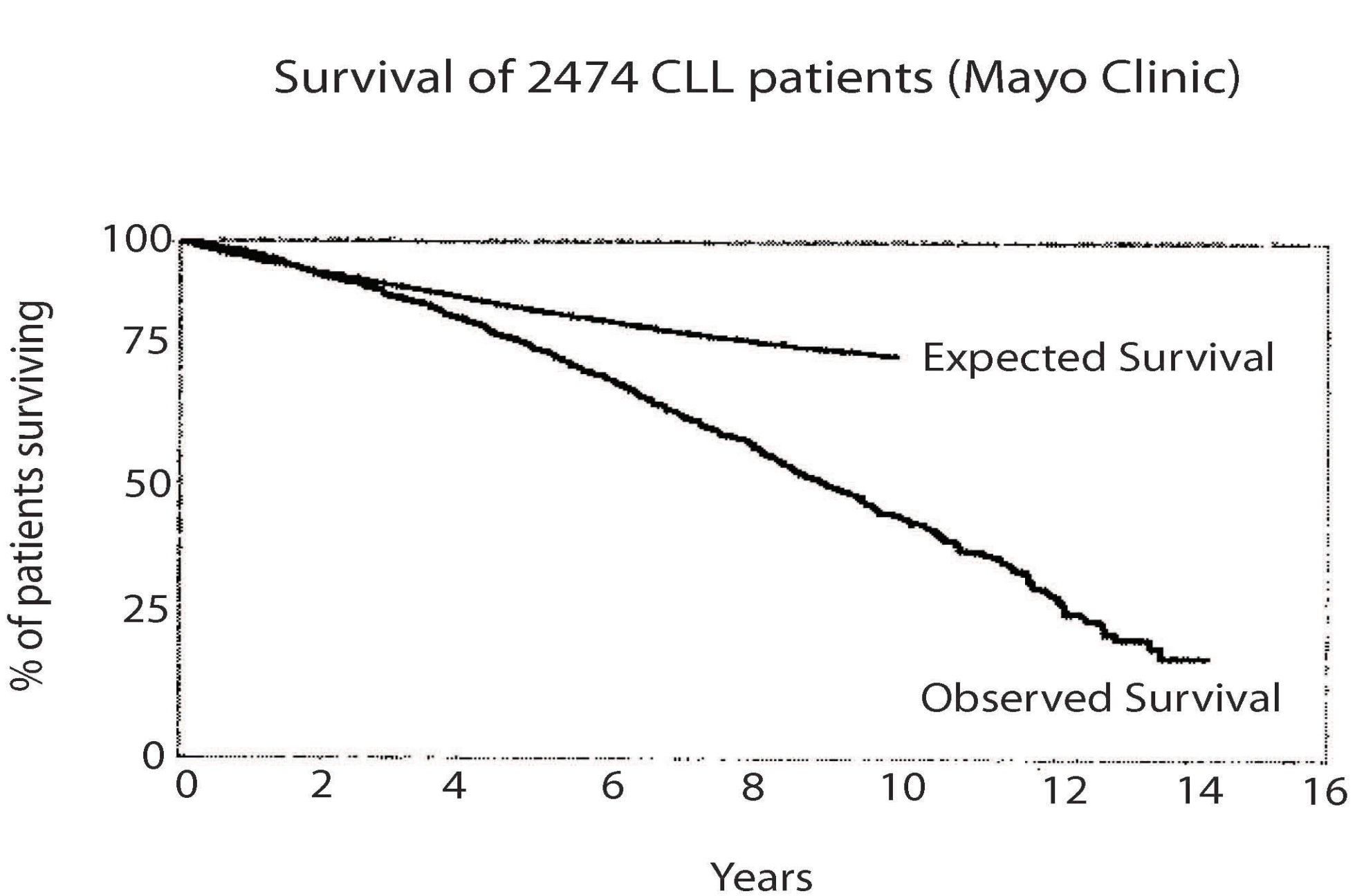
Case #1B

Your next move is to:

1. Biopsy a cervical lymph node
2. Do a bone marrow
3. Send blood for flow cytometry
4. Admit to the hospital for evaluation
5. Involve hospice

Chronic Lymphocytic Leukemia

- Diagnosis – flow cytometry on blood showing monoclonal (κ or λ) lymphocytes with a characteristic immunophenotype
- Prognosis – Stage 0 CLL ~ 14 years
- Treatment – Not curable, so treat for problems such as night sweats/fever/weight loss, obstructing lymph nodes, anemia, thrombocytopenia


Survival of 2474 CLL patients (Mayo Clinic)
% of patients surviving
100
75
50
25
0
0
2
4
6
8
10
12
14
16
Years
Expected Survival
Observed Survival

Chronic Lymphocytic Leukemia Prognosis

- Some have indolent CLL and live as long as age-matched controls, and may never require treatment
- Others have more aggressive CLL (del 17p or del 11q cytogenetic abnormalities), and their lives are much shorter

Case #1C

- You do not give him chemotherapy, but see him every 6 months. Two years later, he notes fatigue, but otherwise feels well.
- CBC: WBC 115,000/μL, Hct 19%, platelets 95,000/μL, corrected reticulocyte count is 5%
- The most likely cause of his anemia is:

1. Marrow replacement with CLL
2. “Richter Syndrome” – development of diffuse large B cell lymphoma
3. Autoimmune hemolytic anemia
4. Myelodysplasia
5. Iron deficiency anemia

Chronic Lymphocytic Leukemia
Complications

- Infections (a common cause of death)
- Autoimmune hemolytic anemia – direct antiglobulin test positive
- ITP
- Richter's Syndrome – transformation to diffuse large B cell lymphoma

Case #2A

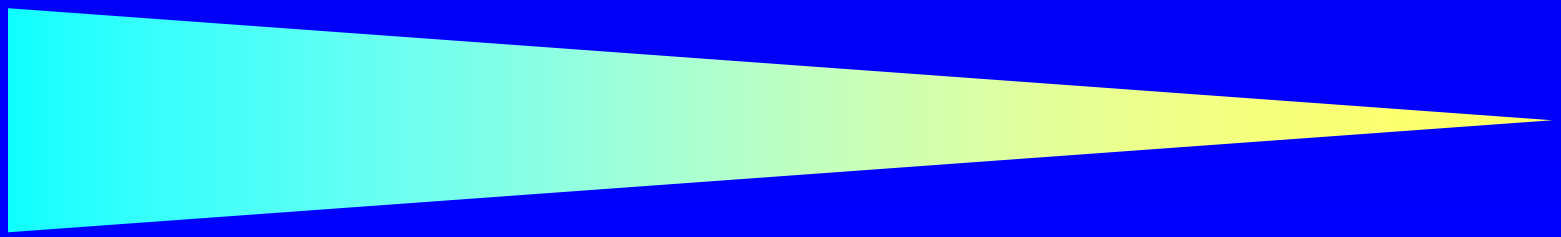
- A 55 year old man presents because of an elevated WBC found on a routine CBC. Exam shows a healthy appearing man. His spleen is palpable 2 cm below the left costal margin
- CBC: WBC 38,000/μL, Hct 45%, Platelets 500,000/μL. Differential: Neutrophils 30,000, Bands 5,000, and a moderate number of metamyelocytes, myelocytes, and promyelocytes. An occasional blast is seen
- The most likely diagnosis is:

1. Acute myeloid leukemia
2. Acute lymphoblastic leukemia
3. Chronic myeloid leukemia
4. Chronic lymphocytic leukemia
5. Leukemoid reaction due to an infection

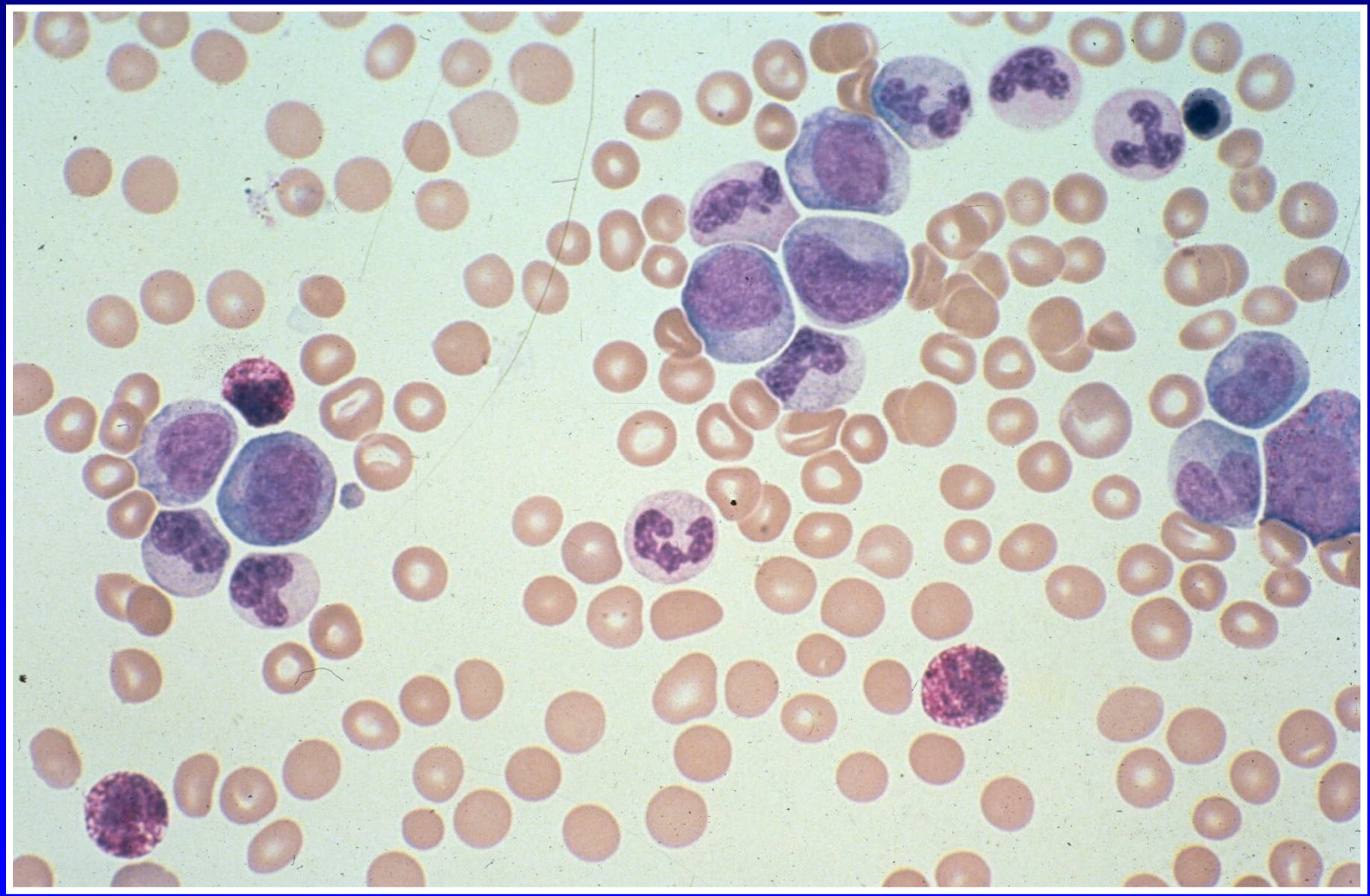
Chronic Myeloid Leukemia

- Median age at diagnosis 60 years
- Symptoms – asymptomatic, fatigue, sweats, fever, LUQ pain (splenic infarct)
- Exam – splenomegaly
- Labs – high WBC with a little bit of everything on the smear

Neutrophils > bands > metamyelocytes > myelocytes > promyelocytes > blasts



CML smear



Case #2B

- He asks you what caused his CML. You answer:

1. Inherited genetic problem
2. Heck, we have no idea
3. A translocation between chromosome 9 and 22, creating a new protein, Bcr-Abl, which has tyrosine kinase activity and is leukemogenic
4. Excess cell phone use

Chronic Myeloid Leukemia

- Diagnosis – RT-PCR to look for Bcr-Abl mRNA in the blood, or cytogenetics to look for t(9;22) in the marrow
- Natural history of untreated CML
  - Chronic phase lasts ~ 4 years
  - Accelerated phase lasts ~ 6 months
  - Blast crisis (AML or ALL) lasts ~ 3 months

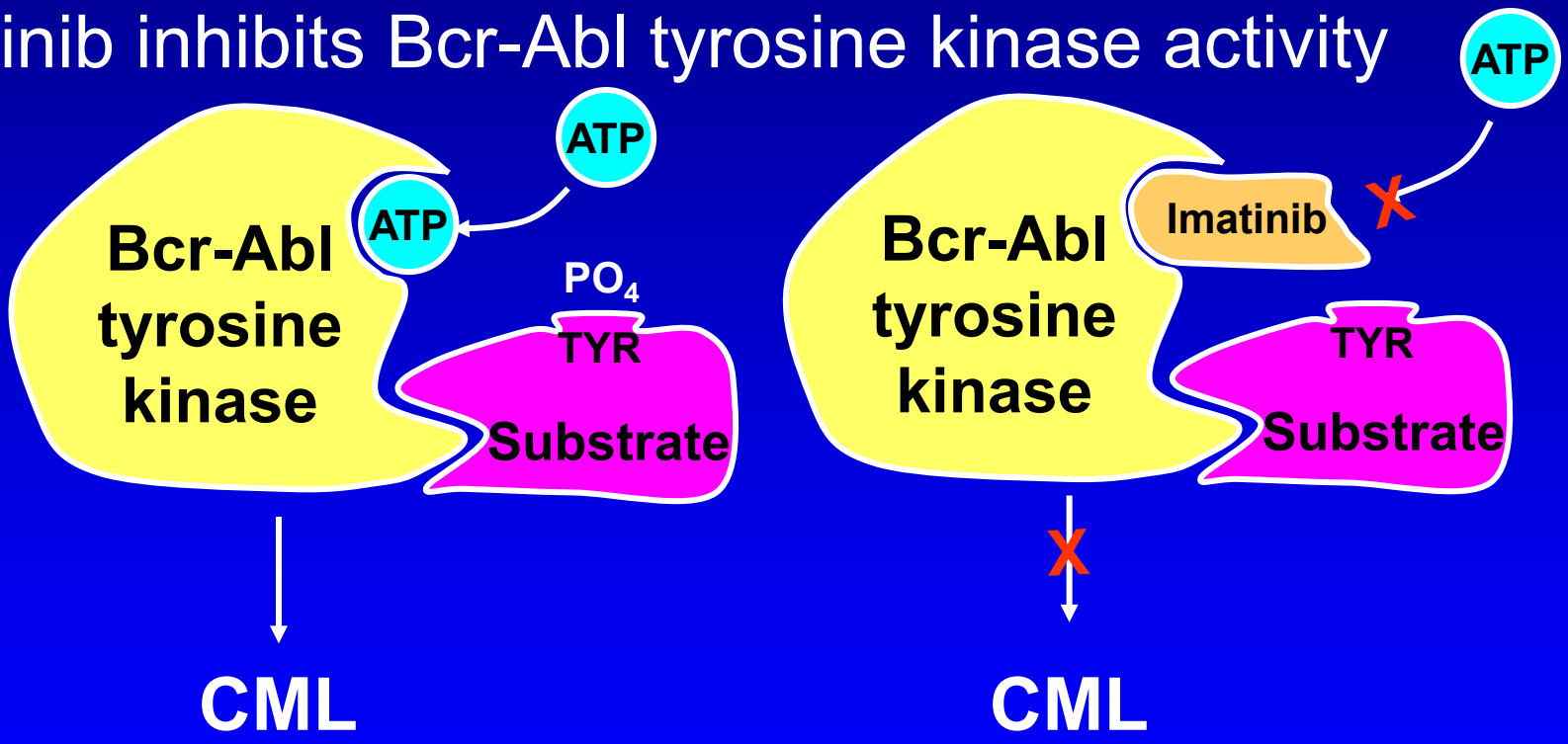
Case #2C

- You meet with him and his wife to discuss treatment options for CML. Which of the following is/are true?

1. An oral medication, imatinib, is very effective but likely not curative
2. Allogeneic stem cell transplantation has an approximately 60-70% chance of curing him, and the risk of developing graft versus host disease
3. Without effective treatment, all patients with CML eventually develop either AML or ALL
4. All are true

Chronic Myeloid Leukemia
Treatment

- Imatinib inhibits Bcr-Abl tyrosine kinase activity



Case #3A

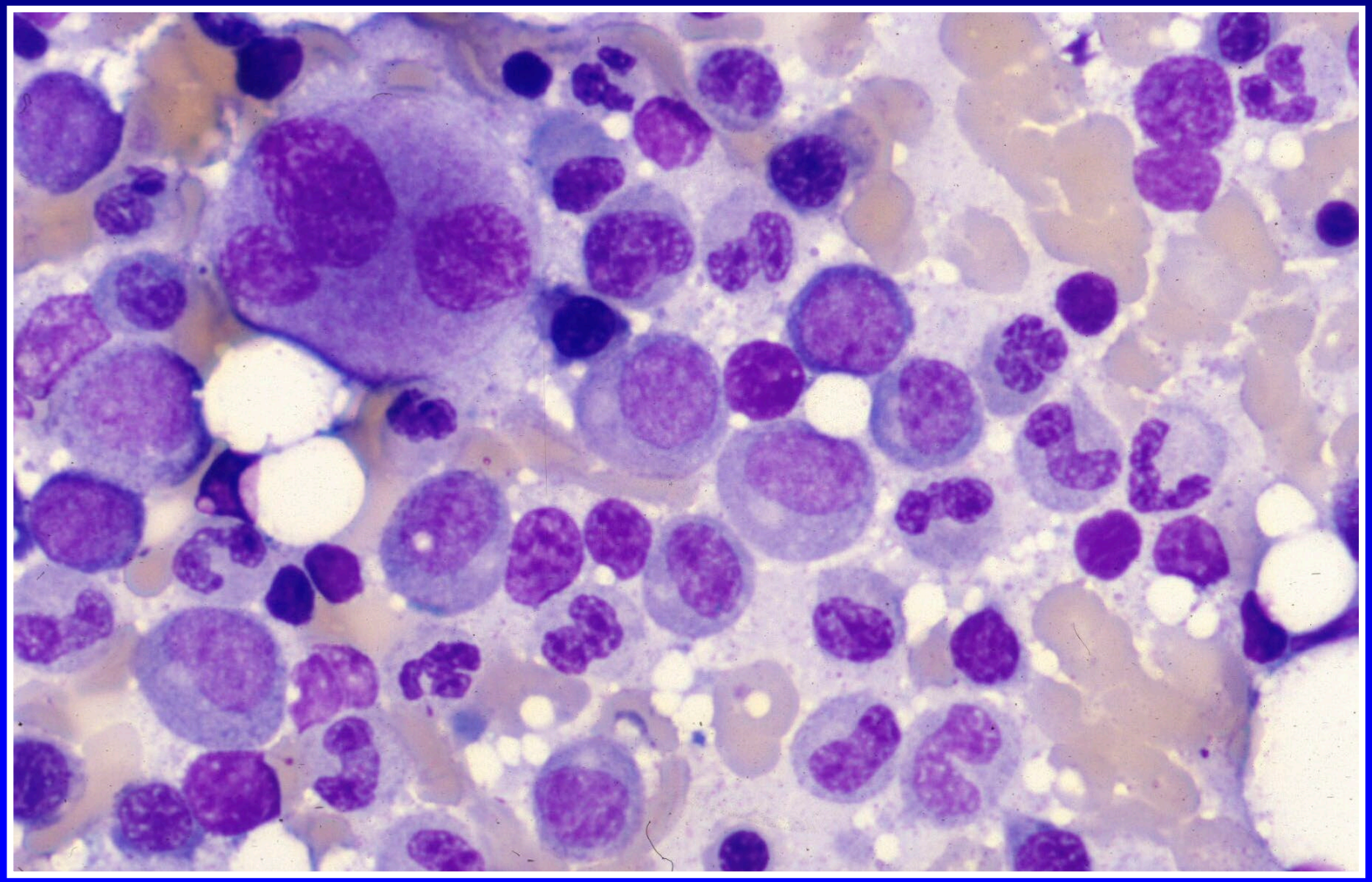
- A 58 year-old woman presents because of nose bleeding and gum bleeding when she brushes her teeth, for the past two weeks
- Exam shows a pale woman with petechiae below her knees
- CBC: WBC 2,500/μL, Hct 25%, platelets 8,000/μL
- WBC differential: neutrophils 1,400, bands 100, lymphocytes 1,000
- The differential diagnosis includes all of the following except:

  1. Acute myeloid leukemia
  2. Aplastic anemia
  3. Myelodysplasia
  4. ITP

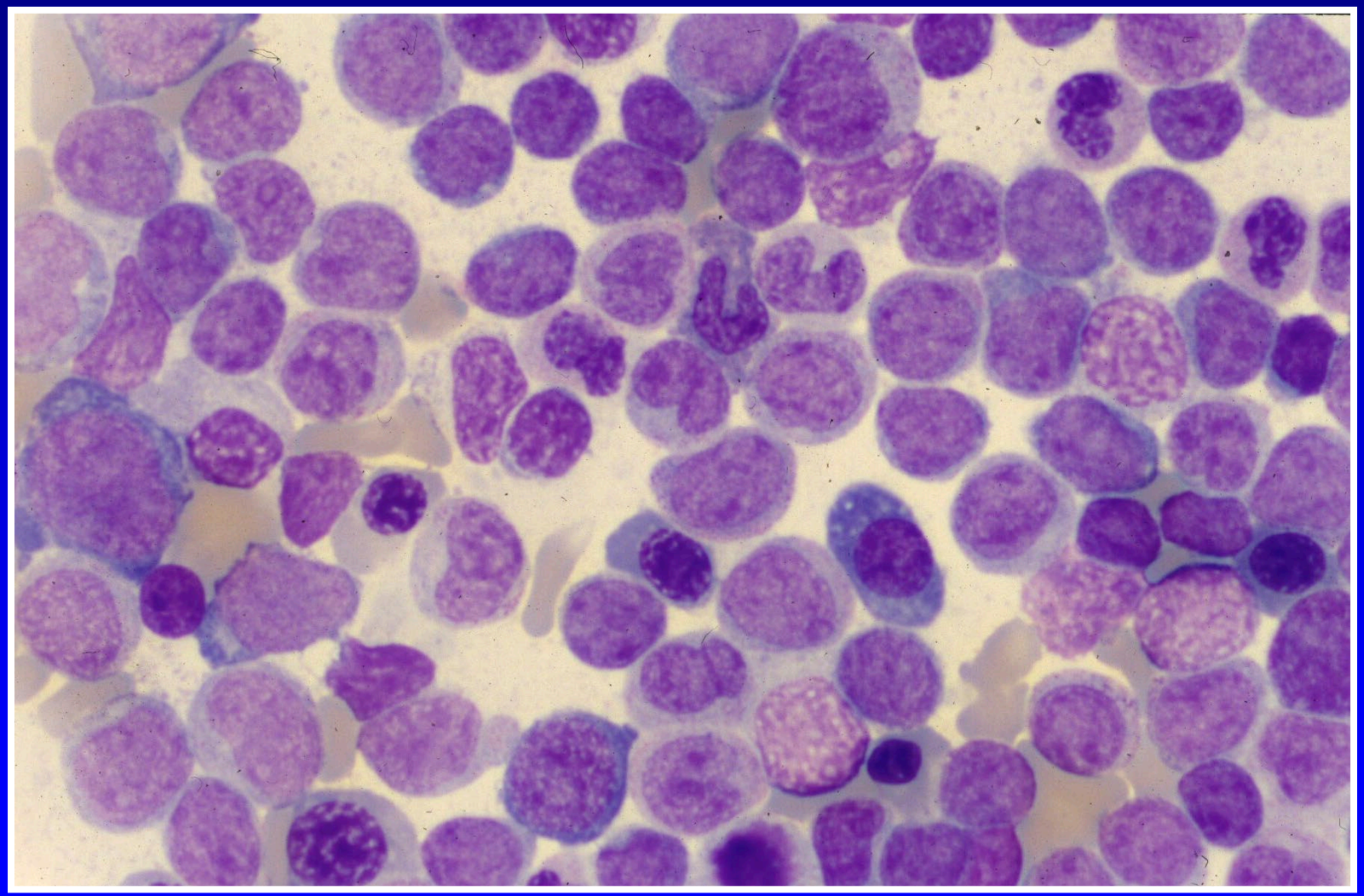
Pancytopenia

- Acute leukemia (blasts fill the marrow)
- Aplastic anemia (empty marrow)
- Myelodysplasia (excess apoptosis of maturing cells in the bone marrow)
- PNH (can evolve into aplastic anemia or AML)
- Myelofibrosis, NHL, drugs, HIV, low Vitamin B_{12} or folate, acute alcohol toxicity …
- Pancytopenia often dictates a prompt bone marrow aspiration and biopsy!

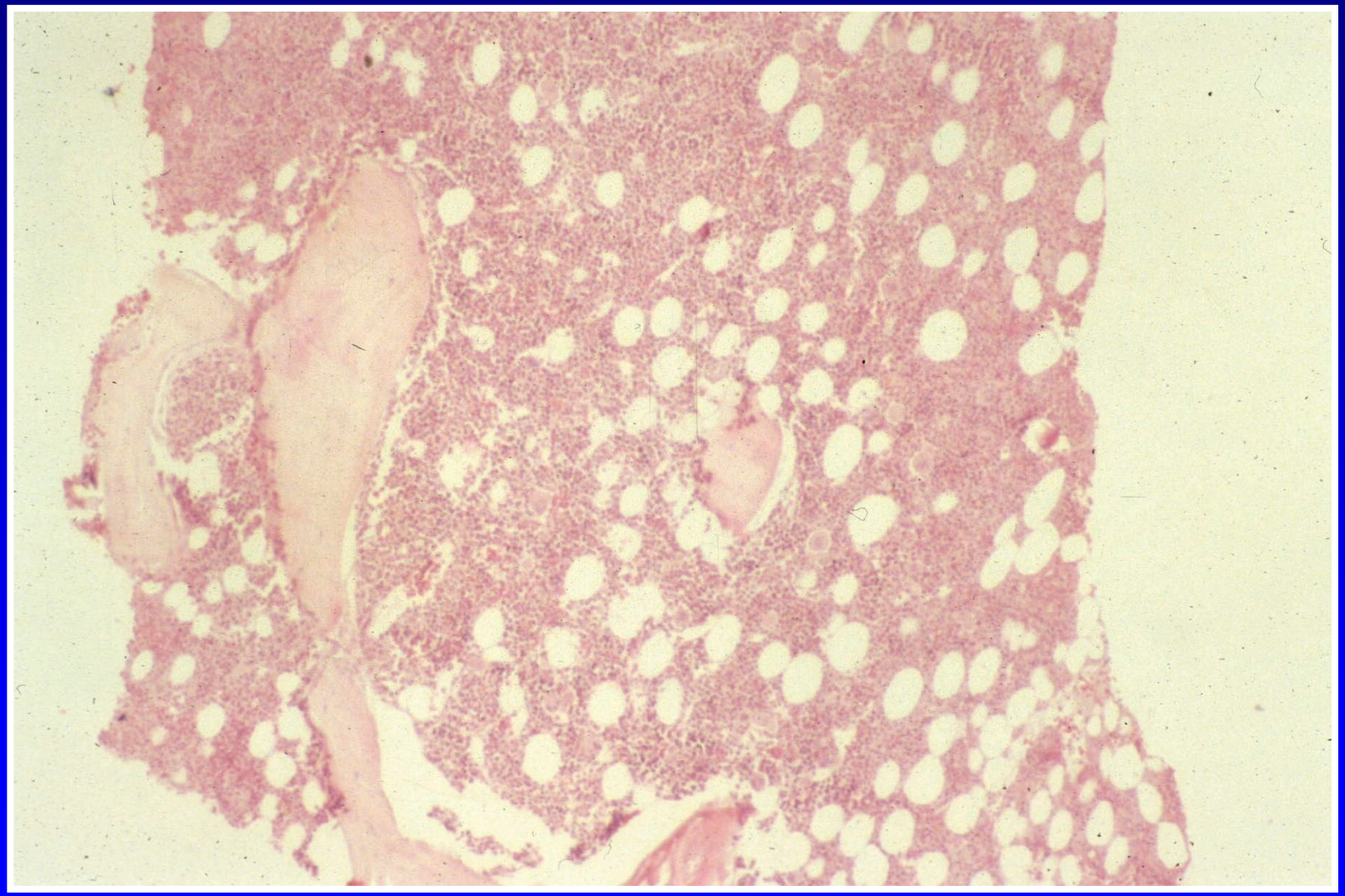
Normal Bone Marrow Aspirate



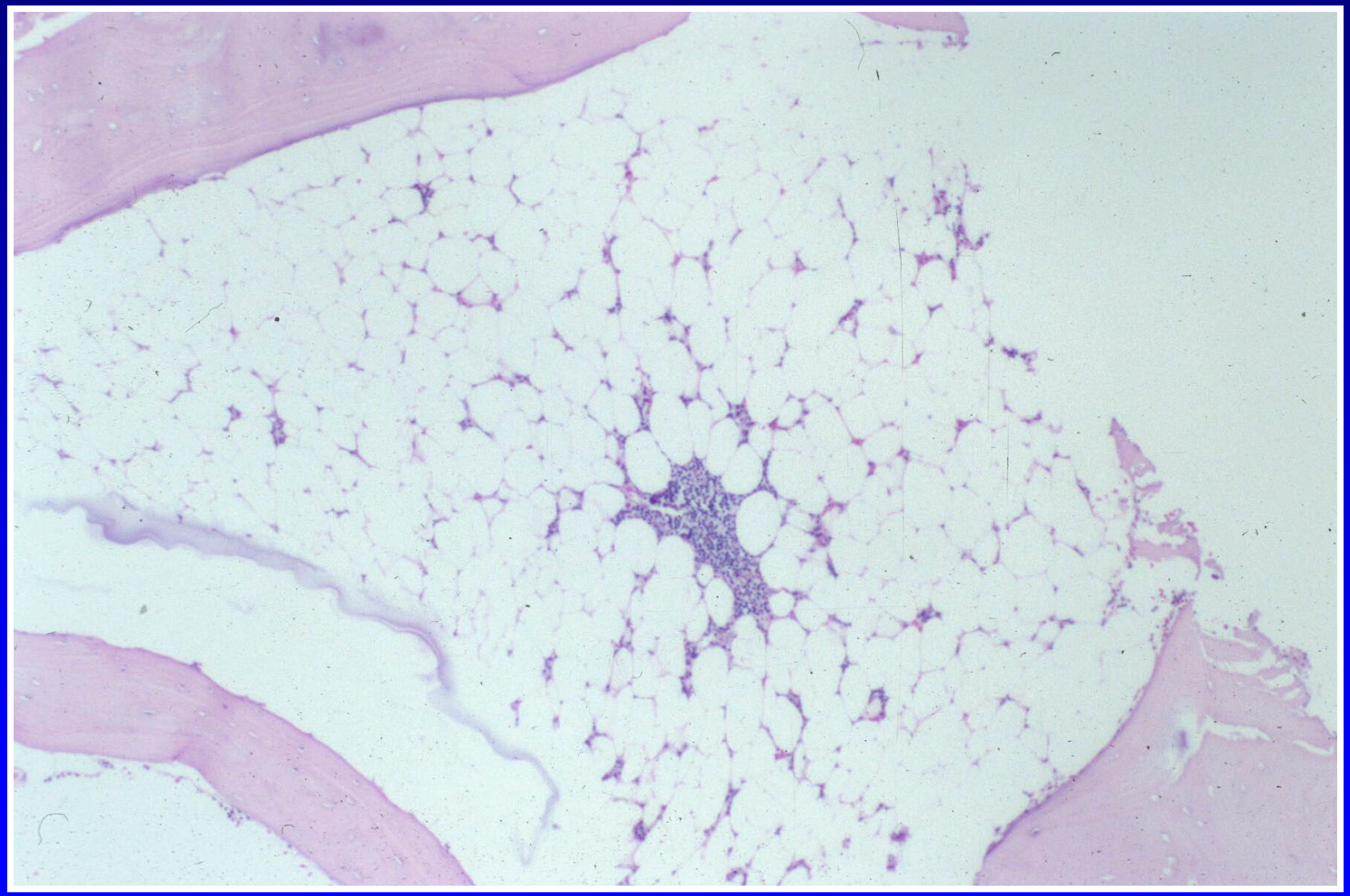
AML Marrow Aspirate



Normal Bone Marrow Biopsy



Aplastic Anemia Bone Marrow Biopsy



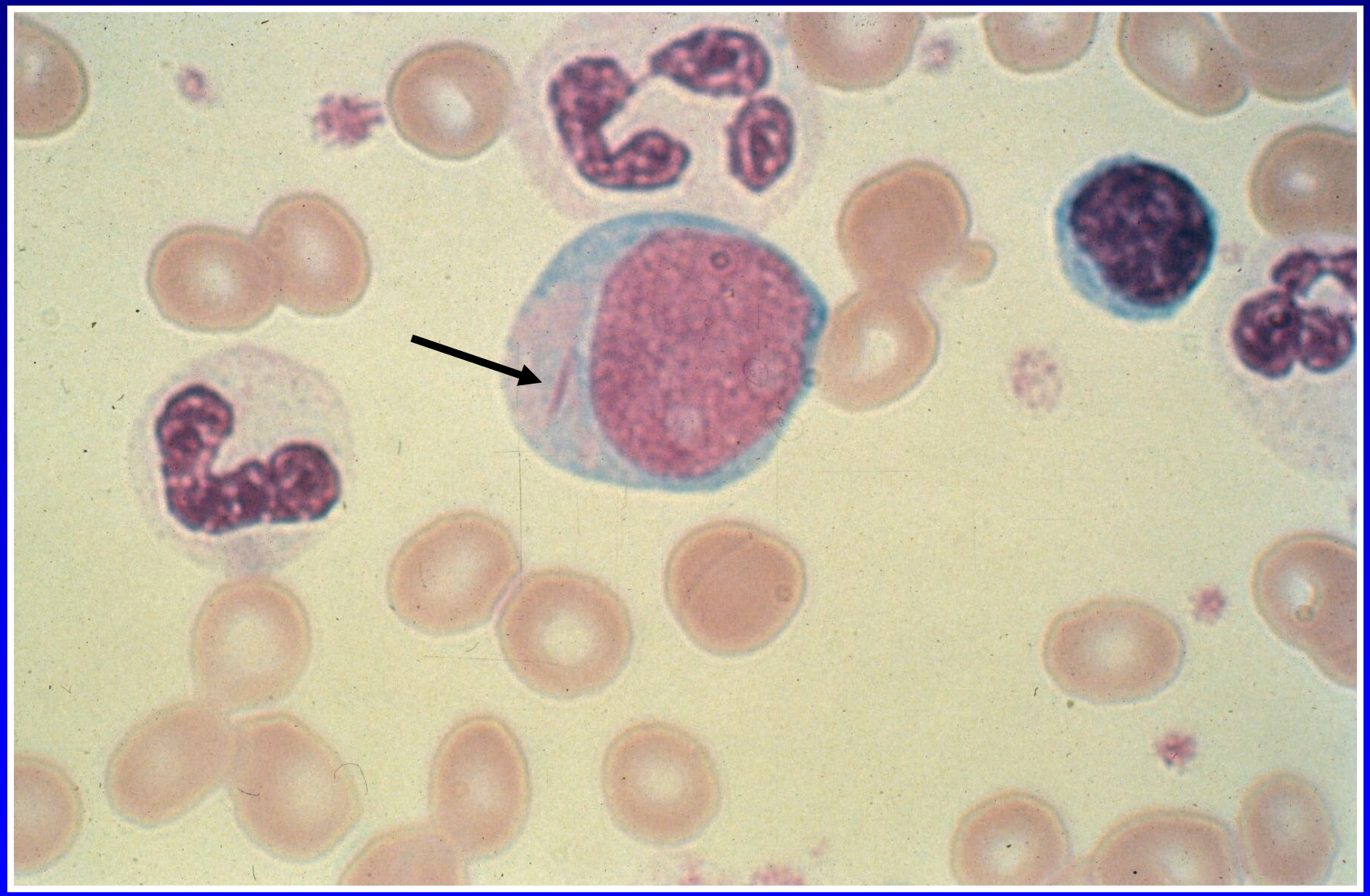
Acute Myeloid Leukemia

- Median age: 65 years, incidence increases with age
- Symptoms: fatigue, nose bleeding, bacterial infections
- Exam:
  - Platelet-type bleeding (petechiae)
  - Adenopathy is *rare*

Acute Myeloid Leukemia

- Lab: High WBC with anemia and thrombocytopenia, OR pancytopenia
- WBC differential: neutrophils and blasts. Do NOT have to have blasts in blood to have AML!
- Auer rods (pink toothpicks in the cytoplasm of blasts) → myeloid leukemia
- Diagnosis: Bone marrow aspirate and biopsy showing ≥ 20% myeloid blasts

Auer Rod



AML World Health Organization Classification

- AML with recurrent genetic abnormalities
  - APL with PML-RARA [t(15;17)]
  - “Core Binding Factor”: t(8;21), inv(16) or t(16;16)
  - mutated NPM1, CEBPA, etc.
  - Many others
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML not otherwise specified

Acute Myeloid Leukemia

- Treatment: Induction chemotherapy and 2-4 cycles of consolidation chemotherapy
- Outcome: Chemotherapy can cure a portion of patients. Autologous or allogeneic stem cell transplant can cure some additional patients.

Acute Promyelocytic Leukemia

- t(15;17) creates a fusion gene PML-RARA
- High risk of bleeding due to DIC and fibrinolysis (a medical emergency)
- Highly curable with “differentiation therapy” with all-trans retinoic acid plus either arsenic trioxide or idarubicin

Prognostic Features in AML

- Patient-related
  - Older age
  - Coexisting medical issues
  - Poor performance status
- Disease-related
  - Prior myelodysplasia
  - Cytogenetic/molecular abnormalities
  - Presence of measurable residual disease after initial 1-2 cycles of treatment

Impact of Cytogenetics/Molecular Abnormalities on Survival in AML in Patients Under 60 Years Old

- Favorable risk: ~60% disease-free survival
  - t(8;21), inv (16), biallelic mutated CEBPA, NPM1 mutation without FLT3 ITD
- Intermediate risk: ~30% disease-free survival
  - t(9;11), (and others)
- Adverse risk: ~10% disease-free survival
  - del (5q), -5, -7, t(6;9), t(9;22)

Case #3B

- Bone marrow shows 40% myeloid blasts, and the diagnosis of AML is established. You recommend induction chemotherapy. The complication that she is most likely to experience:

1. Tumor lysis syndrome (high potassium, phosphate, uric acid; low calcium)
2. Pulmonary/cerebral leukostasis
3. Hyperuricemia
4. Febrile neutropenia
5. CNS hemorrhage

Tumor Lysis Syndrome

- Occurs after effective chemotherapy for rapidly growing chemosensitive tumors (e.g., Burkitt lymphoma, acute leukemia with high blast count)
- Tumor lysis releases intracellular uric acid, phosphate, and potassium → overwhelms renal excretory mechanisms → calcium drops (paresthesias, muscle cramps, tetany, arrhythmia)

Pulmonary/Cerebral Leukostasis in AML

- Patients with high myeloid blast count (>100,000/μL) are at highest risk
- Respiratory distress, hypoxia, diffuse infiltrates on CXR
- Neurologic symptoms: dizziness, confusion, somnolence, delirium

Leukemias: Summary

- CLL: most common leukemia in adults, frequently doesn't require treatment
- CML: BCR-ABL+, targeted drugs like imatinib have drastically impacted outcomes
- AML: intense chemotherapy remains standard if goal is cure (except for APL)
- ALL: call someone like me

Case #4A

- A 68 year old asymptomatic man has a monoclonal spike on his SPEP (IgGλ 1.8 g/dL). You initiate an evaluation, including serum free light chains, skeletal x-ray, bone marrow aspiration and biopsy, 24 hour urine collection. While these studies are underway, you council him that the most likely cause is:

  1. Multiple myeloma
  2. Amyloidosis
  3. Monoclonal gammopathy of undetermined significance
  4. Non-Hodgkin lymphoma
  5. CLL

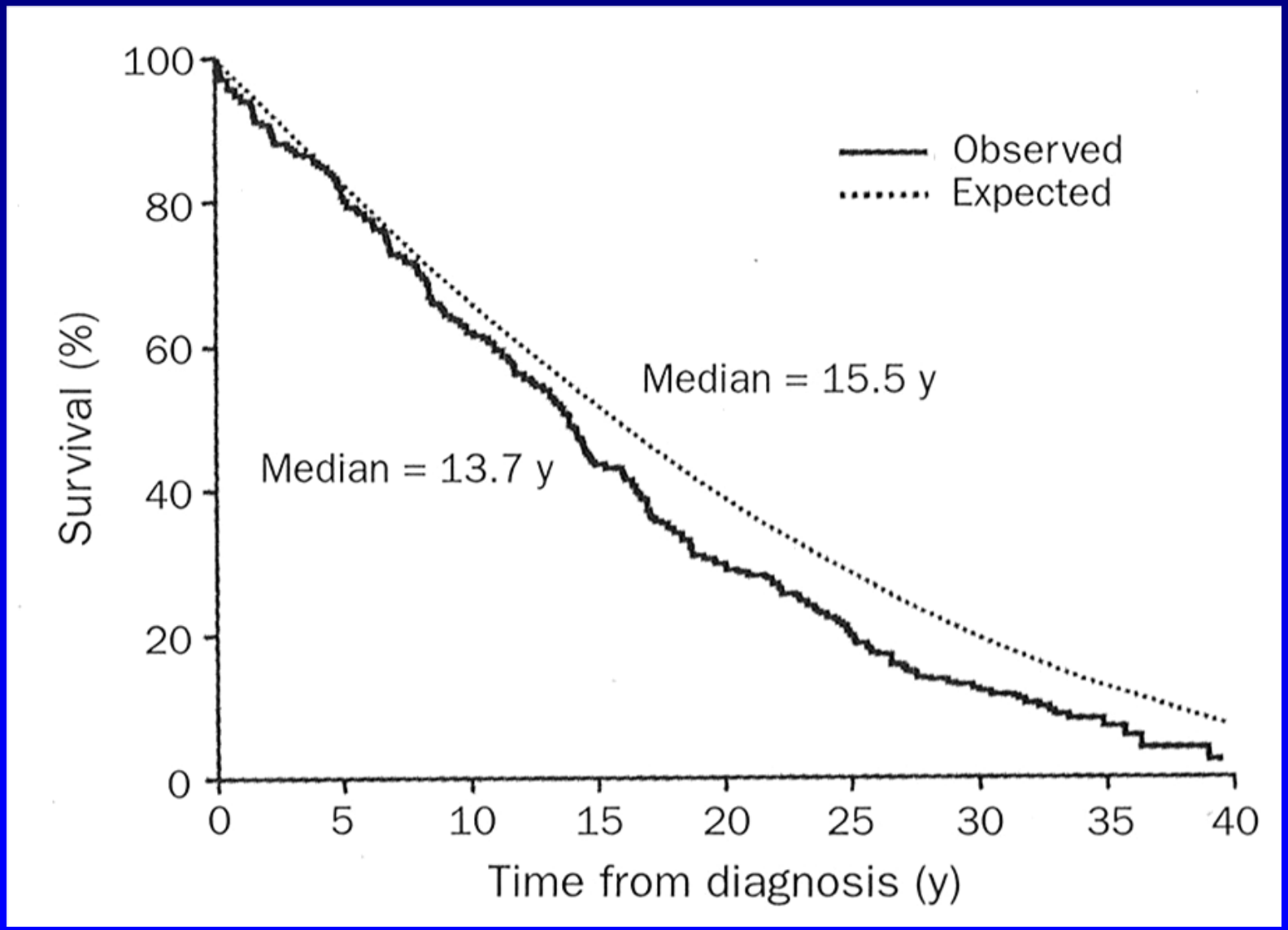
Causes of Monoclonal Spike n=945 (Mayo Clinic)

• MGUS	63%
• Multiple Myeloma	13%
• Amyloid AL	10%
• Non-Hodgkin Lymphoma	6%
• CLL	2%

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Diagnostic criteria:
  - Low monoclonal spike (< 3 g/dl)
  - No lytic lesions in bone
  - No anemia, renal insufficiency, hypercalcemia
  - Less than 10% clonal plasma cells in bone marrow
- Seen in 5% of people older than 70 years
- 25% risk of progression to multiple myeloma during 20 years of follow-up

Survival of 241 Patients with MGUS



Multiple Myeloma

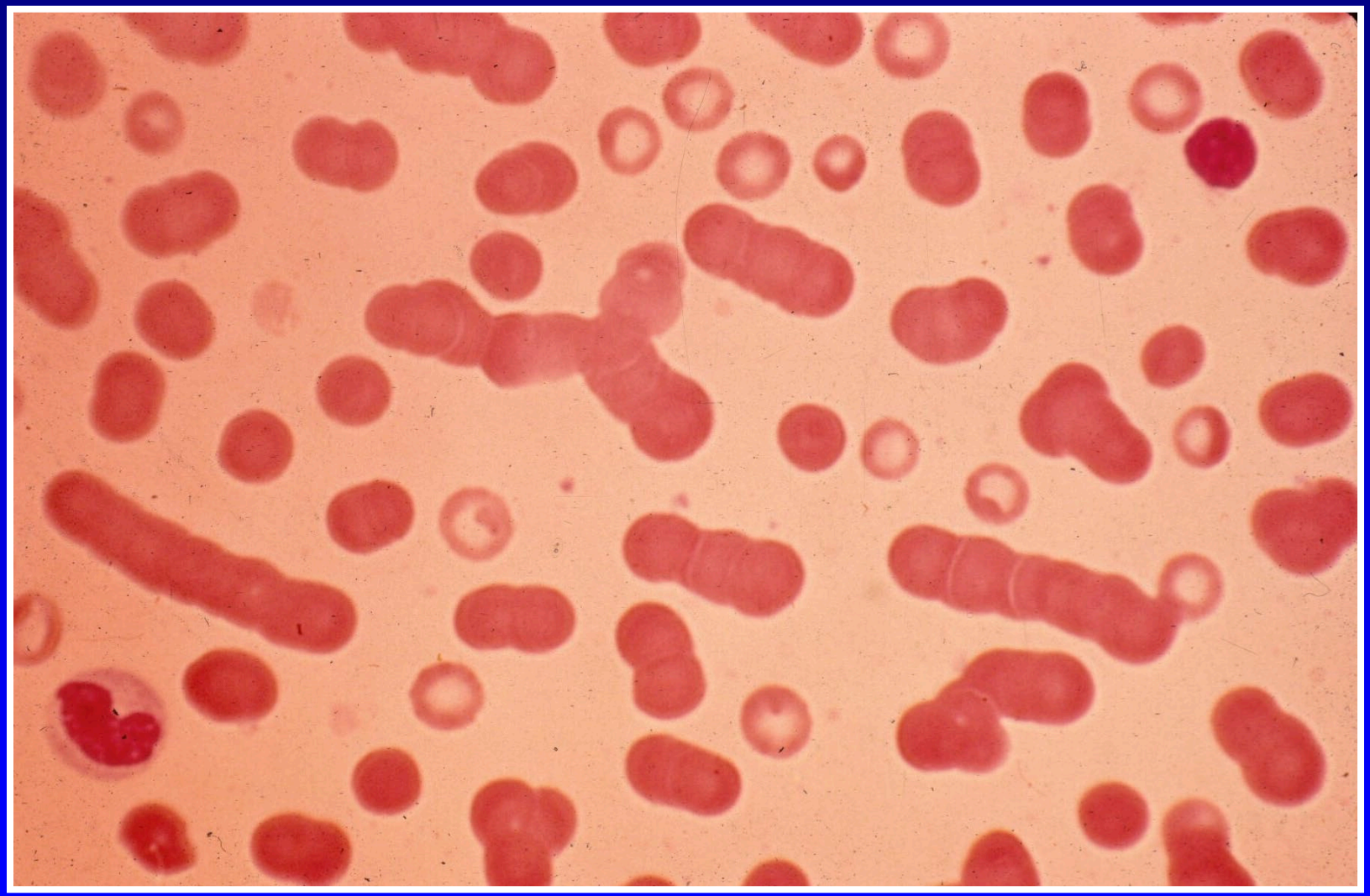
- A monoclonal expansion of B cells with mature plasma cell morphology
- Symptoms: bone pain, fatigue, back pain
- Exam: Pallor, no adenopathy or splenomegaly
- Lab:
  - C: Elevated calcium
  - R: Renal insufficiency
  - A: Anemia in 60%
  - B: Lytic lesions in bone
  - SPEP with monoclonal spike
    - IgG, IgA; rare: IgD, IgM
    - Light chains only (check serum free light chains)
    - Non secretory (no monoclonal spike)

Case #4B

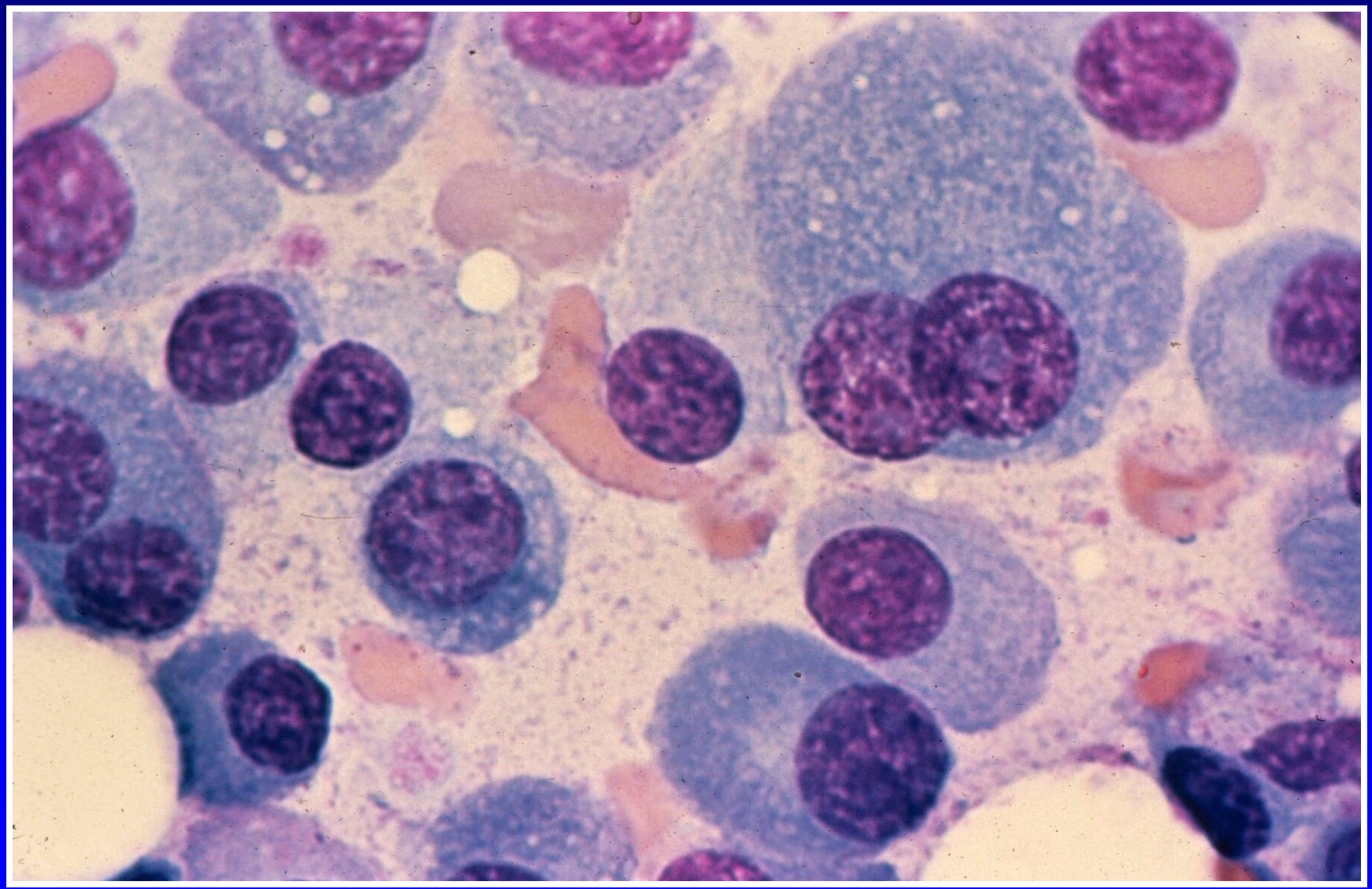
- Unfortunately, the skeletal series shows 3 lytic lesions, none in weight bearing areas. His bone marrow shows 22% clonal plasma cells, and his serum free κ/λ light chain ratio was abnormal at 125. You diagnose multiple myeloma. You recommend:

  1. Watchful waiting (he is asymptomatic)
  2. Zoledronate (to decrease his risk of fracture)
  3. Chemotherapy (to beat back the myeloma)
  4. Zoledronate plus chemotherapy
  5. Prompt autologous stem cell transplant

Rouleaux



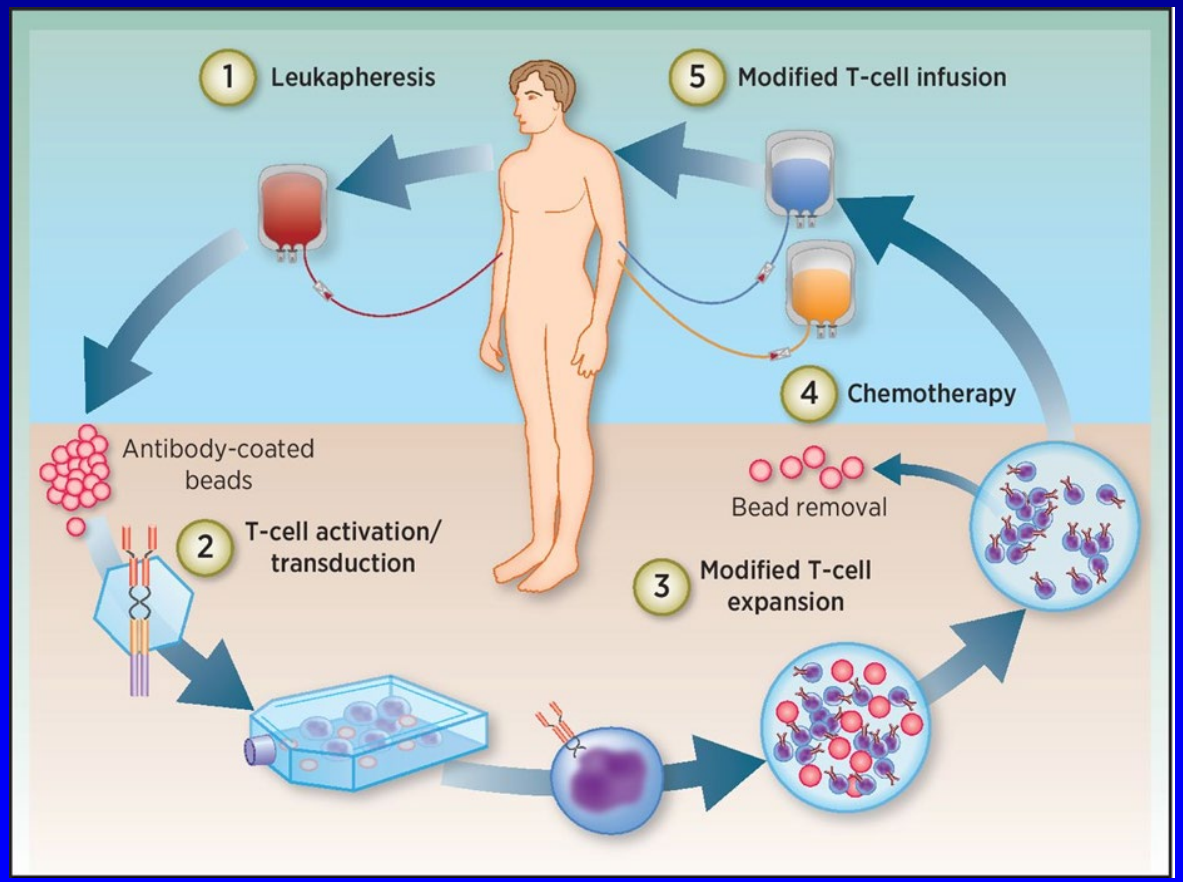
Plasma Cells in the Bone Marrow



Treatment of Multiple Myeloma

- Not curable at present
- Can be managed often for years with a host of agents: proteosome inhibitors, immunomodulatory drugs, monoclonal antibodies, and chimeric antigen receptor-modified (CAR) T cells
- Initial decision is whether the patient is eligible for an autologous stem cell transplant

Chimeric Antigen Receptor-Modified (CAR) T Cells



Maus & June. *Clin Cancer Res*. 2016;22(8):1875-84.

Case #4C

- Which of the following is true?
  1. Bone scan is a better way to look for bone lesions of multiple myeloma than x-ray
  2. Multiple myeloma is more common in Caucasians than in African Americans
  3. Multiple myeloma patients should promptly report new back pain, particularly in the cervical or thoracic area
  4. Zoledronate is not associated with osteonecrosis of the jaw

Complications of Multiple Myeloma

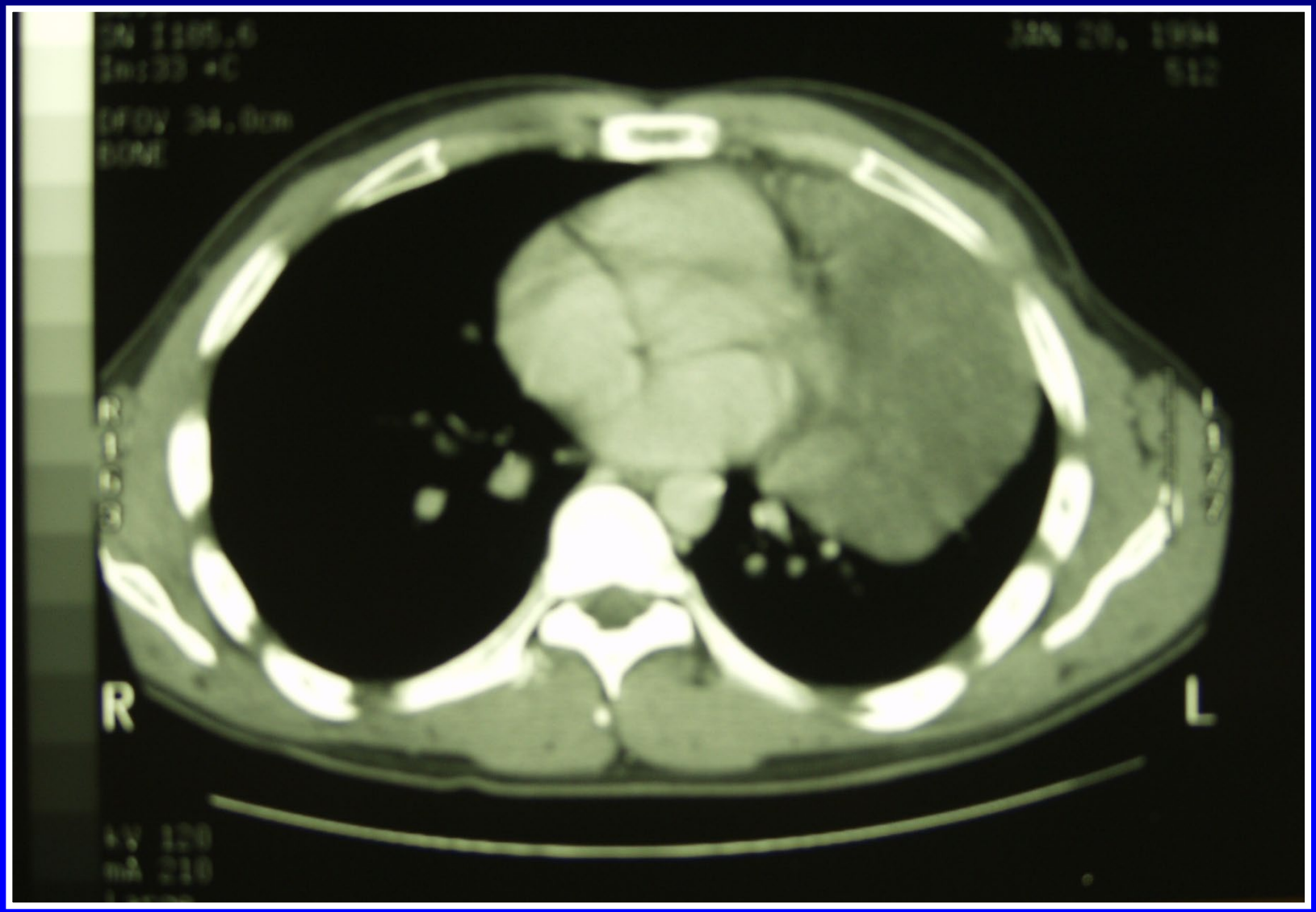
- Osteolytic lesions/pathologic fracture
- Renal failure
- Bacterial infection
- Anemia
- Hypercalcemia
- Spinal cord compression

Case #5

- A 23 year-old man presents because of shortness of breath while playing basketball. Exam shows no adenopathy. CXR shows a huge left mediastinal mass. Which of the following is the least likely diagnosis?

    1. Teratoma
    2. Hodgkin lymphoma
    3. Lymphoblastic lymphoma
    4. Lung cancer

Chest CT



Hodgkin Lymphoma

- Median age 35 years
- Symptoms: Painless adenopathy, fever, night sweats, weight loss, pruritus
- Exam: Rubbery adenopathy (particularly cervical)
- Labs: May have eosinophilia
- Diagnosis: Excisional biopsy of lymph node

Hodgkin Lymphoma

- Staging: Hodgkin lymphoma spreads in an orderly way from lymph node to adjacent lymph node
  - Palpate all lymph node areas
  - PET/CT scan
  - Bone marrow aspirate/biopsy may not be needed
- Staging determines prognosis and treatment

Staging of Hodgkin Lymphoma

- Stage I — One group of nodes involved
- Stage II — Two or more groups of nodes involved, on one side of the diaphragm
- Stage III — Nodes above and below the diaphragm involved
- Stage IV — Involvement of a non-lymphoid site such as bone marrow, liver, lung

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- A — No “B” symptoms
- B — Drenching night sweats, fever, loss of 10% of body weight in 6 months

Hodgkin Lymphoma

- Hodgkin lymphoma is among the most curable of neoplasms – all patients should be treated with the goal of cure
- Stage I-IIA
  - ABVD chemotherapy x 2-4 cycles +/- RT
  - ~90% cured
- Stage IIB, III, IV
  - ABVD x 6 cycles, +/- RT for bulky nodes
  - ~65% cured

Long-Term Complications of Hodgkin Lymphoma Treatment

- Radiation therapy
  - Hypothyroidism
  - Breast cancer (young women)
  - Early onset coronary artery disease
  - Pulmonary fibrosis
  - Lung cancer, sarcoma
- Chemotherapy
  - Sterility (MOPP)
  - Secondary AML (MOPP)
  - Cardiomyopathy (ABVD)
  - Pulmonary fibrosis (ABVD)

Case #6A

- A 37 year-old HIV positive man (CD4 171/μL, viral load undetectable) presents because of a one month history of a mass in his right neck. The mass was increasing rapidly in size. He had lost 3 kg. He did not have fevers or night sweats. He lives alone, and is able to look after himself.
- Exam: Very large right tonsil, crossing the midline but not obstructing the airway. Several enlarged rubbery right cervical nodes, the largest 5x5 cm. No other adenopathy.
- The most likely diagnosis is:

    1. Hodgkin lymphoma
    2. Follicular lymphoma (indolent NHL)
    3. Diffuse large B-cell lymphoma (aggressive NHL)
    4. T cell lymphoma
    5. Castleman disease

Lymphoma in HIV-Positive People

- ~ 50-fold increased incidence of aggressive NHL (in comparison to HIV-negative people)
- ~ 10-fold increased incidence of Hodgkin lymphoma
- Primary CNS lymphoma – CD4 cells < 50/μL (and often < 10/μL)

Case #6B

- Staging studies show stage IV diffuse large B-cell lymphoma. Which of the following is true?

1. It is time for hospice care

2. Because this is not curable, we recommend waiting until he has symptoms (for example, obstructing adenopathy, drenching sweats) and initiating treatment then

3. We recommend starting R-CHOP or R-EPOCH chemotherapy now, and there is a good chance of cure

Non-Hodgkin Lymphoma

- A neoplasm originating in a single lymphocyte (usually a B lymphocyte)
- Symptoms:
  - Painless adenopathy
  - "B" symptoms
    - Fever
    - Sweats (drench the sheets)
    - Weight loss (unintentional, 10% of body weight in 6 months)

Non-Hodgkin Lymphoma

- Exam:
  - Rubbery adenopathy (cervical, axillary, inguinal, look at tonsils, gums)
  - Splenomegaly
  - Hepatomegaly
- Labs:
  - CBC often normal
  - LDH often elevated

Non-Hodgkin Lymphoma

- Diagnosis:
  - Excisional biopsy of a lymph node to permit evaluation of node histology and architecture (nodular vs. diffuse involvement)
  - Flow cytometry for B and T cell markers, FISH for molecular abnormalities
- Pathology and stage determine prognosis and treatment

Classification of NHL

- Indolent
  - Small lymphocytic lymphoma
  - Follicular lymphoma, grade I and II
  - Many others
- Aggressive
  - Diffuse large B-cell lymphoma
  - Anaplastic large cell lymphoma
  - Many others
- High-Grade
  - Burkitt lymphoma
  - Lymphoblastic lymphoma (= ALL)

Treatment of Follicular NHL

- Stage III-IV
  - Watchful waiting (observation of asymptomatic patients)
  - Rituximab (humanized anti-CD20 monoclonal antibody)
  - Rituximab plus Bendamustine
- Stage I-II
  - Radiation therapy if contiguous
  - Options above

Treatment of Diffuse Large B-Cell Lymphoma

- Stage I-II:
  - R-CHOP x 3 cycles plus local radiation therapy (~85% cure)
- Stage III-IV
  - R-CHOP x 6 cycles (>60% cure)
- Some of those who are not cured with R-CHOP can be cured with autologous stem cell transplantation
- Evolving role of CAR-T cells

NHL Treatment Summary

- Indolent NHL: Usually incurable, so treat if there is an indication such as obstructing adenopathy, anemia, “B” symptoms
- Aggressive or high-grade NHL: Always treat up front with the goal of cure

	NHL	Hodgkin Lymphoma
Frequency	5-8 fold more common	Less common
Age	Increases with age	Median age 35
HIV	↑↑↑ Risk	↑ Risk
Diagnosis	Lymph node biopsy	Lymph node biopsy
What determines treatment?	Pathology/Stage	Stage
Curability	Sometimes	~80%

THANK YOU!

Case Answer Key

- 1A: 4
- 1B: 3
- 2A: 3
- 2B: 3
- 2C: 4
- 3A: 2
- 3B: 4
- 4A: 3
- 4B: 4
- 4C: 3
- 5: 4
- 6A: 3
- 6B: 3