Update in Hematology: Just A Few Pearls

David C. Dale, MD

Professor of Medicine

University of Washington

Today's Topics

Anemia and when to worry about malignancy?

What are early signs of hematological malignancy?

How do I care for my patients with malignancies?

Case Study #1

A 59-year-old salesman from La Plaz, Bolivia arrives at your office for a check-up soon after getting a new job at Microsoft in Seattle.

- He is 40 years old and a two to three packs per day (PPD) cigarette smoker with shortness of breath.
- The physical exam showed a big chest and distant breath sounds.
- CBC results: WBC: 10.2, HGB: 17.3, and HCT: 55

What do you do?

a) Advise him to return to recheck HCT and HGB in two months

b) Advise him to stop smoking and recheck HCT and HBG in two months

c) Advise him to get erythropoietin levels checked now

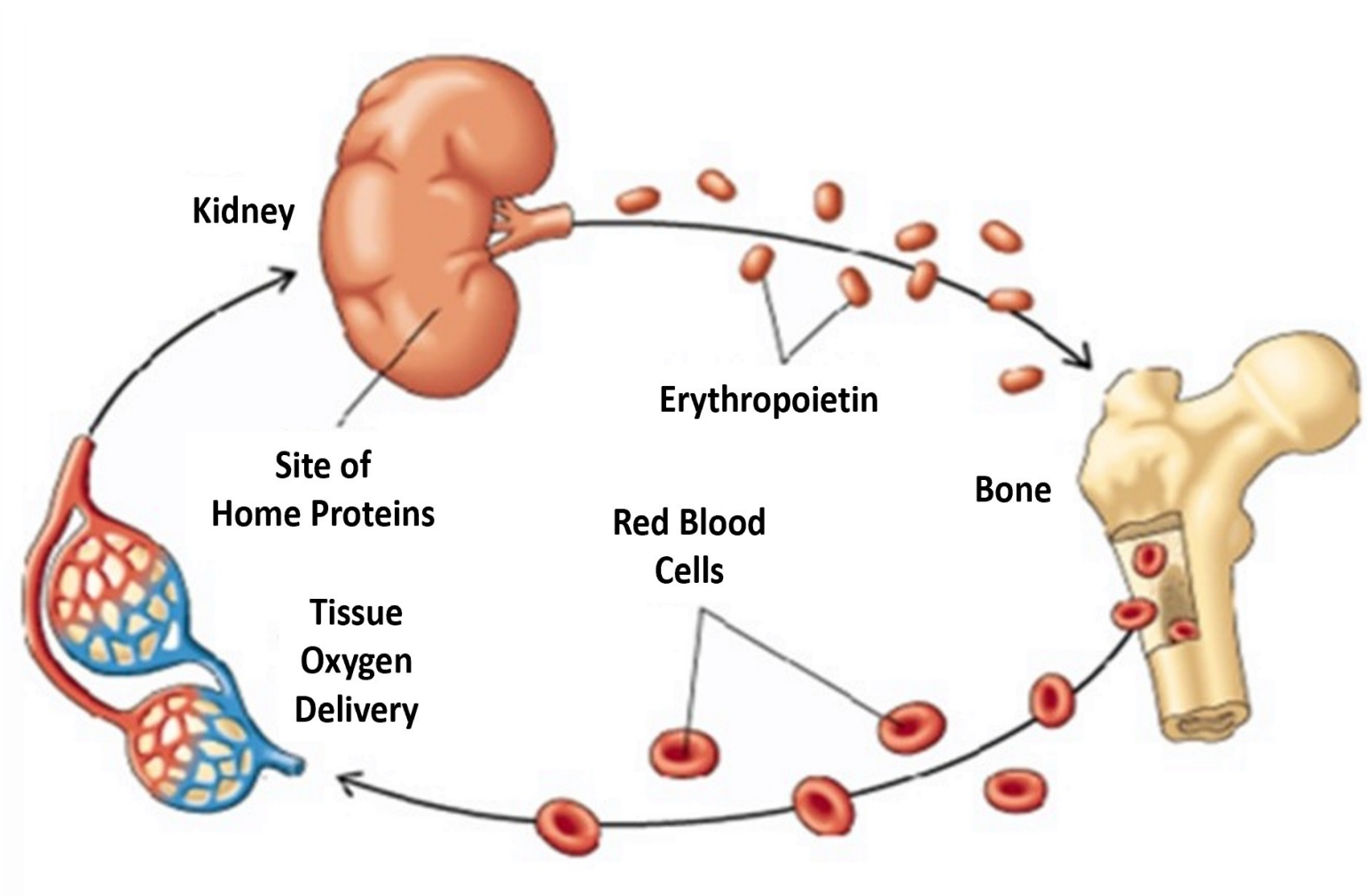
d) Advise him to get genetic testing for the JAK2 sequencing now

e) Advise him to get a full CBC with differentials (including WBC and PLTS)

Normal Values - Erythrocytes

	Female	**Male**
Red Blood Cells (RBC)	4.1-5.1 x 10^6/mm^3	4.5-5.3 x 10^6/mm^3
Hemoglobin (HGB)	12.0-16.0 g/dl 7.4-9.9 mmol/L	13.0-18.0 g/dl 8.1-11.2 mmol/L
Hematocrit (HCT)	36-46%	37-49 %
Mean Corpuscular Volume (MCV)	78-102 mm^3	78-100 mm^3

The Regulation of Erythropoiesis



Polycythemia: Is It Primary or Secondary?

Polycythemia is common in La Plaz, Bolivia at elevations of 12,000 feet.

Moving to sea level will probably cause measurable decrease in HGB levels within two to three months; erythropoietin (EPO) drive is only cause.

In case study #1, if the patient's first clinic visit occurred shortly after arriving in Seattle, his EPO level may be elevated, otherwise, his EPO level will probably be normal and not helpful for confirming his diagnosis as a primary or secondary cause.

How To Make A Polycythemia Vera Diagnosis

- HCT and HGB counts
- WBC may be elevated
- Platelets are often elevated, and sometimes quite high
- Bone marrow may be normal (a bone marrow aspirate or biopsy may not be very helpful)
- EPO levels are usually low
- Genetic testing is definitive, the *JAK2* mutation is almost always found
  - Another genetic test, i.e., *TET2* mutation analysis test identified the *TET2* mutation in about 15-20% of those with the *JAK2* mutation

Primary Care and Polycythemia Vera

Be informed of likely causes of polycythemia vera.

Discourage smoking in every patient.

Be prepared to discuss and assist in management of common symptoms/problems:

- **Itching**
- **Thrombosis**
- **Chemotherapy side effects**

Case Study #2

A 72-year-old retired teacher comes for an office visit complaining of fatigue.

- He says he gets tired from walking on level ground.
- The physical exam is unrevealing; cardiac exam is normal.
- You order a CBC, metabolic panel, liver panel, and an ESR.
- Results are:
  - WBC: 8.0, HCT: 32, PLTS: 220,000
  - Differentials: Normal
  - ESR: 60

What is the next best step?

a) Schedule a return visit and check temporal arteries, bone tenderness, and careful skin and foot exams (you forgot to do this before).

b) Order a chest x-ray to look for signs of tuberculosis or cancer.

c) Order blood cultures.

d) Order a Serum protein electrophoresis (SPEP).

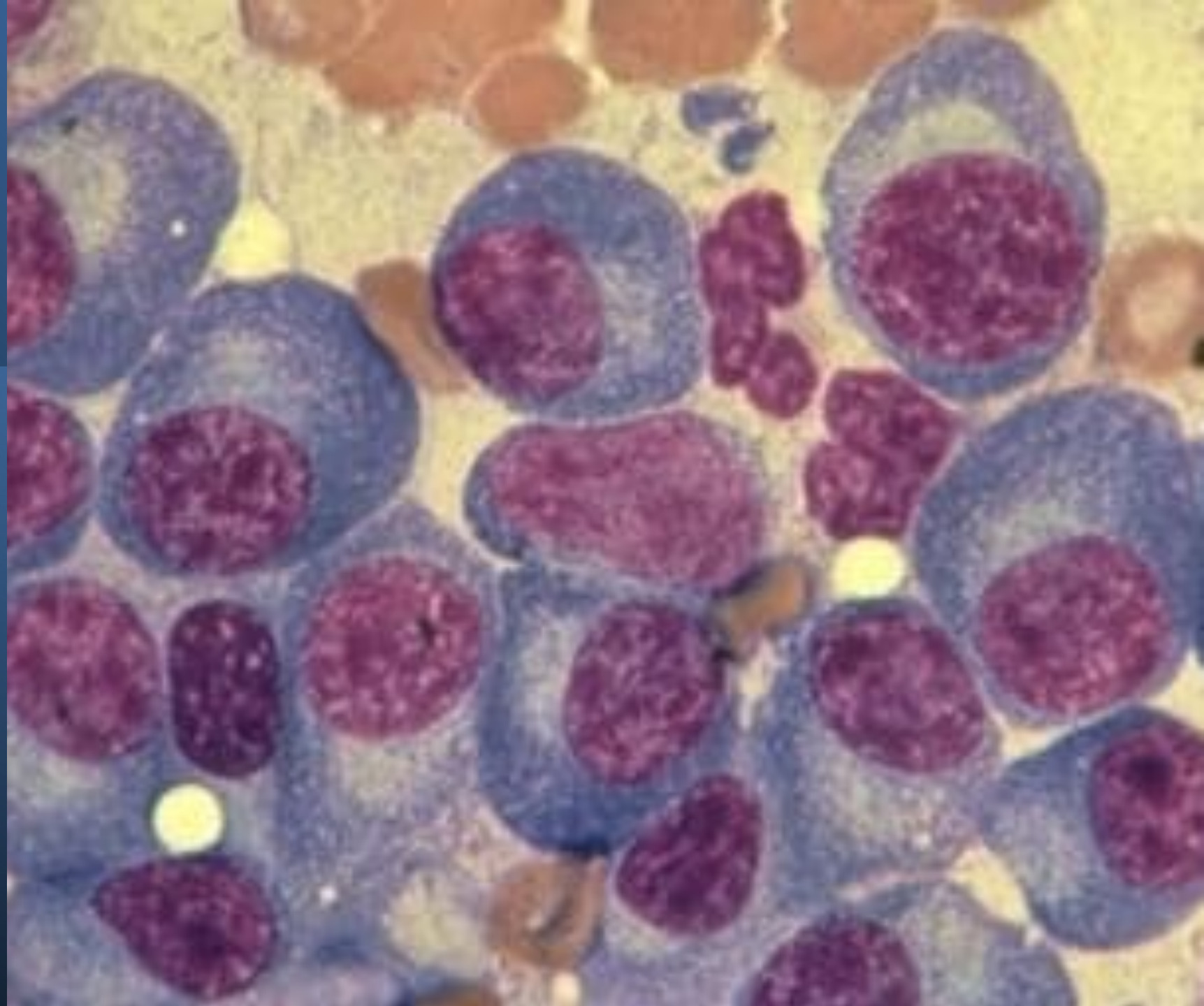
Anemia and Malignancies

- Most malignancies cause anemia.
- Anemia always has a cause. The characteristics of the RBCs may be a clue, e.g., low MCV, rouleaux to cancer diagnosis.
- My diagnostic approach is to always look for a second or third condition, for example:
  - Anemia and iron deficiency with GI symptoms
  - Anemia and gastrointestinal bleeding
  - Anemia and splenomegaly and/or lymphadenopathy
  - Anemia and leukocytosis and/or fever
  - Anemia and recurrent fever and/or elevated sedimentation rate (ESR)

Diagnosis of Multiple Myeloma

- Bone pain of the spine, chest and hips – new and distinctive
- Mild anemia and elevated ESR
- RBC rouleaux on blood smear
- SPEP showing elevated gamma globulins and monoclonal spike (M spike)
- Light chain ratio > 100; evidence of clonality
- Bone marrow with > 10% plasma cells and clonality
- Genetic sequencing to define high and low risk mutations
- Focal lesions on bone scan, accelerate treatment
- Hypercalcemia and renal failure also determines treatment

Plasma Cells in Multiple Myeloma



Treatment of Multiple Myeloma Multiple Options with Complex Making

- Old:
  - Melphalan
  - Prednisone
- Current (for good candidates):
  - Bortezomib
  - Lenalidomide
  - Dexamethasone followed by autologous stem cell transplant (ASCT); then lenalidomide maintenance.
- Current (for poor transplant candidates):
  - Same with dose adjustments and no ASCT.
- Many treatment variations and new drugs/therapies

Primary Care and Multiple Myeloma

- A chronic disease
- May initially require no treatment MGUS
- Knowing when to refer
- Problems are:
  - Worry
  - Bone pain
  - Renal complications
  - Infections
  - Fatigue

Case Study #3

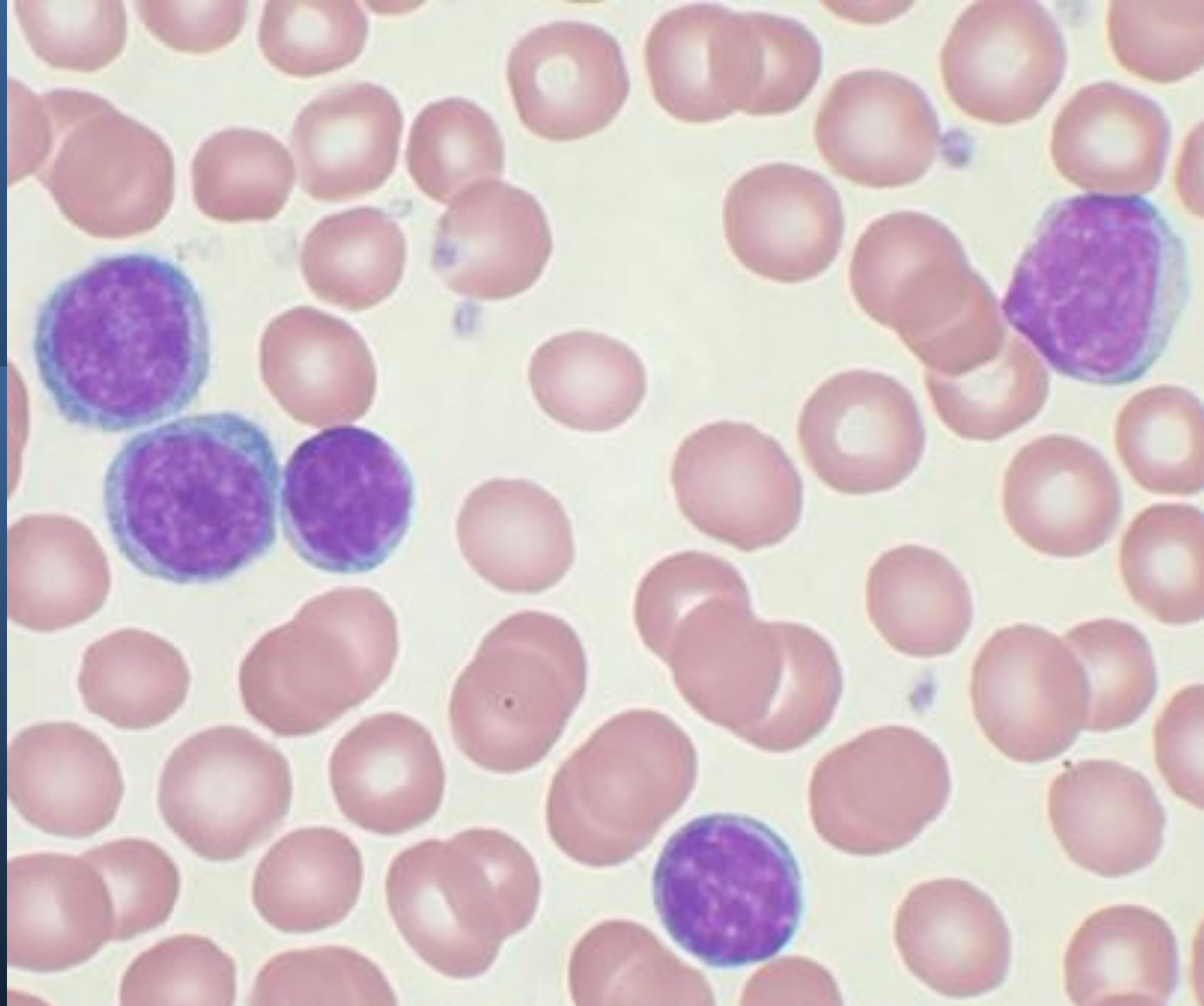
A 69-year-old retired football coach shows up at your office for his annual exam.

- His only complaints: decreasing libido and fatigue.
- The physical exam is unrevealing, but his CBC attracts your attention:
  - WBC: 12,000, HCT: 34, PLTS: 250,000
  - Differentials (Absolute Counts):
    - Polys/Segs: 4.9, Bands: 0.2
    - Lymphs: 6.0
    - Monos: 0.4
    - Eos: 0.4
    - Baso: 0.1

What is your leading diagnosis?

a) Chronic lymphocytic leukemia
b) Chronic myeloid leukemia
c) Acute lymphocytic leukemia
d) Acute myeloid leukemia

Chronic Lymphocytic Leukemia



Chronic Lymphocytic Leukemia and Primary Care

- Most common hematological malignancy
- Older males
- Lymphocytes > 5.0 x $10^{3/}$µL makes diagnosis more likely
- Usually elevated B-cells in blood
- Course very indolent
- Treatment can be delayed
- Follow for infections, anemia, autoimmune complications
- Therapies: targeted therapy, chemotherapy, radiation immunotherapy, and/or transplant
  - Decisions about therapy are patient specific and need thoughtful care

Molecular and Genetic Pathways to Lymphocytic Leukemia

Genomic alteration in 80% of patients

Most common relevant chromosomal aberrations that necessitates careful genetic analysis by a specialist:

- trisomy 12
- 11q deletion, 13q deletion, 17p deletion
- translocations
- complex karyotypes

Mutations cluster in groups related to signaling, chromatin modifiers, cell cycle, DNA damage response, etc.

Standard treatment(s):

- chemotherapy (chlorambucil plus rituximab or fludarabine, cyclophosphamide plus rituximab)
- several other active agents

Novel treatments:

- ibrutinib (*BTK* inhibitor)
- venetoclax (*BCL2* inhibitor)
- idelalisib (*PI3K* inhibitor)

Primary Care and Chronic Lymphocytic Leukemia

Guide	Help	Continue
Guide patient to an expert hematologist for assistance with diagnosis; rarely an emergency.	Help patient and patient's family to understand that life-expectancy is long despite the diagnosis of leukemia.	Continue to manage co-morbidities and understand the significance of adverse effects: minor and transient versus fatal and life-threatening.

Case Study #4

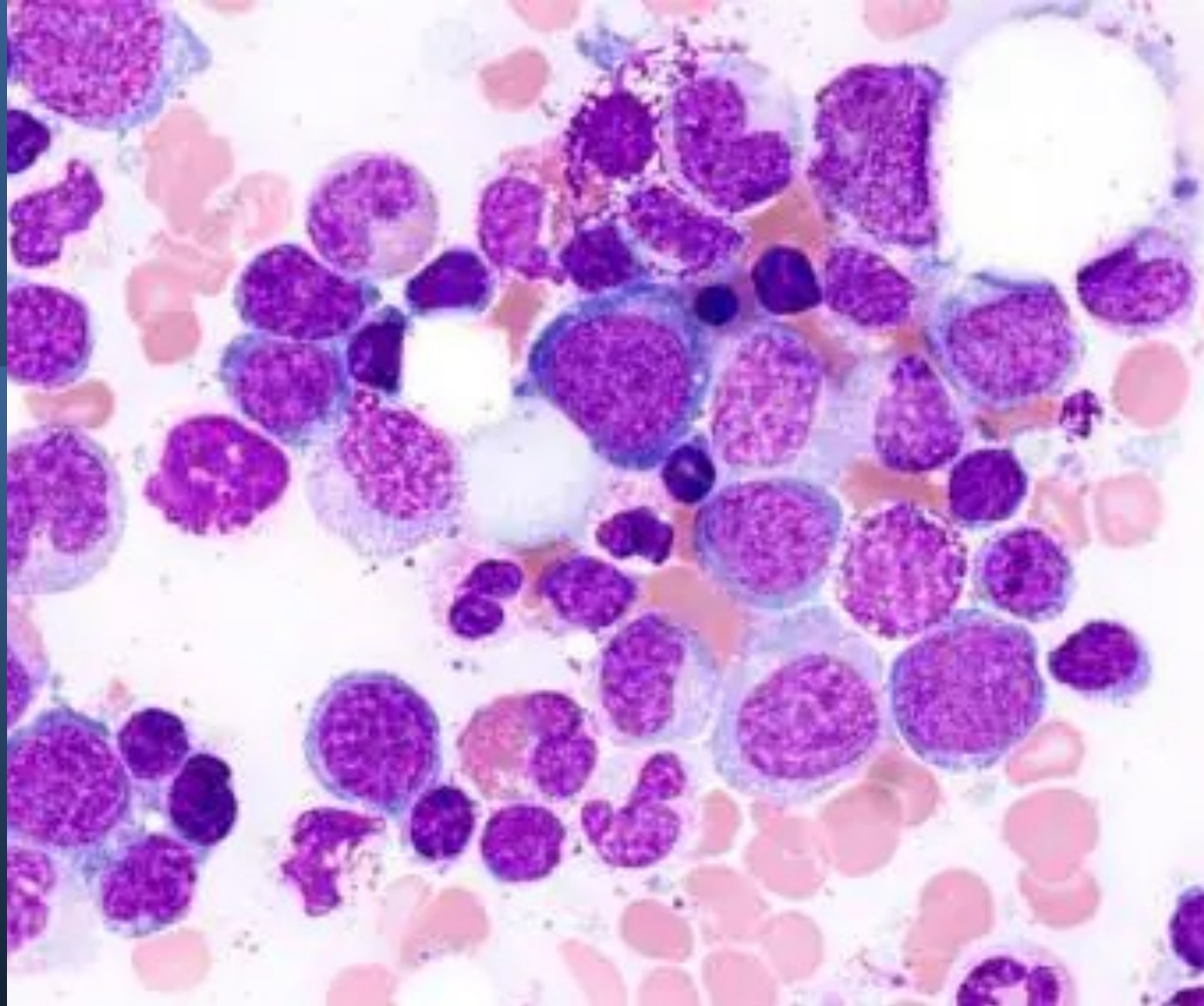
A 38-year-old schoolteacher comes to your clinic office for the first time.

- She presents with fatigue, fever and symptoms of a urinary tract infection.
- The physical exam is unremarkable, but she looks a bit pale.
- You are concerned if she is anemic.
- You do a quick urinalysis and order a urine culture and CBC.
- The CBC is a bit of a surprise. Results:
  - WBC: 1,800, HGB: 7.5, HCT: 27, PLTS: 75,000
  - Polys/Segs: 800, Bands: 100, Lymphs: 800, Monos: 100

What do you do next?

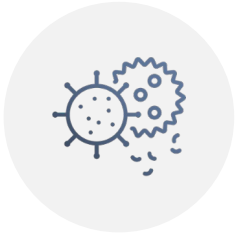
a) Review patient's medications and drug history.
b) Review patient's blood smear with laboratory results.
c) Order iron and total iron-binding capacity (TIBC) tests.
d) Refer patient to a hematologist for a bone marrow and diagnostic help.

Myelodysplastic Syndrome

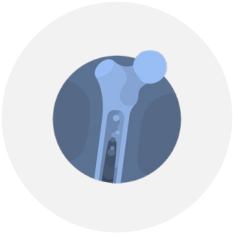


Presentations for Myelodysplasia

GRADUALLY WORSENING ANEMIA, LEUKOPENIA AND THROMBOCYTOPENIA



FATIGUE, FEVER, AND/OR INFECTIONS



BONE MARROW SHOWS DYSPLASIA

GENETIC TESTING MAY SHOW MULTIPLE MUTATIONS

TRANSFUSION RESPONSE DECREASES

Myelodysplastic Syndrome

- Treatment decisions can be difficult.
- Transfusions are transient support and should be used judiciously.
- Several chemotherapy options are available for specialists.
- Hematopoietic stem cell transplant (HSCT) is the only curative therapy.
- Supportive care for patients and patients' families is very important.

Summary

- Precise diagnosis for hematological malignancies is increasingly important; it necessitates an alliance of primary care physicians with specialists in hematology and oncology.
- Improving prognosis for treatment of malignancies increases the importance of recognizing the early signs and symptoms for these conditions.
- Regardless of the specific malignancy, patients and families need supportive care and concern from their long-term primary care provider.
- Each patient provides many opportunities for professional growth and keeping up with “What’s New in Medicine.”