Internal Medicine Board Review:  
Hematology

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Topics to be Covered

- Basics of “Benign” Hematology including
  - Clotting disorders
  - Bleeding disorders
  - Anemia evaluation
  - Hemoglobinopathies

- Basics of “Malignant” Hematology including
  - Acute leukemias
  - Chronic leukemias
  - Myeloproliferative disorders
  - Lymphomas
  - Myeloma

Question 1 - Background

- A 74 year-old Asian woman presents with fatigue, malaise of 2 months duration. PMHx remarkable for DM type II, HTN. She denies melena, hematochezia, hematemesis. Medications include atenolol, ASA. There is no family history of anemia.
- Exam: Thyroid normal, conjunctiva pink, no adenopathy, no splenomegaly.
- Automated CBC shows WBC 4500/ul, Hgb 10 gm/dl, MCV 75fl, plt 520,000/ul
- Peripheral smear is shown on the next slide:

Question 1 - Peripheral Smear
Question 1

- What is the most appropriate test?

1. Hemoglobin electrophoresis
2. Bone marrow biopsy with Prussian blue staining
3. Ferritin, iron, and transferrin levels
4. Serum TSH, free T4 determination
5. Vitamin B12 and RBC folate levels

Goal: Identify/Evaluate Fe deficiency

- Microcytic anemia:
  - Fe deficiency
  - Thalassemias
    - Alpha
    - Beta
  - Pb poisoning
  - (Anemia of chronic disease)
  - (Sideroblastic Anemia)

- Blood Smear
  - Microcytosis
  - Hypochromia
  - Target cells
    - Fe deficiency
    - Thalassemias
    - Liver disease
    - S/p splenectomy
    - abetalipoproteinemia
    - "Weirdness"

Question 2 - Background

- You are consulted for a 35 year-old woman who has been told she requires a hysterectomy for chronic, severe menorrhagia. The patient is concerned because she experienced bleeding excessively after a routine cholecystectomy. She gives a history of heavy menses but no spontaneous bleeding. She has had prolonged oozing from prior dental extractions. She does not take any medications. Family history reveals a sister and aunt with a "bleeding problem."
- CBC shows WBC 7500/ul, Hgb 11.6 gm/dl, platelet 245k/ul
- Review of smear showed no abnormal forms
- PT is 10.4s, aPTT is 25.8s.

Question 2a

What test is most appropriate at this point?

1. Factor XIII activity
2. Antiphospholipid antibody titer
3. Fibrin split products, fibrinogen, reptilase time
4. Von Willebrand factor antigen, ristocetin cofactor activity, FVIII activity level
5. Mixing study
**Goal: Understand Coagulation Testing**

- **PT/aPTT are best initial screening tests for coagulopathy**
  - **Isolated Elevated aPTT**
    - Lupus anticoagulant (does not lead to bleeding; may be associated with thrombosis)
    - Factor VIII, IX, XI deficiency (HMW Kinogen, Factor XII, Prokalirein)
  - **Isolated elevated PT**
    - Warfarin effect
    - Liver disease
    - Fibrinogen deficiency/diastere
  - **Both PT and aPTT elevated**
    - Liver disease (severe)
    - Warfarin, Heparin
    - DIC
    - Factor II, V, or X deficiency

**Question 2b**

- The patient has a von Willebrand panel sent and the vWF Ag, ristocetin co-factor activity, and Factor VIII levels are all less than 30%. A vWF multimer assay shows decreased multimer intensity but normal multimer pattern, consistent with type 1 von Willebrand disease. The best treatment is:
  1. Cryoprecipitate prior to hysterectomy
  2. Hysterectomy with post-procedural Amicar®
  3. Bi-weekly fresh-frozen plasma
  4. Trial of intranasal DDAVP (Stimate®) at menses
  5. Platelet transfusion

**Platelet Disorders (Abnl PFA)**

- Qualitative platelet disorders rare
  - Bernard-Soulier, Glanzmann thrombasthenia, platelet storage diseases
- **Bleeding due to von Willebrand disease common**
  - Type 1: most common (70% of VWD patients): vWF decreased, multimers decreased, DDAVP works well by increasing vWF release from storage sites
  - Type 2A: Ag twice activity; decreased large multimers
  - Type 2B: often thrombocytopenic; DDAVP usually contraindicated (can worsen thrombocytopenia)
  - Type 2N: Factor VIII binding, hemophilia A phenotype
  - Type 3: rare, homozygous, severe quantitative defect
- When type of VWD is unknown for urgent treatment, best to give vWF in the form of intermediate purity VWF concentrate (e.g., Humate-P®)

**Question 3 - Background**

- 68 year old man was found to have a normocytic, normochromic anemia after workup for fatigue. Serum electrophoresis reveals a monoclonal band 0.5 mg/dL, IFE with IgG kappa. Free Light Chain Ratio 1.65 (nL). Urine dipstick reveals no protein, and his bone marrow biopsy demonstrates mixed hematopoiesis and <5% plasma cells. Bone survey shows mild diffuse osteopenia.
- Current laboratory values are:
  - WBC 6200/ul, Hgb 13.3 gm/dl, plt 315k/ul, MCV 98fl
  - Creatinine 1.1, calcium 9.3, albumin 39
  - Ferritin 65, Iron 12, TIBC 140, Saturation 8%
Question 3a

- What is the most appropriate statement about this condition?
  1. His chance of malignant transformation is approximately 1% per year and remains relatively constant
  2. Treatment with a bisphosphonate has been shown to improve disease-related outcomes
  3. High dose chemotherapy with stem cell rescue is superior to conventional chemotherapy in this disease.
  4. The negative urinalysis suggests a lower likelihood of developing renal insufficiency

Goal: Recognize MGUS

- A spectrum of disease
- **MGUS**
  - Less than 3gm Protein
  - <10% plasma cells
  - increased incidence with age
  - Does not require therapy (yet)
  - Regular Monitoring
- **Myeloma**
  - Monoclonal protein
  - Bone Marrow >10% or Plasmacytoma
  - CRAB
- Key Difference is CRAB

More information…

- The patient in the previous scenario sees you in follow-up at 12 months and notes onset of reflux, rare palpitations, easy bruising, and carpal tunnel syndrome with "stocking glove" dysesthesias. After bending over to pick up his shoes, he spontaneously develops bilateral periorbital ecchymoses.
- Repeat serum electrophoresis reveals an increase of the kappa spike to 0.9 mg/dL; Free Light Chain Ratio elevated at 5; WBC 5.1, Hgb 11.8, plt 223; Creatinine 1.6, calcium 8.6, albumin 2.9
- GI evaluation reveals esophageal dysmotility with reflux
- ECG shows sinus rhythm, low voltages, with frequent PACs and PVCs; an echocardiogram shows marked LVH
- Nerve conduction tests reveals sensorimotor neuropathy in hands and feet

Question 3b

What is the most appropriate test at this point?

1. Temporal artery biopsy
2. Abdominal fat pad biopsy
3. Cardiac catheterization and biopsy
4. Electrophysiology studies
5. Urine protein electrophoresis
**Question 3c**

What is the best therapy?

1. Colchicine monotherapy
2. Autologous hematopoietic cell transplant
3. Symptomatic management with metoclopramide, gabapentin, and a proton pump inhibitor
4. Oral melphalan and Decadron
5. Serial plasmapheresis

**Goal: Recognize Amyloidosis**

- Infiltrating process affecting various organs
- Renal involvement portends longer survival, cardiac involvement results in short median survival (5 mos)
- Diagnosis is made by biopsy of affected tissue; abdominal fat pad biopsy also useful because of low risk; bone marrow biopsy needed to rule out primary myeloma
- Treatment: Similar to myeloma

**Question 4 - Background**

- A 25 year-old African-American man presents with substernal chest pain and dyspnea. Vital signs: BP 155/85, HR 110, RR 18, T 37.8°. Oxygen saturation is 99% on room air. Exam shows tachycardia, normal heart sounds, normal breath sounds, no hepatosplenomegaly
- EKG shows sinus tachycardia, borderline left ventricular hypertrophy with repolarization anomalies in V4-V6
- CXR is clear
- CBC shows WBC 10,900/ul, Hgb 7.4 gm/dl, plt 306k/ul, MCV 82fl
- Peripheral smear is shown on the following slide:
Question 4

- Which of the following statements regarding this patient's disease is true?

1. This patient likely has about 25-35% Hgb F seen on hemoglobin electrophoresis
2. With optimal standard management, this patient's life expectancy is unaffected by his hematologic disorder
3. The molecular defect is usually a point mutation on the beta chain of hemoglobin.
4. Hydroxyurea decreases frequency of painful episodes by altering red cell G6PD content

Goal: Understanding Sickle Cell Anemia

- Normal Hgb electrophoresis:
  - 95-98% Hgb A (α2β2)
  - 1-3% Hgb A2 (α2δ2)
  - 0-1% Hgb F (α2γ2)

- Sickle cell anemia is associated with significant morbidity and mortality: median survival about 43 years; need regular ophthalmic care, echo for LVH, Palm HTN

- Some patients have coincident beta thalassemia (Hgb S/b-thal), can have clinical manifestations as Hgb SS

- Most common causes of death: Infection, acute chest syndrome, missed aplastic crisis

- Phenotype AS (sickle carrier state) doesn't usually result in painful episodes but hematuria/hyposthenuria/proteinuria possible

Question 5 - Background

- You are consulted to evaluate anemia, thrombocytopenia, and mental status changes in a 59-year-old woman with HIV, CD4 count 410/μl, no prior infections.
- She was brought to the ER by her partner after progressive lethargy, personality changes, and diaphoresis developed.
- In the ER: BP 95/40, HR 121, T 38.6°C, RR 18, CBC shows WBC 10,600/μl, Hgb 9.7 gm/dl, plt 21k/μl, MCV 101
- Na 134, K 4.1, Cl 101, CO2 18, BUN/Cr 34/2.1, LDH 1381
- PT 11.5s, PTT 32.6s
- Smear is shown on the next slide:

Question 5 - Peripheral Smear
Question 5

The patient is started on broad spectrum antibiotics, cultures of blood and urine are obtained and volume repletion is given.

What therapy is most appropriate for this patient?
1. Platelet transfusion
2. IV steroids
3. Intravenous gamma globulin
4. Plasma exchange
5. Emergent splenectomy

Question 6 - Background

- You are asked to evaluate hypercoagulability in a 62-year-old African-American woman with her first deep vein thrombosis. She presented with new right leg edema and tenderness without pulmonary symptoms. Her PMHx is unremarkable. She takes no medications, and does not smoke. Family history is negative for thrombotic disease.
- WBC 7500/ul, Hgb 12.7gm/dl, plt 361k/ul, PT 11.3s, PTT 32.6s.
- Lower extremity ultrasound shows an extensive occlusive clot involving the superficial femoral vein on the right. A full citrate-anticoagulated tube (blue top) is collected, and patient is therapeutically anticoagulated with low molecular weight heparin followed by warfarin.

Question 6

- (A) Prothrombin mutation 20210A assay
- (B) Mixing study, dilute Russell viper venom test, ANA
- (C) Send pre-anticoagulation blue top for Protein C, Protein S, antithrombin III levels
- (D) DNA-based test for Factor V Leiden

• Which test(s) are most appropriate?
  1. D only
  2. A & B & C & D
  3. A & C & D
  4. A & D
  5. None of these tests are appropriate at this time

Goal: Hypercoagulability Work-up

- DVTs are common, even without inciting events, though many are associated with trauma, immobilization, surgery, cancer, inflammation
- Family history is an important to assess the utility of an expensive workup (Protein C, S; Antithrombin III deficiency are all quite rare)
- Ethnicity is also relevant: Factor V and Prothrombin mutations relatively common among Europeans, but rare for those of Asian and African descent
- Perform age-appropriate cancer screening, especially in older individuals who present with spontaneous venous thromboembolism
- Lupus Anticoagulant Testing may be of value but should NOT be performed until 30 days after VTE, if positive repeat at 90 days.
Question 7 - Background

- A 43 year-old woman with AML who received consolidation chemotherapy with high dose cytarabine 8 days ago c/o melena, dizziness, and fatigue.
- Exam reveals BP 82/40, HR 135, marked pallor, no adenopathy. Stool shows gross melena, strongly heme positive.
- Initial CBC shows WBC 4700/ul, Hgb 6.1gm/dl, Pt 63 (6% neutrophils, 85% lymphs, 6% monos, 3% eos).
- PT 12.1s, PTT 28.4s.
- Volume resuscitation with saline increases her BP to 106/55, HR drops to 100.

Question 7

- Which of the following statements is most accurate?
  1. Transfusions should consist of crossmatched, CMV negative packed red cells; irradiation and a leukoreduction filter should be used.
  2. The patient's prognosis is most accurately reflected by her age at diagnosis.
  3. Allogeneic hematopoietic cell transplantation has no role in the treatment of this patient if her leukemia demonstrates complex cytogenetic abnormalities.
  4. Since this patient is not leukopenic, there is no role for antibiotics at this time.
  5. Because the prognosis is so poor for this patient, she should be encouraged to consider comfort care only.

Goal: Recognize Acute Leukemia Mgmt

- AML: prognosis determined most accurately by cytogenetics; age >60, failure to remit after induction also poor prognostic signs
- Typical treatment is induction followed by consolidation; some will benefit most by transplantation, allogeneic or autologous
- Transfusions are an important issue; leukocyte filters help decrease alloimmunization and transfusion reactions, irradiation prevents transfusion-associated GvHD; CMV products should be used if the patient’s status is unknown or negative.
- Febrile neutropenia is a medical emergency and warrants emergent antibiotics for GNR, GPC (ANGWBC)

Question 8

- Which statement concerning myeloproliferative diseases is correct?
  1. Testing for presence of the t(9;22) translocation (bcr-abl) is unnecessary unless leukocytosis and a leukoerythroblastic peripheral smear are present.
  2. Serum Erythropoietin Level is a useful first step in evaluation, Bone Marrow Biopsy is of secondary importance.
  3. Patients with essential thrombocytosis have a cumulative lifetime risk of conversion to AML of more than 50%.
  4. The presence of a hematocrit <40% rules out the possibility of polycythemia vera.
  5. In a patient with a platelet count over 700,000, the most likely diagnosis will be essential thrombocytosis.
Question 9 - Background

- You are consulted for thrombocytopenia in a 58 year-old woman admitted for elective hysterectomy 1 week ago. Her surgery was uneventful, and post-operatively she was placed on unfractionated heparin 5000 units subcutaneously twice daily. A post-operative CBC showed WBC 11,200/ul, Hgb 12.4 gm/dl, plt 316k/ul.
- Two days later, the patient had a low-grade fever. On exam, the wound was weeping and erythematous and intravenous cefazolin was started.
- On day 6, the patient remained febrile. Vital signs T 101.2°F, BP 102/55, HR 110. She appears ill, and exam reveals fullness and mild tenderness in the lower abdomen. CBC shows WBC 14,100/ul, Hgb 11.7gm/dl, plt 51k/ul.

Question 9 - continued

- Review of the peripheral smear confirms thrombocytopenia and reveals rare schistocytes.
- CT of the abdomen/pelvis reveals a 3 cm hematoma in the left paracolic gutter.
- You should do all of the following EXCEPT:
  1. Discontinue cefazolin and start vancomycin
  2. Start methylprednisolone 100 mg IV every 6 hours
  3. Draw blood for PT, aPTT, fibrinogen, D-dimers
  4. Consider urgent surgery to drain her hematoma pending laboratory results
  5. Discontinue heparin

Goal: Recognize HIT

- Heparin-induced thrombocytopenia: caused by antibodies directed against complexes of heparin and platelet factor 4; manifest as falling platelets about 5-10 days after 1st exposure or 1-2 days after subsequent exposures.
- Often leads to thrombosis by massive activation of platelets and generation of thrombin.
- Timing, Thrombocytopenia, No Other Cause, Thrombosis
- Tests are anti-PF4 Ab ELISA; Serotonin Release Assay/HIPA
- For presumed or confirmed HIT, a direct thrombin inhibitor (argatroban or lepirudin, Hirudin) should be as initial anticoagulation, due to high (50%) risk of thrombosis in confirmed HIT.
- Post-op bleeding in this patient also could represent DIC, drug reaction (cephalosporins)—Low Specificity in ICU setting.

Question 10

- A 78 year old man presents with profound GI bleeding. He has a history of MI 4 years ago, angina managed medically, and hypertension. He is resuscitated with packed red cells and is taken to the ICU where he continues to bleed. Endoscopy is unrevealing other than the finding of fresh blood oozing. The patient is noted to also have epistaxis and a large hematoma at the right groin at the site of a central line placement attempt. Laboratory from the ED show WBC 10,900/ul, plt 249k/ul, creat 1.4, LFTs nl, PT 11.7s, PTT 68.2s.
Question 10

- Which of the following should be the next step to evaluate the patient’s bleeding disorder?

1. Stat Russell Viper Venom Time
2. Mixing study
3. Repeat aPTT with heparin adsorption
4. Euglobulin clot lysis time
5. Diagnostic trial of recombinant human factor VIII followed by repeat aPTT 60 minutes after administration

Goal: Evaluate Isolated Elevated aPTT

- Differential includes
  - Lupus anticoagulant
  - Heparin contamination
  - Factor deficiency (VIII, IX, XI, XII)
  - Factor inhibitor

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Question 11

- A 62 year-old man presents with a slowly growing painless neck mass despite two courses of antibiotics. He otherwise feels well and there is no pharyngitis, hoarseness, dysphagia, odynophagia, fever, weight change, or night sweats. There is no significant past medical history. Medications: none. Habits: never smoked, rare alcohol use.

- Physical exam is unremarkable except for the neck nodule.

- Laboratories show a WBC of 18,600/ul, plt 198k/ul, hgb 13.9gm/dl. Absolute lymphocytes 14,400/ul. A fine needle aspiration is performed and reveals monotonous but mature lymphocytes. Flow cytometry shows CD5 and CD 19 positivity. An excisional biopsy is performed and immunoperoxidase stain for bcl-1 is negative.

Question 11

Which of the following statements regarding this patient is true?

1. Very few patients with this disorder have bone marrow involvement
2. If the same phenotype cells in the biopsy are found circulating in the blood, the prognosis is very poor, with a median survival of 18 months.
3. Fludarabine has been shown to improve overall survival in this disorder
4. Urgent intensive chemotherapy is necessary now; allogeneic hematopoietic cell transplantation should be the next step for optimal outcome.
5. Observation is most appropriate management at this time.
Question 12

- A 72-year-old male presents with progressive fatigue and dyspnea on exertion over three months. He had normal blood counts 3 years ago. No new medications over this period. He denies any ETOH use.
- Physical Exam: mild pallor and occasional bruises on his extremities. Labs: Hemoglobin of 7.8gm/dl, MCV of 109fl, WBC of 3200/ul with 0.8 x 10⁹/ul neutrophils and platelets of 75,000/ul.

Question 12a

Which of the following tests would not be indicated in the work-up of the anemia?

- Vitamin B12 level
- Red Blood cell folate level
- TSH level
- Bone marrow biopsy with cytogenetics
- Serum lead level

Goal: Evaluating Macrocytic Anemia

Nuclear Maturation
- 1. Vitamin B12, Folate
- 2. Chemotherapy, Anti-retrovirals
- 3. Myelodysplasia (MDS)

RBC Membrane
- 4. Liver Disease (often see target cells on smear)
- 5. ETOH
- 6. Hypothyroidism

Other
- 7. Reticulocytosis
- 8. Cold Agglutinins

Question 12a: continued

- All the vitamin levels and TSH were normal. The patient was given a transfusion of RBCs, and the Hgb increased appropriately.
- The patient next underwent a bone marrow biopsy which showed dysplastic red blood cells and uninucleate megakaryocytes; there were <5% blasts. Cytogenetics showed complex changes (t(11,14), +8,-7). The biopsy results and cytogenetics are consistent with Myelodysplastic Syndrome (MDS).
Question 12b

The patient asks you about his prognosis with the diagnosis of myelodysplasia.

What is the least important factor regarding prognosis?

1. Number of blasts in marrow
2. Prior history of smoking
3. Number of cytopenias.
4. Cytogenetics
5. Age at diagnosis

Question 12 – Goal: Understand MDS

1. Frequent cause of anemia in older patients.
2. Clonal stem cell disorder affecting maturation/differentiation
   Usually affects RBC but may affect any/all lines
3. High propensity to convert to acute leukemia.
   (IPSS) The international prognosis scoring system
   1. number of blasts in BM at diagnosis
   2. number of cytopenias
   3. cytogenetics
   4. Age

Question 12c

Which of the following treatments are acceptable options in this case?

1. Supportive care only (transfusions of red blood and platelets as needed)
2. Cytokine therapy (erythropoietin, +/- GM-CSF) plus transfusions as needed.
3. Revlimid (biologic therapy) with #1 or 2 above
4. 5-Azacytidine (low dose chemotherapy) with #1 or 2 above
5. Allogeneic stem cell transplantation (using a matched donor)
6. All of the above

Question 12: GOAL: Treatment in MDS

- Most patients with MDS are older
  - treated with supportive care only (i.e. transfusions).
  - If serum erythropoietin levels low may benefit from EPO
- Treatment decisions are highly dependent on age, performance status and IPSS score (prognosis).
  - Younger, poor prognosis are more likely to receive Therapy
- Two new classes of drugs approved for use in MDS;
  - Thalidomide and Revlimid
  - Hypomethylating Chemotherapy (5-azacytidine and decitabine).
    - response rates of approximately 40% for improving anemias.
**Question 12 – GOAL: Treatment in MDS**

- Intensive chemotherapy can be given to patient who progress to AML
  - Remission rates vary between 30-60% (age dependent) and remission duration is usually <1 year.
- Allogeneic transplantation is the only curative therapy for MDS.
  - Previously reserved for younger (<60 years of age) patients with good performance status.
  - With low IPSS score 60% of patients can be cured.
- Non-myeloablative transplantation (i.e. low-dose or “mini” transplants) up to age 75.
  - Should be done in the context of a clinical trial.

**Additional Topics**

- Heme in pregnancy (TTP → plasma exchange; HELLP syndrome → Thrombotic microangiopathy with elevated transaminases; Tx is to terminate and consider aHUS)
- Porphyrias (commonest is porphyria cutanea tarda w/ Hep C: deficiency in heme pathway; cutaneous photosensitivity; Tx is phlebotomy to reduce hepatic iron avoid sun and aggravating drugs – EtOH, estrogens)
- Hodgkin disease (easy to miss; late risk of coronary artery disease, breast/lung cancer in previously irradiated patients)