

Section 8: Hematology

CHAPTER 47: ANEMIA

Q.1. A 56-year-old man presents with symptoms of severe dyspnea on exertion and fatigue. His laboratory values are as follows:

Hemoglobin 6.0 g/dL (normal: 12–15 g/dL)

Hematocrit 18% (normal: 36%–46%)

RBC count 2 million/ μ L (normal: 4–5.2 million/ μ L)

Reticulocyte count 3% (normal: 0.5%–1.5%)

Which of the following caused this man's anemia?

- A. Decreased red cell production
- B. Increased red cell destruction
- C. Acute blood loss (hemorrhage)
- D. There is insufficient information to make a determination

Answer: A. This man presents with anemia and an elevated reticulocyte count which seems to suggest a hemolytic process. His reticulocyte count, however, has not been corrected for the degree of anemia he displays. This can be done by calculating his corrected reticulocyte count ($[3\% \times (18\%/45\%)] = 1.2\%$), which is less than 2 and thus suggestive of a hypoproliferative process (decreased red cell production).

Q.2. A 25-year-old man with pancytopenia undergoes bone marrow aspiration and biopsy, which reveals profound hypocellularity and virtual absence of hematopoietic cells. Cytogenetic analysis of the bone marrow does not reveal any abnormalities. Despite red blood cell and platelet transfusions, his pancytopenia worsens. Histocompatibility testing of his only sister fails to reveal a match. What would be the most appropriate course of therapy?

- A. Antithymocyte globulin, cyclosporine, and prednisone
- B. Prednisone alone
- C. Supportive therapy with chronic blood and platelet transfusions only
- D. Methotrexate and prednisone
- E. Bone marrow transplant

Answer: A. Although supportive care with transfusions is necessary for treating this patient with aplastic anemia, most cases are not self-limited. Bone marrow transplant is the best option for patients with a suitable donor. Survival rates can approach 90%. If transplant is not an option, antithymocyte globulin and prednisone with or without cyclosporine is the treatment of choice. Response rates have approached 70% to 80% in some studies.

Q.3. A 60-year-old man presents with abdominal pain, diarrhea, and marked weakness. He notes that his symptoms have been present for a few weeks. He has a history of monoclonal gammopathy of undetermined significance (MGUS) and ulcerative colitis. About one month ago he was treated for bronchitis with a 7-day course of trimethoprim/sulfamethoxazole. He does not take any medications presently. His review of symptoms is positive for darkening of his urine. His physical examination shows a pulse of 110/min, blood pressure of 130/80, and a temperature of 99.8° F. His sclerae are icteric, and he is pale. His abdomen is diffusely tender without rebound or guarding. The spleen tip is palpable. His stool is brown, watery, and hemocult positive. Laboratory studies are as follows:

WBC 9000/ \square L

Hemoglobin 7 g/dL

Hematocrit 22%

MCV: 90 fl

Platelets 200,000/ \square L

Reticulocyte count 12%

LDH 500 U/dL

Total bilirubin 5 mg/dL

Direct bilirubin 0.4 mg/dL.

His peripheral smear reveals numerous spherocytes. Direct antiglobulin test is positive with anti-IgG and anti-C3 sera. What is the most appropriate course of therapy for this patient?

- A. Blood transfusion of four units over four hours
- B. Splenectomy and transfusion (if needed)
- C. Chlorambucil and transfusion (if needed)
- D. Steroids and transfusion (if needed)
- E. Transfusion and supportive care alone, but at a slow rate

Answer: D. This patient has a reticulocytosis, which suggests a hemolytic process. The presence of spherocytes on peripheral smear and a positive direct antiglobulin test with anti-IgG point to a diagnosis of warm antibody immune hemolytic anemia. Anti-C3 can also be seen in these patients. The initial treatment for this form of anemia is steroids. If this treatment fails, splenectomy can be attempted. This patient also has symptoms that could be consistent with ulcerative colitis. Ulcerative colitis is associated with warm antibody hemolytic anemia. Lymphoproliferative disorders and collagen vascular disease are also associated, although over half of all cases are idiopathic. A is incorrect; blood transfusions should be given slowly and only if absolutely necessary. C is incorrect because chlorambucil is used to treat cold agglutinin hemolytic anemia associated with MGUS. If this patient had cold agglutinin disease, an anti-IgG would not have been found; only an anti-C3 would be present.

Q.4. A 70-year-old man with no significant past medical history comes into your office for a visit. He is found to have a hemoglobin of 12.9 g/dL (HCT 39%). His MCV is 92 fl. His red cell distribution width (RDW) is elevated at 17.5%. A review of his old records reveals a hemoglobin level of 14.9 g/dL when he last saw a doctor 10 years ago. His creatinine is 0.9 mg/dL. Which of the following statements is correct regarding this patient's condition?

- A. He will be considered anemic if his hemoglobin falls below 12 g/dL
- B. An evaluation of the drop in his hemoglobin is unnecessary as this can be expected with aging
- C. If his hemoglobin continues to decline, his erythropoietin level should decrease
- D. Fetal hemoglobin should make up approximately 1% of the hemoglobin in this elderly man
- E. His elevated RDW suggests that there is poikilocytosis (abnormally shaped red blood cells)

Answer: D. This patient has anemia, defined by a hemoglobin of less than 13 g/dL and his drop in hemoglobin over time. Although many older patients develop anemia, it is not a normal function of aging and does require evaluation. Tissue hypoxemia from decreasing hemoglobin is the major stimulus to erythropoietin production which results in production of red blood cells by the bone marrow. An elevated RDW suggests that there is anisocytosis (variation in size of red cells) but says nothing about the shape. Normal hemoglobin usually consists of about 97% hemoglobin A ($\alpha_2\beta_2$), 2% hemoglobin A2 ($\alpha_2\delta_2$), and 1% hemoglobin F ($\alpha_2\gamma_2$).

Q.5. A 72-year-old man with a history of diabetes, hypertension, congestive heart failure, and mitral regurgitation (s/p MVR) presents to the office complaining of fatigue. On examination, his pulse is 68; blood pressure is 115/68. There is no JVD. His lungs are clear. His heart exam reveals a laterally displaced PMI, good prosthetic sounds, and an I/VI crescendo-decrescendo systolic murmur at the left sternal border. His labs reveal the following:

WBC 5,500/ μ L
Hematocrit 26
Platelets 207,000/ μ L
MCV 94 fL
Creatinine 0.9 mg/dL.

His reticulocyte count is 8%. His PT and PTT are within normal limits. His peripheral smear is shown in [Figure 47Q-1](#). The most appropriate next step in this patient's management is

- A. Obtain an echocardiogram
- B. Perform a bone marrow biopsy

- C. Begin steroids and consider plasmapheresis
- D. Check a glucose-6-phosphate dehydrogenase level
- E. Transfuse 2 units of packed red blood cells

Answer: A. This man presents with anemia and reticulocytosis which suggests a hemolytic process. His peripheral smear shows numerous schistocytes which is consistent with microangiopathic hemolytic anemia (MAHA). The differential diagnosis of MAHA includes thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), disseminated intravascular coagulation (DIC), malignant hypertension, and prosthetic valvular disease. He does not have fever, thrombocytopenia, neurologic changes, or renal disease so TTP and HUS are unlikely. Also, he does not have malignant hypertension. His coagulation times are normal so DIC is also unlikely. New MAHA in a patient with a prosthetic valve requires evaluation of the valve with an echocardiogram to ensure that the valve is functioning appropriately. If it is, a decision regarding supportive care with iron (and possibly transfusion) versus valve replacement must be made.

Q.6. Patients with anemia of chronic disease usually have

- A. A mean corpuscular volume (MCV) of between 80 and 100 fl
- B. An elevated soluble serum transferrin receptor level
- C. A low serum ferritin
- D. An elevated serum iron level
- E. A decrease in their erythropoietin levels

Answer: A. In anemia of chronic disease (ACD), serum iron, total iron binding capacity, and transferrin saturation levels are usually low. The ferritin is usually normal or high. Soluble serum transferrin receptor levels are elevated in iron deficiency but are normal in pure ACD. There is a blunted erythropoietin response in ACD but the rise in level is insufficient to maintain a normal hematocrit. Most cases of ACD are normocytic, despite often being characterized as a microcytic anemia.

Q.7. A 52-year-old man who is complaining of intense fatigue, dyspnea, and diarrhea of 2 months duration comes to your office. He reports losing about 15 pounds over the past few months. He has no past medical history. He reports drinking a glass of wine every night. He takes no medications. His physical examination reveals pallor and tachycardia to 105 beats per minute. He has a blood pressure of 130/80. You obtain blood work that shows the following:

Hemoglobin	8.2 g/dL
Hematocrit	25%
MCV	115 fL

Reticulocyte index	1.2
Platelets	101 K/ μ L

Which of the following statements is correct?

- A. The absence of anti-intrinsic factor antibodies would rule out pernicious anemia.
- B. The normal methylmalonic acid level would essentially rule out folate deficiency.
- C. If this patient had vitamin B12 deficiency from celiac sprue and malabsorption, the urinary excretion of radiolabeled B12 would be low even after administration of oral intrinsic factor (stage II).
- D. A peripheral smear in this patient is likely to reveal target cells and schistocytes.
- E. A bone marrow examination should be done immediately to rule out myelodysplastic syndrome.

Answer: C. This patient presents with a diarrhea and a macrocytic anemia. The differential diagnosis of macrocytic anemia includes vitamin B12 deficiency, folate deficiency, myelodysplastic syndrome, and hypothyroidism. Multiple myeloma, aplastic anemia, and alcohol abuse can also cause macrocytosis and anemia. With this degree of macrocytosis, vitamin B12 or folate deficiency are the most likely. Intrinsic factor antibodies are specific but not sensitive for pernicious anemia (PA). If they are positive, the diagnosis of PA is virtually assured. In folate deficient patients with normal renal function, methylmalonic acid levels are typically normal but homocysteine levels are increased. The diarrhea and macrocytic anemia suggest the possibility of a malabsorptive process such as sprue. If this is the diagnosis the Schilling test is likely to be abnormal even after administration of intrinsic factor, because the vitamin B12 deficiency is not due to a deficiency in intrinsic factor. If the Schilling test were repeated after a few weeks on a gluten-free diet (stage III) it should be normal. The peripheral smear of this patient should not show schistocytes, because the low reticulocyte count rules out hemolysis. Given the likelihood of vitamin B12 or folate deficiency with this presentation, a bone marrow examination does not need to be done at this time.

Q.8. Which of the following laboratory findings are *not* typically seen in a patient with pernicious anemia?

- A. Elevated gastrin level
- B. Elevated methylmalonic acid level
- C. Abnormally low percentage of radiolabeled vitamin B12 excreted after ingestion of oral radioactive vitamin B12 and intrinsic factor with intramuscular administration of unlabeled vitamin B12 (stage II of the Schilling test)
- D. Elevated homocysteine level
- E. All of the above findings are typically seen

Answer: C. Until recently the Schilling test was the primary way to diagnose pernicious anemia. In stage II of the test, oral intrinsic factor is given with oral radiolabeled vitamin B12 to correct the intrinsic factor deficiency seen in PA. Therefore, the absorption of radiolabeled oral B12 is normalized, as shown by an excretion level of greater than 7%. Elevated gastrin levels are seen in about 80% of patients with PA. This test, however, lacks specificity. Methylmalonic acid and homocysteine are metabolites that are both elevated in vitamin B12 deficiency. An elevated methylmalonic acid level is quite specific for vitamin B12 deficiency. Elevated homocysteine levels, however, are seen in other conditions, including folate deficiency.

Q.9. A 36-year-old man presents with fatigue and pallor. He is found to have a hematocrit of 23%. His reticulocyte index is 4. You suspect a hemolytic anemia. Which of the following lab abnormalities are *not* associated with hemolytic anemia?

- A. An elevated haptoglobin level
- B. An elevated LDH
- C. An elevated indirect bilirubin
- D. An elevated reticulocyte count
- E. The presence of hemosiderin in the urine

Answer: A. Patients with hemolytic anemia typically present with an elevated reticulocyte count, LDH, and indirect bilirubin. Hemosiderin may be present in patients with intravascular hemolysis. Haptoglobin is a protein that binds free hemoglobin for uptake by the reticuloendothelial system. During hemolysis the amount of free hemoglobin rapidly exceeds the production of haptoglobin, so levels are typically low.

Q.10. A 60-year-old man presents with fever, fatigue, headache, and myalgias for the past 4 days. He recently returned from a vacation on Martha's Vineyard. On examination, his pulse is 110 and his BP is 110/70. His temperature is 39°C. There is some scleral icterus. His blood work reveals the following:

Hemoglobin 8.2 g/dL

Hematocrit 24%

MCV 94 fL

Reticulocytes 9%

Platelets 150 K/ μ L

Total bilirubin 3.5 mg/dL

Direct bilirubin 1 mg/dL

Lactate dehydrogenase 500 U/dL

A peripheral smear is obtained that reveals intraerythrocytic oval parasites, with some tetrads. What is the most likely vector of this disease?

- A. Anopheles mosquito
- B. Reduviid bug
- C. Brown recluse spider
- D. Ixodes tick
- E. Tsetse fly

Answer: D. This patient presents with hemolytic anemia due to parasitemia. He recently returned from Martha's Vineyard, which is a clue to the diagnosis of babesiosis. Babesiosis is a parasitic disease that is transmitted by the Ixodes tick. In the United States, *Babesia microti* is endemic to areas in the Northeast. Patients can be asymptomatic or can develop life-threatening hemolytic anemia. It is often difficult to distinguish babesiosis from malaria (transmitted by the anopheles mosquito) based on the peripheral smear alone, but epidemiologic information and serology can be helpful. The reduviid bug is the vector of Chagas' disease, while the tsetse fly is the vector for African trypanosomiasis.

Q.11. A 53-year-old woman presents to you for an opinion. She has a history of hypertension, chronic renal insufficiency, and anemia. She recently saw her nephrologist, who suggested that she begin erythropoietin injections for her anemia. All of the following are potential side effects of erythropoietin therapy *except*

- A. Red blood cell aplasia
- B. Hypotension
- C. Iron deficiency anemia
- D. Seizures
- E. Thrombosis

Answer: B. Erythropoietin is widely used for treatment of anemia due to renal failure, renal insufficiency, and some causes of anemia of chronic disease. Its most common side effect is hypertension, so careful monitoring must be done in hypertensive patients. There have been a few cases of red cell aplasia as a result of erythropoietin. Iron deficiency anemia can develop in patients who do not get iron replacement with continued therapy. Thrombosis and seizures have also occurred but the incidence for both of these complications is low.

CHAPTER 48: PLATELET DISORDERS

Q.1. You are asked to evaluate a 56-year-old man with a history of end-stage renal disease and bleeding from a central line site. The patient has recently started

dialysis, his access has not been functioning, and he was admitted with a temperature of 39° C. He had a central line placed on admission, and since its insertion the nurses have been changing blood-soaked bandages every four hours. His labs are as follows:

Hct 26%

MCV 75 fl

Platelet count 175,000/□L

WBC 7000/□L

Prothrombin time 13 seconds

Activated partial thromboplastin time 50 seconds

BUN 120 mg/dL

Creatinine 7.0 mg/dL

Hepzyme (detects heparin contamination)—positive

Which of the following is *not* a treatment option?

- A. Erythropoietin
- B. Cryoprecipitate
- C. Factor VIII concentrate
- D. Dialysis
- E. Conjugated estrogens

Answer: C. The most likely cause of this patient's bleeding diathesis is uremia. His platelet count is normal. The abnormal activated partial thromboplastin time corrects with hepzyme, suggesting that there was contamination of the specimen with heparin. This is a common occurrence in patients with central lines and in patients undergoing dialysis. The treatment options include erythropoietin therapy to try to increase the hematocrit to above 30%, which has been shown to decrease bleeding. Cryoprecipitate, conjugated estrogens, and dialysis have all been shown to be effective in decreasing bleeding from uremic toxins. Factor VIII will not likely be helpful in stopping this patient's bleeding.

Q.2. Which of the following tests is required to confirm the diagnosis of immune thrombocytopenic purpura (ITP) in a young patient with isolated thrombocytopenia?

- A. Review of peripheral blood smear
- B. Antiplatelet antibodies
- C. Bone marrow examination
- D. Liver spleen scan

Answer: A. Immune thrombocytopenia is a diagnosis of exclusion. In an otherwise healthy patient, review of the peripheral blood smear is adequate to suggest the diagnosis and to start therapy. If a patient fails treatment with steroids or is elderly, a bone marrow is indicated to confirm the diagnosis and to rule out another disorder. Antiplatelet antibodies depend on an adequate platelet count to run the test and are not specific or sensitive for the diagnosis of ITP.

Q.3. A 56-year-old male is undergoing preoperative testing for elective spinal surgery three days before his scheduled OR date. The nurse finds on history that the patient is taking aspirin and took the last dose the day before. The surgeon orders a bleeding time, the results of which are normal. What should you recommend?

- A. Repeating the bleeding time
- B. Sending the patient to the OR as scheduled
- C. Giving the patient 6 units of platelets at the time of surgery
- D. Postponing the patient's surgery for 10 days

Answer: D. Only 50% of patients on aspirin will have prolonged bleeding times. The bleeding time is not useful in predicting which patients will bleed with surgery. Transfusion of platelets for a nonemergent procedure puts the patient at risk of the complications of transfusion. Those risks include not only the infectious complications but also allergic and febrile transfusion reactions. Because the effect of aspirin is an irreversible acetylation of cyclooxygenase, it lasts for the lifetime of the platelet. Surgery should therefore be postponed for 10 days and the patient should be reminded to avoid all aspirin products.

Q.4. A 45-year-old man with HIV/AIDS and a CD4 count of 25 is admitted to your medical intensive care unit after having presented to the emergency room with hypoxemic respiratory failure. Chest x-ray done in the emergency room revealed bilateral fluffy infiltrates; pO₂ is 55mm Hg on 4L nasal cannula. Blood pressure is 88/50, respiratory rate is 36/min, temperature is 38.5° C, SpO₂ is 93% on 80% face mask. At the time of admission to the ICU the patient was alert and oriented. He complained of a week of increasing shortness of breath. He denies easy bruising or bleeding. The patient has no known drug allergies and takes no medications. His urine toxicology screen is positive for metabolites of cocaine, quinidine, and opiates. A complete blood count drawn in the emergency room shows an Hgb 9 mg/dL and an Hct of 27%; his WBC is 20,000/μL with 88% neutrophils; his platelet count is 9,000/μL. Basic metabolic panel is unremarkable. Peripheral blood smear is performed, which confirms thrombocytopenia and demonstrates an increased WBC with toxic granulations consistent with infection but does not show any schistocytes. Which of the following is *least* likely to be a cause of thrombocytopenia for this patient?

- A. ITP
- B. Sepsis
- C. Drug effect
- D. TTP

Answer: D. This complicated patient has several possible different reasons for thrombocytopenia. The most likely reason is sepsis, especially if the patient had a previously normal platelet count. Systemic infection alone, without DIC, can cause thrombocytopenia through increased activity of the reticuloendothelial system stimulated by elevated endogenous levels of macrophage colony stimulating factor. If this patient had had a previous history of thrombocytopenia, or if, having resolved the patient's current episode of sepsis the platelet count remained low, this patient might well have ITP related to his HIV. If this patient's thrombocytopenia were related to ITP the therapy could involve either steroids (which should be started empirically in this patient in any event given the high likelihood of PCP), or immunoglobulin (either IVIG or WinRho if the patient is Rh[D] positive). This patient has a third possible reason for his thrombocytopenia, which relates to his drug abuse. Cocaine is frequently cut with drugs like quinidine, which can independently result in thrombocytopenia. This patient does not have symptoms or a peripheral blood smear consistent with the diagnosis of TTP.

Q.5. A 22-year-old woman presents with menorrhagia. She states that since puberty she has always had "excessive" menstrual bleeding, and is concerned that she has "abnormal blood." Which of the following details from the history would be most suggestive of a platelet disorder?

- A. Recurrent hemarthroses
- B. Easy bleeding of skin or mucosa
- C. Bleeding that develops 72 hours following a surgical procedure
- D. A desire to eat ice chips or starch

Answer: B. When evaluating the patient with a suspected platelet disorder, historical details of the bleeding pattern can be useful. Patients with platelet disorders most commonly develop easy bruising, and may have bleeding of skin or mucosa with only minor trauma. Platelet disorders also manifest as bleeding immediately after surgery (there is no 72-hour delay), and may manifest in women with heavy menstrual bleeding. Recurrent hemarthroses, on the other hand, are unusual in platelet disorders, and are more common in individuals with disorders of the clotting cascade (as seen in hemophilia). A desire to eat ice chips or starch is called "pica," and is a behavioral manifestation described with iron deficiency. Platelet disorders may be evaluated with a bleeding time, which will reflect quantitative and qualitative platelet disorders.

Q.6. A 57-year-old woman undergoes mitral valve replacement for rheumatic heart disease. Postoperatively, she is placed on heparin. Five days later, the patient develops a left lower extremity DVT. Laboratory examination shows the following: aPTT ratio: 2.4; PT: 1.2; hematocrit 30.1%; WBC 9000; platelets 97,000. Fibrinogen is normal, and D-dimer is negative. Blood work is unchanged from two days ago, except that thrombocytopenia is new. Which of the following is the most likely explanation for this clinical presentation?

- A. Subtherapeutic dosing of heparin
- B. Antiphospholipid antibody syndrome
- C. Disseminated intravascular coagulopathy
- D. Antiheparin/platelet antibodies

Answer: D. This patient's presentation is suggestive of heparin-induced thrombocytopenia (HIT). HIT develops in predisposed individuals when exposed to heparin, and takes one of two forms. Type 1 HIT is nonimmune mediated, occurs a few days after initiation of heparin, results in thrombocytopenia, but no thrombosis. Type 2 HIT usually begins 5 to 10 days after initiation of heparin, is due to antibodies against the heparin/platelet combination, and thrombocytopenia and thrombosis develop. Treatment for HIT is discontinuation of heparin. If thrombosis is present, other forms of anticoagulation will be needed. Otherwise, this patient is therapeutic on heparin, and has no prior history suggestive of antiphospholipid antibody syndrome. Her blood work is not suggestive of DIC.

CHAPTER 49: COAGULATION DISORDERS

Q.1. A 30-year-old woman is admitted for sudden onset of right arm and leg weakness. An MRI reveals evidence of an acute cerebral infarct. A transesophageal echocardiogram with a bubble study documents the absence of a patent foramen ovale or intracardiac clot. She has a past medical history of several previous miscarriages. Which of the following is true regarding her disease?

- A. She most likely has a positive assay for activated protein C resistance
- B. She most likely has an elevated anticardiolipin antibody titer
- C. She will need indefinite aspirin therapy
- D. She will need indefinite warfarin anticoagulation
- E. B and C
- F. B and D

Answer: F. This patient probably has antiphospholipid antibody syndrome. This disorder would also explain her past history of miscarriages. An elevated anticardiolipin antibody titer (or evidence of a lupus inhibitor as demonstrated by

an abnormal dilute Russell viper venom time), if confirmed on repeat testing in six to eight weeks, would confirm this diagnosis. Activated protein C resistance is associated with venous thromboembolism but does not increase the risk of arterial thromboembolism in the absence of a patent foramen ovale. A diagnosis of antiphospholipid antibody syndrome with clinical thrombotic events requires therapeutic anticoagulation with a vitamin K antagonist.

Q.2. You are called to consult on a 40-year-old woman who develops excessive bleeding during a hysterectomy. This is her first major surgery, but there is a history of excessive bleeding after a wisdom tooth extraction and menorrhagia. There is no history of aspirin or nonsteroidal use. Laboratory studies reveal: PT of 11 seconds, INR of 1.0, and aPTT of 24 seconds. What other tests would you order?

- A. Bleeding time
- B. Factor VIII level
- C. Factor VII level
- D. von Willebrand antigen level/ristocetin cofactor activity
- E. A, B, and D

Answer: E. von Willebrand disease (vWD) is the most common inherited bleeding disorder and is associated with a history of mucosal bleeding (epistaxis, menorrhagia, bleeding with dental surgery, etc.) as described in this patient's history. Although vWD can be associated with abnormal aPTT results, many patients with mild type I vWD have normal aPTT results and therefore, you should not exclude the diagnosis of vWD on the basis of a normal aPTT. The evaluation of a patient for vWD includes the following tests: von Willebrand factor (vWF) antigen, ristocetin cofactor activity, factor VIII level, and vWF multimer analysis. The bleeding time is also commonly used although it appears to be less sensitive than the aforementioned tests and perhaps some newer tests of platelet function, such as the platelet function analyzer 100 (PFA 100). Factor VII deficiency is unlikely given the normal PT. Therefore, a factor VII level will not be useful in the evaluation of this patient.

Q.3. Six days after an abdominal surgical procedure, a 50-year-old man is readmitted to the intensive care unit with hypotension. He had evidence of bleeding from several peripheral phlebotomy needle sticks and his internal jugular central line site. Laboratory studies reveal PT of 20 seconds (normal 10.4–12.9), aPTT of 40 seconds (normal 24.4–34.0), and platelet count of 20,000/ \square L. What other laboratory tests would you order to determine the etiology of this patient's coagulopathy?

- A. D-dimer assay

- B. Fibrinogen level
- C. Antiplatelet antibody test
- D. All of the above
- E. A and B

Answer: E. This patient most likely has disseminated intravascular coagulation (DIC). The D-dimer assay and a fibrinogen level are useful in documenting the presence of DIC. Antiplatelet antibodies are not useful in this situation. DIC occurs when procoagulant proteins, particularly tissue factor, are released into the systemic circulation. Normally, the endothelium serves to prevent tissue factor (which is expressed by the subendothelium) from coming into contact with the bloodstream. Any stimulus that disrupts the protective endothelial layer can produce DIC. Activated endothelial cells or leukocytes can also serve as a source of tissue factor. Excessive tissue factor production activates the extrinsic pathway and subsequently the common pathways of coagulation, resulting in consumption of coagulation factors and platelets. Thrombosis and/or bleeding can result. Treatment focuses on the underlying disorder that is responsible for initiation of the coagulopathy.

- Q.4.** You are consulted to see a 40-year-old woman with a history of two previous deep venous thromboses. Neither event was associated with any identifiable risk factors. She says several family members have also suffered thrombotic events. Which inherited hypercoagulable disorder is she most likely to have?
- A. Activated protein C resistance (factor V Leiden)
 - B. Antithrombin III deficiency
 - C. Protein C deficiency
 - D. Prothrombin A20210G mutation

Answer: A. Factor V Leiden (which causes resistance to activated protein C) is the most common inherited thrombophilic disorder. It is present in as many as 60% of patients with familial recurrent venous thromboembolism. The presence of this mutation in factor V disrupts the activated protein C cleavage site on factor V, dramatically slowing the rate of factor V inactivation. This abnormality disrupts the normal hemostatic balance, which favors excessive thrombin generation and thus clot formation. In contrast to factor V Leiden, antithrombin III, protein C, and protein S deficiencies taken together account for less than 15% of patients with inherited thrombophilia.

- Q.5.** A 40-year-old woman with a history of recurrent deep venous thrombosis and factor V Leiden presents to discuss her management. How long should she take warfarin?
- A. Six weeks

- B. Six months
- C. One year
- D. Indefinitely

Answer: D. Although asymptomatic patients with factor V Leiden should not be prophylactically anticoagulated (because some do not suffer thrombotic events), any patient with factor V Leiden and recurrent idiopathic thrombosis should probably be placed on indefinite anticoagulation. Use of oral contraceptives in the presence of factor V Leiden heterozygosity is associated with a 30-fold increase in risk of venous thromboembolism. There is a several-hundred-fold increase in risk in factor V Leiden homozygotes. Therefore, women with known factor V Leiden should not use oral contraceptives.

Q.6. An 18-year-old high school senior is brought into the emergency department after falling off his motorcycle. His left knee is swollen, erythematous, and warm. An x-ray demonstrates a hemarthrosis as well as evidence of chronic arthropathy. The following laboratory studies are available: PT of 12 seconds, INR of 1.1, and aPTT of 65 seconds. What laboratory studies would you choose to further evaluate this patient?

- A. 1 to 1 mixing study
- B. Factor VIII level
- C. Factor VII level
- D. Factor XII level
- E. A and B

Answer: E. This case illustrates the importance of always considering the possibility of factor inhibitors as an etiology for coagulation disorders. The patient likely has classic hemophilia A. However, factor VIII inhibitors are not uncommon among patients with hemophilia (15%–20% of severe hemophiliacs develop them during their lifetime), therefore, a factor VIII level and mixing studies should be ordered to exclude the presence of a factor VIII inhibitor. The identification of a factor VIII inhibitor is important because hemophiliacs with high titer factor VIII inhibitors will not respond to factor VIII concentrates but instead need to be treated with alternative blood products such as FEIBA (factor VIII inhibitor bypassing activity) or recombinant human factor VIIa (NovoSeven) to achieve hemostasis. This patient clearly does not have factor VII deficiency because his PT is normal. Factor VII deficiency is much less common than hemophilia A or B and its inheritance is autosomal recessive. Bleeding severity is usually mild to moderate and does not always correlate with factor level. Some patients with factor VII levels less than 1% can have severe bleeding similar to patients with hemophilia A or B. Factor VII deficiency results in an isolated prolongation of the PT. FFP or NovoSeven can be used for replacement therapy. Although factor XII

deficiency can cause an isolated prolonged aPTT, it is not associated with a bleeding diathesis.

Q.7. You are asked to consult on a 75-year-old man five days after an emergent cholecystectomy. Preoperative labs were normal. His surgical procedure was uncomplicated. His postoperative course has been complicated by persistent fever and an ileus, which has required placement of a nasogastric tube. Today he was noted to have numerous bruises and bleeding from IV sites. His lab results show a hematocrit of 32%, a platelet count of 140,000/ \square L, a PT of 20 seconds (normal 10.4–12.9), and an aPTT of 43 seconds (normal 24.4–34.0). What are the most likely cause(s) of this patient's coagulopathy?

- A. DIC
- B. Liver disease
- C. Vitamin K deficiency
- D. Factor IX deficiency
- E. A and C
- F. B and D
- G. All the above

What additional test(s) would you order?

- A. Factor IX level
- B. Fibrinogen level
- C. D-dimer
- D. Factor VII level
- E. B and C
- F. A and D
- G. All of the above

Answers: E and E. The patient has an acquired coagulopathy given that his preoperative tests were normal and there were no difficulties with operative hemostasis. During the postoperative period, he has had fevers and no oral intake. It is also likely he is receiving broad-spectrum antibiotics. Each of these factors indicates that he is at substantial risk for vitamin K deficiency. While vitamin K deficiency is the most likely diagnosis, DIC is also possible. The patient is febrile and has evidence of a systemic coagulopathy as seen by his multifocal bleeding in association with abnormal screening coagulation tests and thrombocytopenia. In contrast, liver disease and factor IX deficiency are unlikely as this patient had normal preoperative testing and hemostasis as documented by his preoperative testing and operative course (Answer E is correct for the first question). To determine expeditiously whether the patient has DIC or is vitamin K deficient, measure a fibrinogen level and perform a D-dimer assay. In the presence of DIC,

his D-dimer level will be dramatically elevated and the fibrinogen level will be significantly reduced (usually < 100 mg/dL). While low factor IX and VII levels are likely to be present in DIC they are also present in vitamin K deficiency and thus will not aid in the differentiation between these two diagnostic possibilities (Answer E is correct for the second question).

Q.8. A 75-year-old man who underwent an urgent cholecystectomy has postoperative bruising. His PT and PTT are elevated but were normal on preoperative testing. He has a fibrinogen of 550 mg/dL (normal 150–450 mg/dL) and a D-dimer level of 3.52 mg/L (normal 0.4–2.2 mg/L). What is the appropriate treatment for this patient?

- A. FFP
- B. Vitamin K 10 mg IV
- C. Vitamin K 10 mg SC
- D. Recombinant human Factor VIIa (NovoSeven)
- E. Heparin anticoagulation
- F. All of the above

Answer: C. The elevated fibrinogen level is not consistent with DIC being the cause of the observed coagulation test results, as the fibrinogen level should be low to account for these results. Although the D-dimer is slightly elevated, this level is not specific for DIC and can be seen in any hospitalized patient. FFP and recombinant human factor VIIa are useful treatment for patients who have serious or life-threatening bleeding associated with vitamin K deficiency or warfarin anticoagulation. However, these aggressive measures are not necessary in the patient presented above who does not have these clinical features. Similarly, intravenous vitamin K is not appropriate in this instance. Although IV vitamin K results in more rapid correction of vitamin K deficiency, it is rarely associated with anaphylaxis. Therefore, IV vitamin K should be reserved for life-threatening bleeding. Consequently, subcutaneous vitamin K is the most appropriate choice of therapy in this case.

Q.9. You are asked to see a 20-year-old college student who has developed bleeding 24 hours after his appendectomy. Intraoperative hemostasis was normal. His screening coagulation studies are normal including his PT, aPTT, and thrombin time. His platelet count is 300,000/ \square L. His past bleeding history, however, is remarkable for bleeding as a baby from his umbilical cord and after circumcision. In addition, he tends to bleed excessively after minor trauma and has poor wound healing. What additional tests studies should you order?

- A. Factor VII level
- B. Alpha-2-antiplasmin level

- C. Factor XIII level
- D. Fibrinogen level
- E. B and C
- F. All of the above

Answer: E. This patient most likely has factor XIII deficiency. He has delayed bleeding after surgery and a history of poor wound healing, which are hallmarks of this disorder. Deficiency of alpha-2-antiplasmin, a natural inhibitor of the fibrinolytic enzyme, plasmin, can also cause delayed bleeding and should be investigated as well, although poor wound healing is not particularly associated with this disorder. In contrast, this patient's lab results and history are not consistent with a fibrinogen defect (which would certainly result in a prolonged thrombin time and possibly abnormal PT and aPTT results) or a deficiency of factor VII (which would be associated with an abnormal PT). Factor XIII deficiency and defects in the fibrinolytic cascade, such as alpha-2-antiplasmin and PAI-1 deficiency, are several disorders that should be considered in any patient with bleeding in the presence of a normal PT, aPTT, and thrombin time. The endpoint of normal coagulation studies, such as the PT and the aPTT, is the formation of a visible clot. Factor XIII catalyzes the formation of covalent cross-links between fibrin strands in the substances of the clot. This activity is not tested by standard clotting assays, which only look for the presence of clot formation not clot strength. In patients with bleeding despite normal coagulation studies, consider von Willebrand disease and platelet disorders (e.g., Bernard-Soulier syndrome, Glanzmann's thrombasthenia, storage pool disease), and acquired disorders of platelet function.

Q.10. You are called to see a 52-year-old rabbi who had a cholecystectomy six days ago for acute cholecystitis. His coagulation studies were normal preoperatively. He has a low-grade fever and scattered ecchymoses on his skin. He is also bleeding from his IV catheter site. His labs show a newly developed coagulopathy of undetermined etiology. The laboratory results reveal the following:

PT 22 seconds (control is 8.3–10.5 seconds)
INR 2.0
aPTT 53 seconds (normal 22.2–33.4 seconds)

What laboratory tests would you order next to evaluate this patient?

- A. 1 to 1 mixing study
- B. Factor XI level
- C. 1 to 1 mixing study, D-dimer assay, and fibrinogen level
- D. Ristocetin cofactor and von Willebrand factor antigen
- E. Anticardiolipin antibodies and a dilute Russell's viper venom time

Answer: C. The patient has a prolongation of both the PT and the aPTT. Therefore, involvement of factors in the common pathway is likely. A mixing study will help to determine whether a deficiency state or an inhibitor is present. The patient has just had an operation and is febrile, so ruling out the presence of disseminated intravascular coagulation (DIC) with a D-dimer assay and a fibrinogen level is reasonable. Ordering only a mixing study is insufficient. Although the patient is of Ashkenazi Jewish ethnicity and Factor XI deficiency is much more common among this ethnic group than the general population, the presence of normal coagulation studies preoperatively make this diagnosis unlikely. Furthermore, factor XI deficiency would prolong only the aPTT. Ristocetin cofactor and von Willebrand factor antigen is useful to diagnosing von Willebrand's disease, but this disorder is usually congenital and is associated with a normal PT and aPTT. Similarly, anticardiolipin antibodies and a dilute Russell's viper venom time are useful in working up antiphospholipid antibody syndrome, but this syndrome is associated with clinical thromboses, not bleeding and ecchymoses.

Q.11. A 65-year-old man is transferred from the intensive care unit to the surgical floor three days after undergoing cardiac bypass surgery. The surgery was uncomplicated, but he develops a serious wound infection and is treated with broad-spectrum antibiotics. Ten days later, he is noted to have spontaneous bleeding from his Foley catheter and central line site. Coagulation studies are sent and reveal a PT of 24 seconds (normal 8.3–10.5), INR 2.1, aPTT of 56 seconds (normal 22.2–33.4). The D-dimer is positive undiluted. The fibrinogen is 250mg/dL (normal). A mixing study corrects both the PT and aPTT. What is the most likely diagnosis?

- A. Disseminated intravascular coagulation (DIC)
- B. Vitamin K deficiency
- C. Factor XIII deficiency
- D. Factor IX deficiency
- E. Lupus anticoagulant

Answer: B. Both coagulation tests correct on a 1 to 1 mixing study indicating a deficiency state. The most likely diagnosis in this setting is vitamin K deficiency. Vitamin K is necessary for the synthesis of active forms of factors II, VII, IX, X, and the anticoagulant proteins C and S. Common causes of vitamin K deficiency include biliary disease (which interferes with the delivery of bile necessary for the absorption of fat-soluble vitamins like vitamin K), a poor diet, and use of broad-spectrum antibiotics (which kill intestinal bacteria that represent a significant source of vitamin K). In addition, some antibiotics with the MTT side chain (moxalactam, cefamandole, cefaperazone) can interfere with vitamin K metabolism potentiating the deficiency state. Many of these factors are present in patients after surgical procedures. In this patient, broad-spectrum antibiotics are

the most likely culprit. Unless a patient is having serious bleeding, vitamin K deficiency can be treated with subcutaneous vitamin K, which corrects coagulation abnormalities in 8 to 12 hours. Fresh frozen plasma is required for immediate correction. The presence of a normal fibrinogen level and an insignificant level of D-dimer make DIC an unlikely culprit. Factor XIII is important for cross-linking fibrin strands and making a clot resistant to fibrinolysis. A deficiency is more likely to result in bleeding at the surgical wound site. Factor IX deficiency (Christmas disease) is a congenital bleeding disorder. It would have caused severe bleeding before the age of 62 years. A lupus anticoagulant is not present since the mixing study corrected.

Q.12. A 60-year-old truck driver with new-onset bruisability presents to your office for evaluation. He has chronic hypertension that is controlled with ramipril. On review of systems, he describes an unintentional weight loss of 10 pounds over the last six months. He is taking no medications. His physical exam reveals splenomegaly and several scattered ecchymoses. Labs are notable for the following:

PT: 12 seconds (normal 8.3–10.5 seconds)

aPTT: 28 seconds (normal 22.2–33.4 seconds)

Bleeding time: 3 minutes (normal)

Platelet count: 230,000/ μ L

Hematocrit: 33%

Creatinine: 1.1 mg/dL

What diagnostic test would be most appropriate?

- A. Fat pad biopsy
- B. Factor XIII level
- C. Factor IX level
- D. Platelet aggregation studies
- E. Serum erythropoietin level

Answer: A. The combination of new easy bruisability, splenomegaly, and anemia may represent amyloidosis. Amyloidosis is most commonly seen in conjunction with a plasma cell dyscrasia (e.g., multiple myeloma) or as primary amyloidosis (where light chains are deposited in organs such as the skin, spleen, liver, kidneys, and heart causing organ dysfunction). Amyloid results in bleeding because it collects in vessel walls making them fragile and more likely to rupture after incidental trauma. This tendency results in the classic “raccoon eyes” sign seen in amyloidosis patients after Valsalva maneuvers and “pinch purpura.” This case is an important reminder not to forget that disorders of the vessel wall can also produce bleeding manifestations. Other causes of vessel wall fragility and purpura include steroid use, vasculitis, inherited connective tissue disorders (e.g.,

Ehlers-Danlos syndrome), old age, and scurvy. Although this patient has normal screening tests for coagulation and platelet function, Factor XIII deficiency is unlikely given the recent onset of his bleeding disorder and the presence of splenomegaly (which would not be explained by this deficiency state). Deficiency of Factor IX is associated with a prolonged aPTT, would have probably presented earlier in life, and is not associated with splenomegaly. Platelet aggregation studies are unlikely to shed light on this patient's bleeding disorder given a normal bleeding time. In the setting of normal renal function, an erythropoietin level is also not likely to be helpful in diagnosing his underlying condition.

Q.13. A 40-year-old construction worker is referred to you after his preoperative workup for a hernia operation reveals a prolonged aPTT. He has never had any problem with bleeding and has had several dental procedures performed without incident in the past. He denies a family history of bleeding. His physical examination is unremarkable. Laboratory studies show the following:

PT 11 seconds (normal 8.3–10.5 seconds)

aPTT 95 seconds (normal 22.2–33.4 seconds)

1 to 1 mixing study corrects

What is the most likely cause of his prolonged aPTT?

- A. Factor VIII deficiency
- B. Factor IX deficiency
- C. Factor VIII inhibitor
- D. Factor XII deficiency
- E. von Willebrand's disease

Answer: D. Unlike the other options listed, factor XII deficiency does not result in a bleeding diathesis. This patient has withstood several prior surgeries (dental extractions) without bleeding complications. Factor VIII and IX deficiencies and von Willebrand's disease are unlikely given the absence of bleeding despite surgical challenge. Most of these patients would have clinical symptoms. No treatment is necessary for Factor XII deficiency.

Q.14. A 44-year-old man presents to the emergency room with new-onset atrial fibrillation with a rapid ventricular response. His past medical history is notable only for hypertension. His rate is controlled with intravenous diltiazem and he is admitted to the hospital. An echocardiogram shows left ventricular hypertrophy and mildly dilated right and left atria. He has no valve abnormalities. He is converted to oral diltiazem and started on warfarin. On discharge, which of the following medications will *not* potentiate the effect of the warfarin and possibly lead to bleeding?

- A. Erythromycin

- B. Amiodarone
- C. Isoniazid
- D. Omeprazole
- E. Phenytoin

Answer: E. All of the drugs listed will potentiate the effects of warfarin and possibly cause bleeding except phenytoin. Phenytoin increases the metabolism of warfarin and may lead to a subtherapeutic INR.

Q.15. A 60-year-old woman is admitted to the hospital for a deep venous thrombosis. She has no dyspnea and is otherwise stable. She is started on heparin and on day 2 is begun on warfarin. Three days later, she develops black, necrotic skin on her breasts and thighs. She is afebrile and her WBC is 9000. Which of the following is *false* regarding her condition?

- A. She may not have been therapeutic on heparin before instituting the warfarin
- B. She may have an underlying prothrombin gene mutation
- C. Her condition is due to a rapid depletion of protein S levels before other procoagulant factors
- D. She may have an underlying factor V Leiden mutation
- E. She should be restarted on heparin

Answer: C. This patient has warfarin skin necrosis as suggested by the clinical setting and physical findings. This condition is thought to be due to a rapid decline in protein C levels (not protein S) with the institution of warfarin, preceding the decline of the procoagulant factors II and X. This tips the balance in favor of coagulation, which occurs predominantly in areas of adipose tissue (breasts, buttocks, thighs). To avoid warfarin skin necrosis, heparin should be therapeutic before instituting warfarin and there should be some overlap in the therapies. Several underlying hypercoagulable states (e.g., factor V Leiden mutation, prothrombin gene mutation, antiphospholipid antibody syndrome) may predispose a patient to warfarin skin necrosis. Treatment is heparin anticoagulation and skin grafting, if necessary.

Q.16. Which of the following patients does *not* require a workup for a hypercoagulable state?

- A. A 28-year-old woman with a history of three miscarriages
- B. A 45-year-old man with a deep venous thrombosis after partial colectomy for Crohn's disease
- C. A 43-year-old woman with Budd-Chiari syndrome
- D. A 55-year-old woman with a deep venous thrombosis and a family history of deep thromboembolic disease

E. A 62-year-old man with his second admission for deep venous thrombosis in the last three years

Answer: B. The 45-year-old man with a deep venous thrombosis in the setting of being bedridden after a large surgery probably does not require any further hypercoagulable workup. Any patient with unexplained recurrent pregnancy loss (choice A), thromboses in unusual sites (choice C), a family history of thromboses (choice D), or recurrent thromboses (choice E) deserves further workup. Initial hypercoagulable workup generally includes a factor V Leiden, prothrombin gene mutation, antiphospholipid antibody testing, homocysteine level, antithrombin III activity, and protein C and S activities.

CHAPTER 50: ACUTE AND CHRONIC LEUKEMIAS

Q.1. What is the most common leukemia to present in adults in the United States?

- A. ALL
- B. AML
- C. CML
- D. CLL
- E. Hairy cell leukemia

Answer: B. AML is the disease responsible for most of the new cases of leukemia in the U.S. according to the American Cancer Society's *Cancer Statistics 2004*. New cases show the following estimated (approximate) values annually: AML, 12,000; CLL, 8200; CML, 4600; adult ALL, 3800; and hairy cell leukemia, less than 1000.

Q.2. A 31-year-old woman is diagnosed with acute promyelocytic leukemia. She is stabilized, and initiated on treatment with all-*trans*-retinoic acid, idarubicin, and cytarabine. Approximately 10 days into her treatment course, she is noted to have a temperature of 38.3° C (100.9° F) and has begun to have chest discomfort, shortness of breath, and swelling in her legs. Her laboratory studies are as follows:

Hemoglobin: 10.0 g/dL

Leukocyte count: 15,000 μ L

Platelet count: 35,000 μ L

Blood urea nitrogen: 40 mg/dL

Serum creatinine: 2.2 mg/dL

Urinalysis: 2+ protein, 5–10 RBCs, 10–15 WBCs/hpf

Chest radiograph shows diffuse infiltrates in both lower lung fields. Which of the following is the most likely cause of the patient's recent symptoms?

- A. Pneumonia
- B. Retinoic acid ("differentiation") syndrome
- C. Leukemic infiltration due to refractory disease
- D. Pulmonary embolism
- E. Disseminated intravascular coagulation

Answer: B. Retinoic acid, or "differentiation syndrome," is a well-recognized reaction to the initiation of all-trans-retinoic acid (ATRA) in patients with APL. Patients present with fevers and clinical symptoms of "capillary-leak syndrome," including SOB, hypoxia, fluid retention and edema, renal insufficiency, etc. Risk factors include a high white count APL or a rapid elevation of WBC with the initiation of ATRA. ATRA-syndrome may present up to a month into induction therapy. Steroids, the early initiation of chemotherapy to lower the WBC, and aggressive support are the mainstays of treatment.

Q.3. Which of the following statements about AML and ALL is/are correct?

- A. Both AML and ALL carry similar prognoses in children and adults
- B. Induction chemotherapy is similar; however, only AML is treated with additional cycles of chemotherapy
- C. Most of the time, the diagnosis of ALL versus AML is made by cellular morphology
- D. None of the above

Answer: D. None of the statements is correct. Childhood ALL represents one of the success stories in oncology with a nearly 80% long-term survival rate expected compared to less than 30% in adults with ALL. The treatment plans for AML and ALL are quite different: AML treatment is based on several cycles of systemic chemotherapy mostly using cytarabine and anthracyclines while ALL uses a broader array of agents (including anthracyclines, vinca alkaloids, steroids, alkylating agents, methotrexate, etc.) given for numerous cycles prior to a maintenance program of up to two years. Another important difference is that ALL requires prophylaxis of the CNS with intrathecal chemotherapy. Morphology alone is often unreliable for distinguishing between AML and ALL and special stains marking the myeloid versus lymphoid antigens are generally used to help determine the most accurate diagnosis.

Q.4. During a routine health maintenance examination a 54-year-old man, who was previously healthy and asymptomatic, is found to have an enlarged spleen. His laboratory studies are as follows:

WBC: 35,000/ μ L (3% promyelocytes, 2% myelocytes, 4% metas, 5% basophils, 59% neutrophils, 19% bands, 8% lymphs)

Hematocrit: 40%

Platelets: 525,000/ μ L

Philadelphia chromosome detected

Known curative treatment options for this patient include

- A. Interferon- α
- B. Imatinib mesylate (gleevec)
- C. Hydroxyurea
- D. Allogeneic bone marrow transplantation
- E. Both B and D

Answer: D. Allogeneic bone marrow (or stem cell) transplant remains the only known curative option for patients with chronic myeloid leukemia (CML). In recent years, interferon has been replaced by imatinib mesylate (gleevec) as the front-line therapy for patients with CML. This agent is very effective in stabilizing the blood counts and can produce cytogenetic remissions in 60% to 70% of patients treated upfront; however, its ability to "cure" patients appears limited as most remain with molecular detection of the disease (bcr/abl positive). Hydroxyurea is often used to lower the WBC in patients presenting with CML but its role as long-term therapy is limited.

- Q.5.** You are called by the laboratory with panic values on a 45-year-old woman who is in the hospital with acute myelogenous leukemia. She is mentating normally but is mildly dyspneic at rest. Her examination is notable for petechiae on her skin and crackles at both lung bases. Her white blood cell count is 110,000 μ L, her hematocrit is 22%, and her platelet count is 18,000 μ L. Her glucose is reported to be 11 mg/dL and the potassium is 7.1 mEq/dL. You are concerned about the patient's shortness of breath, so a blood gas is drawn which shows a pO_2 of 33. Her electrocardiogram does not show peaked T-waves. What should you do next?
- A. Give D50, start treatment for hyperkalemia, and place patient on O_2
 - B. Draw a sample and immediately separate the blood cells from the plasma
 - C. Send a blood gas on ice for immediate processing
 - D. Both B and C
 - E. A, B, and C

Answer: D. An elevated WBC utilizes O_2 and glucose. The excess number of cells that die in the test tube cause the K^+ to increase. These are phenomena in the test tube and not in the patient. Answers B and C are the steps you take to determine whether they are patient related or test tube related.

- Q.6.** A 60-year-old man presents with fatigue and early satiety. His physical examination is notable for an enlarged spleen. His blood work reveals leukocytosis

with a neutrophilia, mild anemia, and thrombocytosis. Which of the following statements is correct?

- A. If his bone marrow aspirate or peripheral smear reveals Auer rods, he most likely has chronic myelogenous leukemia
- B. The presence of splenomegaly suggests that he has acute myelogenous leukemia
- C. A lumbar puncture with evaluation of the CSF for CNS involvement of the leukemia is only indicated if he has headaches or other signs of leptomeningeal involvement
- D. If he has acute myelogenous leukemia, the Philadelphia chromosome would be present, which is true in 95% of cases

Answer: C. In addition to the leukocytosis, this patient has thrombocytosis and splenomegaly, which make CML the most likely diagnosis. Auer rods are virtually pathognomonic for AML but not CML. Evaluation of the CSF is mandatory in all patients with acute lymphocytic leukemia but should be guided by symptoms in acute and chronic myelogenous leukemia. The Philadelphia chromosome (9:22 translocation) is seen in over 95% of patients with CML but not AML.

Q.7. A 33-year-old woman with a history of Hodgkin's lymphoma presents with increasing weakness and fatigue. She was diagnosed with Hodgkin's lymphoma seven years ago when she presented with enlarged left cervical, mediastinal, and axillary lymph nodes. She was treated with mantle radiation, but did not receive chemotherapy. Exam shows no adenopathy, chronic radiation induced skin changes, elevated JVP, normal S1 and S2, dullness at the right lung base, and mild bilateral lower extremity edema. She had a negative exercise stress test two weeks ago for an episode of substernal chest pain. The study most likely to confirm her diagnosis is

- A. Staging abdominal and chest CT
- B. Left heart catheterization
- C. Right heart catheterization and cardiac biopsy
- D. Serum LDH

Answer: C. The patient is in heart failure. Given her history of mantle field radiation, her heart failure is likely due to either constrictive pericarditis or restrictive cardiomyopathy from the radiation exposure. Radiation can also cause premature atherosclerosis, but her recent negative stress test argues against an ischemic source of her current symptoms. Equalization of diastolic pressures between the right and left ventricle favors a diagnosis of constrictive pericarditis, but can also be seen with restrictive cardiomyopathy. Cardiac biopsy may be needed to distinguish these two entities.

Q.8. A 32-year-old computer programmer presents with a complaint of persistent, nonproductive cough. He has been having fevers and is anorexic, having lost 10 pounds over the past month. His lung examination is clear to auscultation and percussion. His chest x-ray shows an anterior mediastinal mass. The most likely diagnosis is

- A. Hodgkin's lymphoma
- B. Tuberculosis
- C. Cryptococcoma
- D. Retrosternal goiter

Answer: A. In a young patient with a mediastinal mass, the most common diagnosis is Hodgkin's lymphoma followed by non-Hodgkin's lymphoma.

CHAPTER 51: MYELODYSPLASTIC SYNDROME

Q.1. A 32-year-old woman is seen for refractory anemia. Her past history is important for treatment for Hodgkin's disease 10 years ago with combination chemotherapy containing an alkylating agent. Her laboratory studies reveal a white blood cell count of 3900/ μ L, a hematocrit of 29% with an MCV of 102 fl, and a platelet count of 150,000/ μ L. Her reticulocyte count is low. Vitamin B₁₂ and folate levels are normal. Her peripheral smear reveals a few nucleated red blood cells and a few bilobed neutrophils. Her bone marrow is normocellular with a blast percentage of 4%. Cytogenetic analysis fails to reveal any chromosomal abnormalities. She has received conflicting opinions about treatment and is seeking a second opinion. She has seven siblings. What would be the most appropriate course of treatment to recommend?

- A. Growth factors, G-CSF, and erythropoietin
- B. Allogeneic bone marrow transplant
- C. Aggressive chemotherapy with topotecan and cytarabine
- D. Supportive care

Answer: B. This patient has myelodysplastic syndrome. Growth factors will increase the neutrophil counts in most patients. The hemoglobin will increase in a small fraction of patients when endogenous erythropoietin is low. The responses have a median duration of about one year; this would not provide long-term benefit. Aggressive chemotherapy can result in complete responses, but almost none of them are durable. With supportive care, she will be transfusion-dependent, need platelet support, and will survive a median of four years. Allogeneic bone marrow transplant has a treatment-related risk of 30% mortality in her age group but does have the potential for long-term disease-free survival. Taking all these factors into account, a thorough discussion with the patient would

occur, but most oncologists would recommend an allogeneic bone marrow transplant.

Q.2. Which of the following is a poor prognostic indicator for patients with myelodysplastic syndrome?

- A. Isolated anemia with normal platelets and white blood cell count
- B. Normal cytogenetic studies
- C. Twenty-five percent blasts in the bone marrow
- D. Young age

Answer: C. The International Prognostic Staging System (IPSS) uses three indicators to assess prognosis: number of cell lines affected, cytogenetic abnormalities present, and percentage of blasts in the bone marrow. Patients with normal cytogenetic studies, 5q minus syndrome, 20q minus, and minus Y have better prognosis than those with other cytogenetic findings. Patients with only one cell line affected have a better prognosis than those with more than one affected lineage. Finally, patients with a lower percentage of blasts in the bone typically do better than those with more blasts.

Q.3. A 78-year-old man is seen for fatigue. Past medical history is relevant for no toxic occupational exposures. He has had annual physical examinations. Two years ago his hemoglobin was 13 and last year it was 11.9. His review of systems is otherwise normal. His physical examination is normal. His laboratory values are as follows:

<u>Laboratory Studies</u>		<u>Value</u>	<u>Normal</u>
WBC	3500	4500–11,000 /cu mm	
Hemoglobin		9.3	13.9–16.3 g/dL
MCV	104	80–100 fl	
Platelet count	175	150–350 K/cu mm	
BUN	23	7–22 mg/dL	
Creatinine	1.1	0.6–1.3 mg/dL	
Prothrombin time	12.3	10.8–13.0 sec	
APTT	30.3	23.4–33.5 sec	
Fibrinogen	256	150–450 mg/dL	
ALT/AST	33/41	0–40 IU/L	
Alk Phos	101	30–120 IU/L	
Total bilirubin	0.7	0.2–1.2 mg/dL	
LDH	225	122–220 IU/L	
Uric acid	3.4	2.4–6.4 mg/dL	

Review of the peripheral blood smear shows macroovalocytes, hypogranular neutrophils, and occasional large platelets. A bone marrow biopsy is performed and shows hypercellularity (90%) with mild dysplastic changes. The blast percent is 2%. What is the most likely diagnosis?

- A. Pernicious anemia
- B. Myelodysplastic syndrome
- C. Iron deficiency anemia

D. Smoldering acute leukemia

Answer: B. The patient has an asymptomatic illness extending back two years based on the hemoglobin; that makes it insidious. His WBC is low, platelets are low-normal, and the hemoglobin is low. This is true of myelodysplasia and pernicious anemia but not of iron deficiency anemia. His MCV is high, but would be even higher in pernicious anemia. The bone marrow biopsy is hypercellular with dysplasia and a low percent of blasts. This is possible in pernicious anemia but more likely in myelodysplasia. A B₁₂ level would be done to secure the diagnosis, but the most likely diagnosis is myelodysplasia with the subcategory being refractory anemia. Of note, smoldering leukemia as a diagnosis disappeared years ago with the current system of MDS diagnosis.

Q.4. Which of the following is *not* a reasonable treatment option for a 78-year-old male patient with myelodysplastic syndrome?

- A. Growth factors
- B. 5-Azacytidine
- C. Transfusion support
- D. Allogeneic bone marrow transplant
- E. All of the above are reasonable treatment options

Answer: D. The typical older age of patients with MDS at the time of presentation impacts the options for treatment. In younger patients with good performance status, a curative approach with bone marrow transplantation is often the treatment of choice. However, in an elderly patient's supportive care including growth factors, transfusions, and treatments such as 5-azacytidine are options.

Q.5. A 55-year-old man presents with pancytopenia. He notes an occupational exposure to benzene. A bone marrow examination is performed and reveals a hypocellular marrow. Cytogenetic analysis does show an abnormality (monosomy 7). Which of the following statements best summarizes the patient's condition?

- A. The patient most likely has aplastic anemia because he has a hypocellular bone marrow
- B. The patient most likely has aplastic anemia because he has a cytogenetic abnormality consistent with this diagnosis
- C. The patient most likely has myelodysplastic syndrome because he has a hypocellular marrow
- D. The patient most likely has myelodysplastic syndrome because he has a cytogenetic abnormality consistent with the diagnosis

Answer: D. Most cases of myelodysplastic syndrome present with a hypercellular bone marrow; however, in 20% of cases, a hypocellular bone marrow is seen, making it difficult to distinguish from aplastic anemia. Both

aplastic anemia and myelodysplastic syndrome have been associated with exposure to benzene. Cytogenetic abnormalities are present in about 50% of patients with myelodysplastic syndrome but are not seen with aplastic anemia.

Q.6. A 48-year-old woman presents to her local doctor for her routine physical exam. In review of symptoms she notes a mild increase in fatigue and increased difficulty on her usual five-mile morning runs. Otherwise she feels fine. Her routine blood work shows some surprises, including a white blood cell count of $2900/\mu\text{L}$, a hematocrit of 30% with an MCV of 95 fl, and a platelet count of $76,000/\mu\text{L}$. Repeat analysis yields similar results. Vitamin B₁₂ and folic acid levels are within normal limits. A bone marrow biopsy is performed and shows a hypocellular marrow. Which one of the following diagnoses is *least* likely?

- A. Aplastic anemia
- B. Myelodysplastic syndrome
- C. Paroxysmal nocturnal hemoglobinuria (PNH)
- D. Parvoviral infection

Answer: D. The patient above presents with pancytopenia and no evidence of nutritional deficiencies. Her bone marrow is hypocellular, which can present a diagnostic dilemma. Aplastic anemia, PNH, and MDS can all present with hypocellular marrows and the diagnosis can sometimes be difficult. Additional testing is required for final diagnosis. Although myelodysplastic syndrome typically present with a normocellular or hypercellular marrow, they can occasionally present with a hypocellular marrow and can then be confused for aplastic anemia or PNH. In order to diagnose, tests such as cytogenetics and CD59 are helpful. There are classic cytogenetic abnormalities that are seen in MDS such as 5q minus syndrome, 20q minus, and monosomy 7. Additionally, in PNH, there is an abnormality in the GpI anchor protein resulting in loss of CD59 expression. CD34 expression can also be assessed on the bone marrow specimens with levels being extremely low in aplastic anemia. Parvovirus is often cited as a cause of pancytopenia incorrectly. Infection more often leads to an isolated anemia within the context of pure red cell aplasia.

Q.7. A 67-year-old man presents with anemia and fatigue. He does not drink alcohol and denies any significant occupational exposures to chemicals. His MCV is 105 fl. His folate level is normal. His vitamin B₁₂ level is 292 pg/mL. Methylmalonic acid and homocysteine levels are normal. A peripheral blood smear is shown in **Figure 51Q-1**. What is the most likely cause of this man's anemia?

- A. Myelodysplastic syndrome
- B. Folate deficiency
- C. Vitamin B₁₂ deficiency

D. Beta-thalassemia trait

Answer: A. This man presents with a macrocytic anemia and normal vitamin B₁₂ and folate levels. His methylmalonic acid level and homocysteine levels are also normal, further suggesting that folic acid and cyanocobalamin stores are replete. The peripheral smear shows a multilobulated neutrophil, as well as a bi-lobed neutrophil (pseudo Pelger-Huët cell). These are both findings consistent with myelodysplastic syndrome. Beta-thalassemia trait can cause a mild chronic anemia but it would be microcytic in nature.

Q.8. A 55-year-old woman presents to you for symptoms of mild dyspnea on exertion. You order a workup including a CBC with differential, a CXR, and goes over a thorough history. The patient has otherwise been healthy with no other signs of infection or chronic lung disease. Her CXR is clear and her CBC shows a WBC of 4.4, a hematocrit of 32 with an MCV of 105, and platelets of 160k. Looking over her previous blood counts you realize that she has had a hematocrit ranging from 33 to 37 for over 4 years. Vitamin B₁₂ and folate levels are normal. A bone marrow biopsy is done showing mild dysplasia and cytogenetics showing a 5q minus abnormality. What should this patient's treatment be?

- A. Allogeneic bone marrow transplantation
- B. 5-Azacytidine
- C. Hospice
- D. Supportive care: Growth factors and transfusion support

Answer: D. The specific MDS clinical entity called 5q minus syndrome typically involves older women with refractory macrocytic anemia. Platelet counts and neutrophil counts are typically conserved, yielding a clinical course requiring transfusions but with minimal problems with bleeding or frequent infections. The bone marrow often shows hypolobated micromegakaryocytes and less than 5% blasts. The course is typically indolent and thus supportive care is usually the only treatment indicated. A new drug, lenalidomide, was recently approved for the treatment of patients with the 5q minus syndrome and hence would be a reasonable option as well.

Q.9. Which of the following statements regarding myelodysplastic syndromes (MDS) is correct?

- A. Aggressive chemotherapy designed to target clonal cells has had no impact on survival
- B. The risk for the development of MDS after chemotherapy is greatest between 15 and 25 years post treatment
- C. The MCV is usually low

D. Mortality from MDS usually results from cardiovascular events (e.g., MI and stroke) precipitated by refractory anemia

Answer: A. Presently, aggressive chemotherapy has not been shown to significantly improve survival rates. Therapy designed to affect clonal maturation (e.g., azacitidine) has shown promising results, however. The risk for development of MDS is greatest seven years after chemotherapy. Thereafter, the incidence declines. Since MDS generally presents as a macrocytic anemia, the MCV is usually high. Mortality usually results from transformation to acute myelogenous leukemia and from infection or bleeding from neutropenia and thrombocytopenia.

Q.10. A 62-year-old man with a history of seizure disorder (on phenytoin) presents with fatigue and pancytopenia. A bone marrow biopsy is done which reveals a hypocellular marrow. Cytogenetic studies reveal a chromosomal abnormality. What is the most likely diagnosis?

- A. Aplastic anemia
- B. Myelodysplastic syndrome
- C. Pernicious anemia
- D. Phenytoin toxicity

Answer: B. This man has pancytopenia with a hypocellular marrow and a cytogenetic abnormality. Even though most cases of myelodysplastic syndrome cause a hypercellular marrow, 20% can be hypocellular and thus be confused with aplastic anemia. If a chromosomal abnormality is detected, myelodysplastic syndrome is likely. This should not be seen with any of the other conditions.

CHAPTER 52: BLOOD SMEAR AND BONE MARROW REVIEW

Q.1. A 40-year-old man with a history of vitiligo comes to you for evaluation of fatigue. He states that he has no energy throughout the day even though he is sleeping well and eating well. His weight has been stable and his mood is good. Examination is notable for mild pallor and hypopigmentation consistent with vitiligo but is otherwise normal. His peripheral blood smear is shown in [Figure 52Q-2](#). What is the most likely diagnosis?

- A. Pernicious anemia
- B. Iron deficiency
- C. Anemia of chronic disease
- D. Thalassemia

Answer: A. The peripheral blood smear shows a hypersegmented polymorphonuclear cell suggestive of a megaloblastic process such as vitamin B₁₂

or folate deficiency. Vitiligo is associated with other autoimmune diseases including pernicious anemia, making this the correct answer. There is no evidence of hypochromia (which would suggest iron deficiency) or microcytosis (suggestive of thalassemia). Anemia of chronic disease is not associated with hypersegmented polymorphonuclear cells.

Q.2. A 55-year-old man is admitted with atypical chest pain. His routine labs are normal except for a platelet count of 55,000 and a K⁺ of 6.4. His peripheral blood smear (PBS) is shown in [Figure 52Q-3](#). What is the most likely diagnosis?

- A. Pseudothrombocytopenia
- B. Idiopathic thrombocytopenic purpura
- C. Thrombotic thrombocytopenic purpura
- D. Type IV renal tubular acidosis

Answer: A. The PBS is essentially normal. The red cells are the size of a lymphocyte with one-third central pallor. The lymphocyte nuclei are small and compact. The neutrophils do not have more than four lobes. Most importantly, an adequate number of platelets are seen on this PBS. In a small percentage of the population, anticoagulant in the blood collection tube will cause platelets to aggregate and release potassium. The aggregation also causes an artificially low platelet count. People with ITP will also have a normal PBS, with the exception of thrombocytopenia. TTP patients will show evidence of a microangiopathic hemolytic anemia.

Q.3. A 54-year-old male with chronic hepatitis C infection comes to the clinic to ask about treatment options for hepatitis. He has had hepatitis C infection since a blood transfusion 20 years previously. His chief complaint at the time of his visit is fatigue, which in the past has been attributed to his hepatitis C. However, you order a TSH (normal) and a CBC to exclude other causes. The CBC shows a hematocrit of 38% with an MCV of 103. WBC and platelets are slightly decreased. His peripheral blood smear is shown in [Figure 52Q-4](#). Which of the following best describes the abnormality demonstrated?

- A. Anisocytosis
- B. Poikilocytosis
- C. Target cells
- D. Spherocytosis
- E. Basophilic stippling

Answer: C. This peripheral blood smear shows uniformly sized RBCs with a target center consistent with target cells. Target cells are seen with abnormal hemoglobin (e.g., hemoglobin C) as well as with liver disease (as in this patient). The uniformity of RBC size excludes anisocytosis, which refers to a smear

demonstrating a wide range of RBC sizes. Poikilocytosis, or differently shaped RBCs, is also incorrect because the shape of the RBCs in this peripheral smear is uniform. Spherocytes, as in hereditary spherocytosis, do not have any areas of pallor when examined on a peripheral blood smear; this is not descriptive of the cells pictured here. Basophilic stippling, in which dark, punctate dots are contained within the RBC, is not seen here. Consistent with liver disease, this man also has a mild macrocytosis and mild pancytopenia (often caused by splenomegaly).

Q.4. A 62-year-old man without a significant past medical history comes in for his yearly physical. He has no complaints. On physical examination, everything is normal except for some mild right axillary adenopathy. You also note splenomegaly. Concerned, you order a CBC, which shows a WBC of 30,000, hematocrit of 37% (MCV is 88), and platelet count of 140,000. Reviewing lab data from previous examinations, you note that his WBC five years ago was 15,000, and two years ago was 18,000. His peripheral blood smear is shown in **Figure 52Q-6**. What is the most likely diagnosis?

- A. Vitamin B₁₂ deficiency
- B. Mononucleosis (Epstein-Barr virus infection)
- C. Acute myelogenous leukemia (AML)
- D. Chronic lymphocytic leukemia (CLL)
- E. Essential thrombocytosis (ET)

Answer: D. The peripheral blood smear in this case shows a predominance of lymphocytes, with their characteristic small size and thin rim of cytoplasm, which correlates with the report of an elevated WBC. Noted on this slide are "smudge cells," commonly seen in CLL. With vitamin B₁₂ deficiency, we would expect to see hypersegmented polymorphonuclear cells (i.e., 5% of the cells with 5 lobes or greater), which are absent from this blood smear. Mononucleosis results in "atypical" lymphocytes with large, open nucleoli. AML is unlikely; clinically, the patient has a chronic elevation of his WBC and his peripheral blood smear shows small, compact lymphocytes, not an increase in immature blasts. With essential thrombocytosis, large numbers of platelets should be seen. Both the report of his CBC and his peripheral blood smear fail to demonstrate an elevated platelet count.

Q.5. An 80-year-old man presents with six months of fatigue and is found to have pancytopenia. Other laboratory data, including liver function tests, are normal. On physical exam he is found to have marked splenomegaly without other significant lymphadenopathy. His peripheral blood smear reveals numerous lymphocytes with projections, and you suspect hairy cell leukemia. Confirmation of the diagnosis can be made by

- A. Bone marrow aspirate

- B. Bone marrow aspirate and biopsy
- C. Splenic biopsy
- D. Sending blood for peripheral flow cytometry

Answer: D. The diagnosis of hairy cell leukemia is best made by examining the peripheral blood by flow cytometry. There are typical aberrant cell surface markers on hairy cells that are pathognomonic for the disease. This is true of most lymphoproliferative disorders that contain circulating cells, although a bone marrow may be necessary for full staging, evaluation of degree of fibrosis, and/or evaluation of etiologies of cytopenias (e.g., anemia due to bone marrow infiltration vs. a hemolytic anemia, both of which can be seen in CLL and other lymphoproliferative disorders). Note that often a diagnosis of aggressive large cell lymphoma may be strongly considered from cell morphology and/or FACS, but confirmation must be made by a core biopsy of a lymph node so lymph node architecture can be assessed.

Q.6. An 85-year-old woman presents with mild pancytopenia and macrocytosis. The remainder of her physical exam and laboratory data is normal. On bone marrow biopsy her cellularity is 40%. You tell her

- A. Her bone marrow is hypocellular and she has mild aplastic anemia
- B. Her bone marrow is normocellular, and other etiologies must be pursued
- C. Her bone marrow is hypercellular, and myelodysplastic syndrome must be considered

Answer: C. The typical normal cellularity of bone marrow can be determined as 100 minus the age of the patient. Thus, this 85-year-old woman should have a cellularity of approximately 15%. A hypercellular bone marrow is consistent with myelodysplastic syndrome.

Q.7. A 75-year-old man undergoing routine screening is found to have an IgG kappa monoclonal gammopathy of 1.4 grams. His physical examination is unremarkable. His CBC and tests of kidney function are normal, and the remainder of his physical exam is normal. You recommend

- A. Bone marrow biopsy and aspirate, with staining of biopsy for kappa cells
- B. Flow cytometry on peripheral blood to look for lymphoma
- C. Kidney biopsy to look for subclinical kidney disease
- D. Repeat evaluation in six months

Answer: D. The normal labs and exam in this man suggest that he has a monoclonal gammopathy of unknown significance, with a rate of progression to myeloma of approximately 1% per year. A high percentage of elderly people have a gammopathy, and it is not necessary, prudent, or efficient to evaluate all such people with a bone marrow.

Q.8. A 59-year-old woman with diabetes is admitted with pneumococcal pneumonia with bacteremia. Despite responding to antibiotic therapy, her white blood count continues to climb (her WBC was normal two months prior to admission, when a complete blood count was obtained prior to colonoscopy). A peripheral blood smear is obtained, and is shown here (Fig. 52Q-8). The most likely explanation for this patient's elevated WBC is

- A. Sepsis
- B. Acute myeloid leukemia
- C. Chronic myeloid leukemia
- D. Chronic lymphocytic leukemia
- E. Leukemoid reaction

Answer: E. The peripheral blood smear demonstrates immature WBCs, including metamyelocytes and myelocytes. Her normal WBC two months prior would make any chronic leukemia unlikely. With sepsis, microangiopathic hemolytic anemia results in schistocytes, and may also demonstrate thrombocytopenia or toxic granulation of WBCs. These changes are not demonstrated in the peripheral blood smear shown. While immature WBCs (metamyelocytes and myelocytes) are shown here, no blast forms suggestive of leukemia are seen. Leukemoid reactions occur in response to infection, and are the best explanation of the clinical presentation and peripheral blood smear shown.