A 53-year-old man comes to the office due to a 3-day history of right leg swelling and pain. He has had no chest pain or dyspnea. The patient describes himself as healthy, and his last visit to the doctor was 10 years ago. He has had no weight loss or abdominal pain. The patient smokes and has a 30-pack-year history. He has an active lifestyle and has not recently traveled. The patient's mother died of breast cancer, and his father has congestive heart failure. Temperature is 37 C (98.6 F), blood pressure is 140/80 mm Hg, pulse is 70/min, and respirations are 14/min. Oxygen saturation is 97% on room air. Normal vesicular breath sounds and cardiac sounds are heard on chest auscultation. Abdominal examination is unremarkable. The right leg is swollen and tender up to midthigh. Results of complete blood cell count and coagulation studies are within normal limits. Duplex ultrasonography demonstrates incompressible popliteal and femoral veins, and anticoagulation is started immediately. Chest x-ray is unremarkable. Which of the following is most appropriate in evaluation of this patient's current condition?

A. Age-appropriate cancer screening
B. CT scan of the abdomen
C. Positron emission tomography of the chest
D. Protein C, protein S, and antithrombin tests
E. Serum carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen tests

Correct answer is
57% answered correctly

Explanation:

This patient has **deep venous thrombosis** (DVT) of the popliteal and femoral veins. Risk factors for venous thromboembolism (VTE) include **inherited** (eg, factor V Leiden, prothrombin gene mutation, protein C deficiency) and **acquired** (eg, immobilization, surgery, **malignancy**, medications) factors. Initial evaluation is directed at identifying major causes of VTE or factors that can increase the risks of anticoagulation therapy; evaluation should include careful history, physical examination, and limited diagnostic testing (eg, blood counts, serum chemistries, coagulation studies, fecal occult blood testing, chest x-ray).

In the absence of any clear provoking factors (eg, recent surgery, immobilization), patients with a first episode of VTE, such as this man, should be referred for **age-appropriate cancer screening** (eg, **colonoscopy**) to evaluate for malignancy as a potential risk factor for VTE. In addition, any suspicious symptoms of malignancy (eg, weight loss, unexplained pain) warrant consideration for more extensive cancer evaluation (eg, CT scan of the abdomen) **(Choice B)**.

(Choice C) Because of this patient's smoking history, he should be offered screening for lung cancer with low-dose CT scan of the chest. However, he has a normal chest x-ray and no symptoms concerning for lung cancer (eg, hemoptysis, cough), so positron emission tomography of the chest would not be appropriate.

(Choice D) Testing for an inherited thrombophilia (eg, factor V Leiden; deficiency of protein C, protein S, or antithrombin III) is generally considered only if the patient's history is suggestive of a genetic predisposition (eg, recurrent VTE; multiple or unusual sites of thrombosis; family history of VTE, particularly at a young age).

(Choice E) Carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen are tumor markers generally used to trend disease progression in patients with diagnosed pancreatic and gastrointestinal tract cancer, respectively. They are not effective screening tests.

Educational objective:
In the absence of any clear provoking factors (eg, recent surgery, immobilization), patients with a first episode of venous thromboembolism should be referred for age-appropriate cancer screening (eg, colonoscopy) to evaluate for malignancy as a potential risk factor for this disease.

Time spent:3 Seconds

QID:2208

Subject:
Medicine

System:
Hematology & Oncology (Hemostasis and thrombosis)

A 68-year-old man is evaluated for exertional fatigue. He used to play tennis actively but now is having a hard time finishing a set. His only other medical problem is hypertension. He does not use tobacco, alcohol, or illicit drugs. Temperature is 37 C (98.6 F), blood pressure is 126/86 mm Hg, and pulse is 82/min. Mild mucosal pallor is present. There is no lymphadenopathy. Cardiopulmonary examination is normal. There is no splenomegaly or lower extremity edema. Laboratory results are as follows:

Complete blood count	
Hemoglobin	9.4 g/dL
Mean corpuscular volume	92 μm^3
Platelets	180,000/mm^3
Leukocytes	5,100/mm^3
Serum chemistry	
Sodium	136 mEq/L
Potassium	4.4 mEq/L
Bicarbonate	26 mEq/L
Blood urea nitrogen	14 mg/dL
Creatinine	1.3 mg/dL
Calcium	10.7 mg/dL
Glucose	100 mg/dL
Liver function studies	
Total protein	9 g/dL
Albumin	3.7 g/dL
Total bilirubin	0.9 mg/dL
Alkaline phosphatase	100 U/L
Aspartate aminotransferase	30 U/L
Alanine aminotransferase	29 U/L

Peripheral blood smear is shown in the exhibit. Which of the following is most likely to be found on the patient's bone marrow biopsy?

A. Clonal plasma cell proliferation
B. Hypocellular and fibrotic bone marrow
C. Hypoplastic fat-filled marrow
D. Megaloblastic erythroid hyperpıasia
E. Ring sideroblasts

. Correct answer is
83% answered correctly

Explanation:

Multiple myeloma (MM) is a plasma cell neoplasm that often presents with **constitutional symptoms** (weight loss, fatigue) or bone pain. MM should be suspected in elderly patients with laboratory findings of **hypercalcemia**, **normocytic anemia**, renal insufficiency, and a **protein gap** (difference between total protein and albumin >4 g/dL). A protein gap indicates elevated nonalbumin protein in the serum; it may be seen with polyclonal gammopathies (infection, connective tissue disease) or excessive monoclonal protein (MM, Waldenström macroglobulinemia). Serum protein electrophoresis (SPEP) can determine if a protein gap is caused by a monoclonal or polyclonal source. In MM, SPEP typically shows a monoclonal spike (**M-spike**). Diagnosis is then confirmed by bone marrow biopsy (**>10% clonal plasma cells**).

This patient's peripheral blood smear shows **rouleaux** formation (stacking of red blood cells like coins), a finding seen with elevated serum protein.

(Choice B) Patients with myelofibrotic disorders may have hypocellular, fibrotic bone marrow. Manifestations of myelofibrosis include fatigue, anemia, and hepatosplenomegaly. Elevations in protein gap and hypercalcemia are not typical features of myelofibrosis, making MM more likely.

(Choice C) In aplastic anemia, bone marrow biopsy often shows a hypoplastic, fat-filled marrow. Despite its name, aplastic anemia causes pancytopenia (not simply anemia). This patient has a normal leukocyte and platelet count.

(Choice D) Megaloblastic erythroid hyperplasia is seen in megaloblastic anemia, typically caused by vitamin B_{12} or folate deficiency. Megaloblastic anemia would cause an elevated mean corpuscular volume (>100 μm^3) and would not explain the protein gap or hypercalcemia.

(Choice E) Ring sideroblasts are seen in the sideroblastic anemias, which typically present with microcytic anemia with hemoglobin <7 g/dL. Sideroblastic anemia would not account for the protein gap or hypercalcemia found in this patient.

Educational objective:
Multiple myeloma (MM) is a plasma cell neoplasm that infiltrates the bone marrow and may cause a monoclonal protein elevation (M-spike). MM is associated with hypercalcemia, anemia, renal insufficiency, and an elevated protein gap (>4 g/dL).

Time spent:0 Seconds
Subject:
Medicine

QID:2864
System:
Hematology & Oncology (Plasma cell disorders)

A 65-year-old woman comes to the office due to 2 months of lethargy. She is a reporter for the local newspaper and notes severe fatigue in the afternoons and evenings that has required her to reduce her workload. The patient has not had any fevers, night sweats, or weight changes. She does not use tobacco or illicit drugs but drinks a glass of red wine nightly. She is current on her health maintenance and does yoga 3 times a week. Temperature is 37.1 C (98.8 F), blood pressure is 112/72 mm Hg, and pulse is 88/min. The patient is thin but well nourished. There are large, firm, mobile lymph nodes in her bilateral cervical and supraclavicular chains. Cardiopulmonary and abdominal examinations are normal. Laboratory results are as follows:

Hemoglobin	12 g/dL
Platelets	224,000/mm^3
Leukocytes	53,800/mm^3
Neutrophils	12%
Lymphocytes	84%
Monocytes	4%

Peripheral blood smear reveals lymphocytosis with small, mature lymphocytes. Which of the following is the most likely diagnosis?

A. Chronic lymphocytic leukemia
B. Chronic myeloid leukemia
C. Hairy cell leukemia
D. Hodgkin lymphoma
E. Infectious mononucleosis
F. Lymphoblastic leukemia

. Correct answer is
82% answered correctly

Explanation:

Chronic lymphocytic leukemia	
Clinical features	• Lymphadenopathy (cervical, supraclavicular, axillary) • Hepatosplenomegaly • Mild thrombocytopenia & anemia • Often asymptomatic
Diagnosis	• Severe lymphocytosis & smudge cells • Flow cytometry • Lymph node & bone marrow biopsy not generally needed

Prognosis	• Median survival 10 years
	• Worse prognosis with:
	  ◦ Multiple chain lymphadenopathy
	  ◦ Hepatosplenomegaly
	  ◦ Anemia & thrombocytopenia

Complications	• Infection • Autoimmune hemolytic anemia • Secondary malignancies (eg, Richter syndrome)

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the United States. It is almost always seen in the **elderly** (median age at diagnosis is 70). Patients are often asymptomatic but can present with **extreme fatigue**, B symptoms (eg, night sweats, fevers), infection, or weight loss. Lymphadenopathy and splenomegaly are often present on physical examination. Dramatic **lymphocytosis** is the classic hallmark of CLL. Peripheral smear reveals **mature lymphocytes** with the presence of smudge cells (a pathognomonic characteristic of CLL).

(Choice B) Chronic myeloid leukemia is a myeloproliferative disease of neutrophil lineage. Peripheral blood smear shows a massive leukocytosis with a variety of neutrophil precursor cells (eg, promyelocytes, myelocytes). This patient has a dramatic elevation in lymphocytes, not neutrophils.

(Choice C) Hairy cell leukemia is a rare lymphocytic leukemia that often presents with splenomegaly and pancytopenia (including leukopenia). This patient does not have splenomegaly and her leukocyte count is very elevated, making this diagnosis unlikely.

(Choice D) Hodgkin lymphoma often presents with painless lymphadenopathy and B symptoms (night sweats, fevers) in the setting of a normal peripheral blood smear and complete blood count. Massive lymphocytosis is unlikely in Hodgkin lymphoma.

(Choice E) Infectious mononucleosis commonly causes lethargy in young patients, often with fever, splenomegaly, and pharyngitis. Although it can cause lymphocytosis, the white cell count is typically 12,000-18,000/mm^3. This patient is elderly with severe lymphocytosis.

(Choice F) Patients with lymphoblastic leukemia have a dramatic increase in blasts on peripheral blood smear. These patients also tend to be more acutely symptomatic (eg, infections due to neutropenia, bleeding due to thrombocytopenia, B symptoms, splenomegaly).

Educational objective:
Chronic lymphocytic leukemia is seen almost exclusively in elderly patients. Peripheral smear is characterized by a marked leukocytosis with mature lymphocytes and smudge cells.

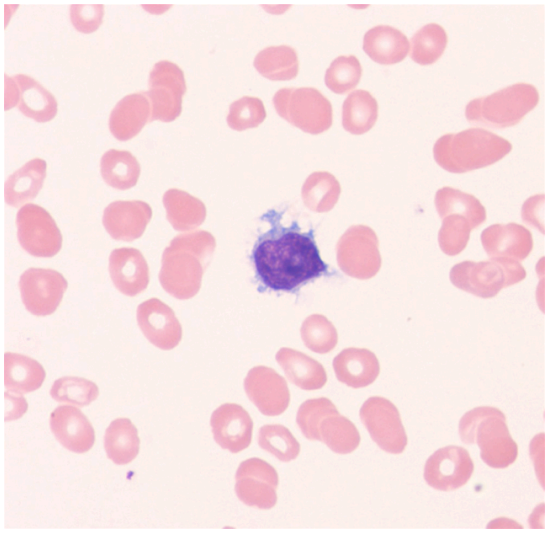
Time spent:1 Seconds
Subject:
Medicine

QID:2865
System:
Hematology & Oncology (White blood cell disorders)

A 60-year-old man comes to the office after he was found to have a "low blood count" when attempting to donate blood. The patient is in his usual state of health and feels well. He has no chronic medical problems but has been treated for pneumonia twice during the past year. The patient takes no medications and does not use tobacco or alcohol. Temperature is 37 C (98.6 F), blood pressure is 120/80 mm Hg, and pulse is 76/min. Physical examination reveals mucosal pallor. There are no enlarged lymph nodes. The abdomen is soft and nontender. The spleen tip is palpable 5 cm below the left costal margin; the liver is normal in size. Stool guaiac is negative. Complete blood count results are as follows:

Hemoglobin	9.6 g/dL
Mean corpuscular volume	83 fL
Platelets	130,000/mm^3
Leukocytes	14,000/mm^3

Peripheral blood smear shows predominant lymphocytes with features as seen in the image below.



Which of the following is the most likely diagnosis?

A. Acute lymphoblastic leukemia
B. Chronic lymphocytic leukemia
C. Gaucher disease
D. Hairy cell leukemia
E. Hodgkin lymphoma
F. Infectious mononucleosis
G. Myelodysplastic syndrome

. Correct answer is
76% answered correctly

Explanation:

Hairy cell leukemia	
Features	• **Clonal B-cell neoplasm** • Middle-age/older adults • *BRAF* mutation

Manifestations	• **Pancytopenia** due to bone marrow fibrosis
	  ◦ Granulocytopenia (infections)
	  ◦ Anemia (fatigue, weakness)
	  ◦ Thrombocytopenia (bleeding, bruising)
	• **Splenomegaly** (early satiety)
	• Hepatomegaly/lymphadenopathy rare

Diagnosis	• Peripheral smear – **"hairy" leukocyte cells** • **Bone marrow biopsy** with flow cytometry
Treatment	• Chemotherapy (for moderate/severe) • Life expectancy is often near-normal

This patient with 2 recent episodes of pneumonia has splenomegaly, anemia, thrombocytopenia, mild leukocytosis, and peripheral blood smear evidence of a leukocyte with "hairy" cytoplasmic projections suggesting the diagnosis of **hairy cell leukemia**.

Hairy cell leukemia is a chronic **B-cell malignancy** that occurs primarily in people age >50. Manifestations arise due to the neoplastic infiltration of the bone marrow, spleen, and peripheral blood as follows:

- **Bone marrow infiltration** – causes bone marrow **fibrosis** with **cytopenias**. This may lead to recurrent infections (granulocytopenia), bleeding/bruising (thrombocytopenia), or fatigue/weakness (anemia).
- **Splenic infiltration** – causes **splenomegaly**. Mass effect may lead to symptoms of abdominal fullness or early satiety (gastric compression).
- **Peripheral blood infiltration** – peripheral blood smear shows abnormal circulating lymphocytes with **"hairy"** cytoplasmic projections. Although most patients are leukopenic due to bone marrow infiltration, a minority (such as this patient) have mild leukocytosis due to increased circulating lymphocytes.

Hairy cell leukemia does not typically cause hepatomegaly, lymphadenopathy, or B symptoms. Diagnosis requires **bone marrow biopsy** with flow cytometry.

(Choice A) Acute lymphoblastic leukemia is seen primarily in children (not adults) and usually manifests with symptoms related to neutropenia, anemia, or thrombocytopenia. Lymphadenopathy is common, and peripheral blood smear typically shows lymphoblasts (small cells, scant cytoplasm), not lymphocytes with "hairy" projections.

(Choice B) Chronic lymphocytic leukemia is usually characterized by significant leukocytosis (often >100,000/mm^3), lymphadenopathy and B symptoms (unlike this patient). Peripheral smear typically shows "smudge cells".

(Choice C) Gaucher disease is a lysosomal storage disease that may manifest with massive splenomegaly and cytopenias. However, hepatomegaly is universal and a "hairy" leukocyte would not be seen on peripheral smear.

(Choice E) Hodgkin lymphoma is a B-cell neoplasm with characteristic Reed-Sternberg cells that usually manifests with a mediastinal mass or a painless, enlarged lymph node (often cervical).

(Choice F) Infectious mononucleosis may be associated with splenomegaly and atypical lymphocytosis. However, patients tend to be young and have the classic triad of fever, tonsillar pharyngitis, and lymphadenopathy (unlike this patient).

(Choice G) Myelodysplastic syndrome is a malignant stem cell disorder that may cause anemia, leukopenia, and/or thrombocytopenia. Splenomegaly and leukocytosis are not typical features of myelodysplastic syndrome.

Educational objective:
Hairy cell leukemia is a chronic B-cell neoplasm that infiltrates the bone marrow, spleen, and peripheral blood, resulting in cytopenias, splenomegaly, and peripheral smear evidence of atypical lymphocytes with "hairy" cytoplasmic projections. Hepatomegaly, lymphadenopathy, and B symptoms are uncommon. Diagnosis is made with bone marrow biopsy.

A 50-year-old man comes to the office due to progressive fatigue and weakness over the past year. He becomes tired early in the day and also finds it difficult to remember things. The patient drinks several beers daily and is vague when prompted to clarify the quantity. He lives in a house with 4 friends. He used to be a line-order cook but has not been employed in several years. Vital signs are within normal limits. Laboratory results are as follows:

Leukocytes	5,500/mm^3
Hemoglobin	7.0 g/dL
Hematocrit	22%
Platelets	196,000/mm^3
Red blood cells	1.7 million/mm^3
Mean corpuscular volume	116 μm^3
Mean corpuscular hemoglobin (MCH)	36 pg/cell
Reticulocytes	0.3%

Peripheral blood smear shows macro-ovalocytes, anisocytosis, poikilocytosis, and basophilic stippling. Which of the following is the best next step in management of this patient?

A. Blood lead levels
B. Bone marrow biopsy
C. Direct antiglobulin test
D. Iron studies
E. Serum B_{12} and folate levels

Correct answer is
66% answered correctly

Explanation:

Common causes of macrocytic anemia*
• Folate deficiency • Vitamin B_{12} deficiency • Myelodysplastic syndromes • Acute myeloid leukemias • Drug-induced (eg, hydroxyurea, zidovudine, chemotherapy agents) • Liver disease • Alcohol use disorder • Hypothyroidism
*Mean corpuscular volume >100 μm^3.

This patient's presentation is consistent with **macrocytic anemia**, usually suggested by abnormal red blood cell (RBC) indices, including an **elevated** (ie, >100 μm^3) **mean corpuscular volume** (MCV), elevated mean corpuscular hemoglobin (amount of hemoglobin), and normal mean corpuscular hemoglobin concentration (low values seen with microcytosis; elevated values seen with spherocytosis or some hemolytic anemias).

Macrocytic anemia is due to 2 primary etiologies, which the peripheral blood smear and reticulocyte count findings can help distinguish:

- **Megaloblastic** causes (eg, impaired DNA synthesis due to deficiency in B12 or folate, crucial one-carbon donors in nucleotide production): **MCV values >110-115 μm^3** are almost exclusively associated with these anemias, which are also typically characterized by **low reticulocyte count** (inability to efficiently generate new erythrocytes).

- Nonmegaloblastic causes (eg, alcohol use, hypothyroidism, drugs, liver disease): These are associated with increased, normal, or decreased reticulocyte count.

Other findings suggestive of megaloblastosis include hypersegmented neutrophils (mean lobe count >5), RBCs of various sizes (anisocytosis) and shapes (poikilocytosis), and basophilic stippling (nonspecific; ribosomal remnants due to impaired erythrocyte maturation). Hemolysis markers (eg, lactate dehydrogenase, indirect bilirubin) may be slightly elevated (increased intramedullary and peripheral hemolysis), and mild thrombocytopenia and leukopenia can occur (increased apoptosis).

Patients in whom megaloblastic anemia is suspected should undergo serum **vitamin B_{12} and folate level** testing; methylmalonic acid and homocysteine levels can be added for those with inconclusive or borderline results. Workup for nonmegaloblastic causes can be undertaken when initial evaluation is unrevealing.

(Choice A) Lead poisoning is associated with basophilic stippling but would cause microcytic (MCV <80 μm^3) rather than macrocytic anemia. Basophilic stippling can also be due to thalassemia, alcohol use, or vitamin deficiency.

(Choice B) Bone marrow biopsy helps diagnose myelodysplasia, which usually causes cytopenia in ≥1 cell lines. Although patients can develop macrocytosis, bone marrow biopsy is invasive and would not be performed prior to laboratory workup.

(Choice C) Direct antiglobulin test can help diagnose autoimmune hemolytic anemias. Patients typically have hemoglobin of 7-10 g/dL with elevated reticulocyte count, bilirubin, and lactate dehydrogenase. The haptoglobin is also markedly decreased, and peripheral smear usually shows spherocytes. However, it would not cause very high MCV.

(Choice D) Measuring iron levels is useful for evaluating patients with microcytic anemia (MCV <80 μm^3).

Educational objective:
Macrocytic anemia can be due to megaloblastic (eg, B_{12} or folate deficiency) or nonmegaloblastic (eg, alcohol use disorder, hypothyroidism, drugs, liver disease) etiologies. Peripheral smear, reticulocyte count, and B_{12} and folate levels can aid diagnosis.

Time spent:4 Seconds	**QID**:2872
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 63-year-old man comes to the office due to fatigue. Medical history includes hypertension, for which he takes lisinopril, and osteoarthritis of the right knee, for which he has taken naproxen daily for the past 3 months. Blood pressure is 123/78 mm Hg, and pulse is 78/min. Examination shows that the right knee is mildly deformed due to bony overgrowth; there is no focal tenderness or edema. Laboratory results are as follows:

Hemoglobin	9 g/dL
Mean corpuscular volume	72 μm^3
Platelets	300,000/mm^3
Leukocytes	7,200/mm^3
Creatinine	1.2 mg/dL

Which of the following laboratory findings is most likely present in this patient?

	Serum iron	Serum ferritin	Transferrin (total iron-binding capacity)	Transferrin saturation
A.	↓	↑	↓	↓
B.	↓	↓	↑	↓
C.	↓	↓	↑	↑
D.	↑	↑	↓	↑
E.	Normal	Normal	Normal	Normal

Correct answer is

71% answered correctly

Explanation:

Iron studies in microcytic anemia					
	MCV	**Iron**	**Ferritin**	**Transferrin (TIBC)**	**Transferrin saturation (iron/TIBC)**
Iron deficiency	↓	↓	↓	↑	↓
Thalassemia	↓↓	Normal/↑	Normal/↑	Normal/↓	Normal/↑
Anemia of chronic disease (inflammation)	Normal/↓	↓	Normal/↑	↓	Normal/↓
MCV = mean corpuscular volume; **TIBC** = total iron binding capacity.					

This patient with chronic use of **nonsteroidal anti-inflammatory drugs** (NSAIDs) (eg, naproxen) now has fatigue and **microcytic anemia**. The most likely cause is **chronic blood loss** due to NSAID-associated gastropathy, resulting in **iron deficiency**, a common cause of microcytic anemia.

Expected laboratory studies associated with iron deficiency include the following:

- **Low serum iron and ferritin** (which reflects total body iron stores).
- **Increased serum transferrin**, which has an inverse relationship with serum iron. Transferrin, the primary iron transport protein in the plasma, is often reported as **total iron-binding capacity** (TIBC).
- **Low transferrin saturation**, which is the ratio of serum iron to TIBC.

(Choice A) Anemia of chronic disease (ACD) (ie, anemia of inflammation) is characterized by sequestration of iron in response to hepcidin and certain inflammatory cytokines. Serum iron is low, but ferritin is an acute phase reactant that may be increased due to the underlying inflammatory condition. Transferrin is reduced in response to inflammation, so TIBC is low; transferrin saturation is typically normal or mildly low due to reduced circulating iron. The low level of inflammation in osteoarthritis does not usually cause ACD.

(Choice C) This combination of markers is not seen because transferrin saturation is the calculated ratio of serum iron to TIBC. As a result, having low iron and a high TIBC must correspond to a low transferrin saturation.

(Choice D) An elevated serum iron, ferritin, and transferrin saturation with low TIBC suggests iron overload, as in hemochromatosis. Patients receiving frequent transfusions for anemia related to hemoglobinopathies (eg, thalassemia major) may also develop iron overload, but this would not be seen in a newly diagnosed patient. It is also unlikely that significant thalassemia or another hemoglobinopathy would not be diagnosed until age 63.

(Choice E) Given this patient's significant microcytic anemia, his iron studies would not likely be entirely normal regardless of the diagnosis.

Educational objective:
Nonsteroidal anti-inflammatory drugs can cause chronic blood loss, leading to iron deficiency anemia. Iron deficiency anemia usually demonstrates a low serum iron, low ferritin, elevated total iron-binding capacity (TIBC), and low transferrin saturation (ie, iron/TIBC).

Time spent:1 Seconds	**QID**:2877
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 56-year-old man comes to the office due to an episode of transient right eye blindness that lasted an hour. He has had no weakness in his extremities or speech changes. He last saw a physician 3 years ago. The patient has smoked a pack of cigarettes daily for 30 years. Temperature is 37 C (98.6 F), blood pressure is 160/94 mm Hg, pulse is 78/min, and respirations are 14/min. Pulse oximetry is 98% on room air. BMI is 32 kg/m^2. There is no carotid bruit. Facial plethora is present. Cardiopulmonary examination is normal. Abdominal examination reveals splenomegaly. There is no lower extremity edema, and peripheral pulses are intact. Laboratory results are as follows:

Complete blood count	
Hemoglobin	20 g/dL
Hematocrit	60%
Platelets	545,000/mm^3
Leukocytes	13,800/mm^3
Serum chemistry	
Sodium	141 mEq/L
Potassium	3.6 mEq/L
Blood urea nitrogen	16 mg/dL
Creatinine	0.7 mg/dL
Glucose	96 mg/dL

In addition to counseling about smoking cessation, which of the following is the best therapy for this patient?

A. Anticoagulation
B. Phlebotomy
C. Plasma exchange
D. Prednisone
E. Splenectomy

Correct answer is
79% answered correctly

Explanation:

Polycythemia vera	

Manifestations	• ↑ Blood viscosity
	  ◦ **Hypertension**
	  ◦ **Erythromelalgia** (burning cyanosis in hands/feet)
	  ◦ Transient visual disturbances
	• ↑ RBC turnover (gouty arthritis)
	• **Aquagenic pruritus**
	• Bleeding

Examination	• Facial plethora (ruddy cyanosis) • Splenomegaly
Laboratory findings	• **Elevated hemoglobin** • Leukocytosis & thrombocytosis • **Low erythropoietin** level • ***JAK2* mutation** positive
Complications	• **Thrombosis** • Myelofibrosis & acute leukemia

Treatment	• **Phlebotomy** • Hydroxyurea (if ↑ risk of thrombus)

RBC = red blood cell.

Polycythemia vera (PV) is a clonal **myeloproliferative** disorder characterized by **erythrocytosis**. Most cases are associated with a *JAK2* mutation. Patients are often asymptomatic at diagnosis but may present with symptoms related to increased blood viscosity (eg, **transient visual disturbances**, **hypertension**, thrombosis) and increased red blood cell (RBC) turnover (gouty arthritis). Itching after warm showers (aquagenic pruritus) is common. Physical examination often shows **facial plethora** (ruddy cyanosis) and **splenomegaly**. Unlike other causes of erythrocytosis (eg, chronic hypoxia, erythropoietin [EPO]-producing tumors), patients with PV usually have **normal oxygen saturations** and **low EPO levels**. Complete blood count often shows an increase in all 3 cell lines.

Serial **phlebotomy** is the mainstay of treatment for PV; it creates a relative iron deficiency and reduces hematocrit levels to normal range. Bone marrow suppressive drugs (eg, hydroxyurea) may be added in patients at high risk of thrombosis (eg, previous thrombosis, advanced age).

The terms polycythemia and erythrocytosis are often used interchangeably; however, not all polycythemia is truly erythrocytosis. Polycythemia implies a laboratory finding of elevated hematocrit and may be diagnosed as relative (usually due to a reduction in plasma volume) or absolute (due to increased RBC production). Only absolute polycythemia involves erythrocytosis (increased RBC mass). Absolute polycythemia/erythrocytosis is seen in patients with PV and secondary polycythemia (eg, chronic hypoxia, EPO-secreting tumors).

(Choice A) Anticoagulation is used in the treatment of thromboembolic disease, antiphospholipid antibody syndrome (APLAS), and PV with evidence of thrombotic event. Transient ocular blindness in PV is not an indication for anticoagulation as it is due to microvascular sludging (from severe erythrocytosis), not thromboembolism. APLAS would not cause hypertension, facial plethora, splenomegaly, or thrombocytosis.

(Choice C) Plasma exchange removes toxic substances (eg, autoantibodies, immune complexes, endotoxins, cryoglobulins) from plasma. It is used in conditions such as thrombotic thrombocytopenic purpura (characterized by microangiopathic anemia and thrombocytopenia) and hemolytic uremic syndrome (characterized by acute kidney injury).

(Choice D) Prednisone is useful in tamping immune activation and is used in managing some forms of autoimmune hemolytic anemia (AIHA).

(Choice E) Splenectomy is useful in many antibody-mediated hematologic disorders (eg, AIHA, idiopathic thrombocytopenia). In PV, the primary problem is myeloproliferation within the bone marrow; splenectomy would not reduce the hematocrit.

Educational objective:
Polycythemia vera is a myeloproliferative disorder characterized by erythrocytosis. It often presents with hypertension, transient vision disturbances, aquagenic pruritus, or thrombosis. Facial plethora and splenomegaly are common on physical examination. Treatment is primarily serial phlebotomy; bone marrow suppressive drugs (eg, hydroxyurea) may sometimes be added if there is a high risk of thrombosis.

Time spent:1 Seconds
Subject:
Medicine

QID:2883
System:
Hematology & Oncology (Red blood cell disorders)

A 51-year-old man comes to the office due to frequent itching, especially after bathing. He otherwise feels well except for occasional headaches and dizziness. He has no fever or weight loss. The patient has not visited a doctor in 10 years and does not take medications. He does not use tobacco, alcohol, or illicit drugs. The patient's sister has bipolar disorder, and both parents died in a car accident many years ago. Temperature is 36.7 C (98 F), blood pressure is 140/80 mm Hg, pulse is 76/min, and respirations are 14/min. BMI is 30 kg/m^2. His face has a ruddy cyanotic appearance. Oropharynx is clear. There is no lymphadenopathy in his cervical, supraclavicular, or axillary chains. Jugular venous pressure is normal. Cardiopulmonary examination shows no abnormalities. Abdomen is soft and nontender; the spleen is palpable 4 cm below the left lower ribs. Laboratory results are as follows:

Hemoglobin	21.5 g/dL
Hematocrit	64%
Platelets	521,000/mm^3
Leukocytes	14,800/mm^3

Which of the following is most likely to be seen on further workup?

A. Elevated erythrocyte sedimentation rate
B. Elevated serum iron levels
C. Low resting arterial oxygen saturation
D. Low serum erythropoietin level
E. Positive BCR-ABL fusion protein

. Correct answer is
70% answered correctly

Explanation:

Polycythemia vera	

Manifestations	• ↑ Blood viscosity
	  ◦ **Hypertension**
	  ◦ **Erythromelalgia** (burning cyanosis in hands/feet)
	  ◦ Transient visual disturbances
	• ↑ RBC turnover (gouty arthritis)
	• **Aquagenic pruritus**
	• Bleeding

Examination	• Facial plethora (ruddy cyanosis) • Splenomegaly
Laboratory findings	• **Elevated hemoglobin** • Leukocytosis & thrombocytosis • **Low erythropoietin** level • ***JAK2* mutation** positive
Complications	• **Thrombosis** • Myelofibrosis & acute leukemia

Treatment	• **Phlebotomy** • Hydroxyurea (if ↑ risk of thrombus)
RBC = red blood cell.	

This patient with **aquagenic pruritus** (itching after bathing), **facial plethora** (ruddy cyanosis), **splenomegaly**, and elevations in all 3 cell lines on complete blood count likely has **polycythemia vera** (PV).

PV is a clonal **myeloproliferative** disorder characterized by **erythrocytosis** (increase in red blood cell mass). It is a **primary form** of polycythemia, almost always caused by a ***JAK2* mutation**. Normally, red blood cell production is dependent on erythropoietin (EPO), a cytokine released by the kidneys (and liver) in response to **tissue hypoxia**; EPO activates the JAK2 tyrosine kinase, which differentiates late myeloid cells into erythrocytes. In PV, red blood cell production is driven by a constitutively active *JAK2* gene rather than by tissue hypoxia; therefore, **EPO levels tend to be low**.

Secondary forms of polycythemia (eg, due to chronic hypoxia or EPO-secreting tumors) are caused by circulating factors (usually EPO) that stimulate the bone marrow to produce more red blood cells. These forms of polycythemia are often characterized by high EPO levels.

(Choice A) Erythrocyte sedimentation rate (ESR) is increased in inflammatory or infectious states due to elevated circulating plasma proteins (usually fibrinogen). In PV, there is a higher relative concentration of erythrocytes to fibrinogen, which causes a low (not high) ESR.

(Choice B) Serum iron levels are low in most patients with PV due to increased hematopoiesis with subsequent increased iron utilization.

(Choice C) Patients with hypoxia-driven forms of secondary erythrocytosis may have low resting arterial oxygen saturations. Patients with PV usually have normal oxygen saturations; the erythrocytosis in PV is EPO (hypoxemic) independent.

(Choice E) The BCR-ABL fusion protein is usually seen in chronic myeloid leukemia (CML). CML is typically associated with severe leukocytosis (with leukocytes often >100,000/mm^3) and anemia. This patient has mild leukocytosis and severe erythrocytosis, making PV far more likely.

Educational objective:
Polycythemia vera is a myeloproliferative disorder marked by erythrocytosis. It is a form of primary polycythemia, almost always caused by a mutation of *JAK2* in a myeloid precursor cell. Erythropoietin levels tend to be low (unlike most causes of secondary polycythemia).

Time spent:0 Seconds
Subject:
Medicine

QID:2884
System:
Hematology & Oncology (Red blood cell disorders)

A 55-year-old woman comes to the office due to 3 months of night sweats. She has tried using a fan and sleeping without a comforter, but she continues to awaken several nights a week with bedsheets so drenched that she has to change them. During this time, she has unintentionally lost 5 kg (11 lb). The patient traveled to Vietnam with her church group 6 months ago and wonders if she may have "caught something." She took her antimalarial pills and received her pretrip vaccinations as recommended and has not had fevers. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 37.4 C (99.4 F), blood pressure is 144/78 mm Hg, and pulse is 96/min. She has pale mucosa but no scleral icterus. There is no cervical lymphadenopathy. Cardiopulmonary examination is normal. A spleen tip is palpable when she exhales completely. Laboratory results are as follows:

Hemoglobin	8.7 g/dL
Platelets	610,000/mm^3
Leukocytes	66,800/mm^3
Neutrophils	32%
Bands	12%
Eosinophils	3%
Basophils	5%
Monocytes	4%
Metamyelocytes	12%
Myelocytes	23%
Lymphocytes	9%

Which of the following is expected in this patient?

A. Absence of measurable erythropoietin in urine
B. Decreased leukocyte alkaline phosphatase score
C. Positive acid-fast stain of the blood
D. Positive Coombs test
E. Positive Giemsa-stained blood smear
F. Presence of Auer rods

Correct answer is
38% answered correctly

Explanation:

Comparison of leukemoid reaction & chronic myeloid leukemia (CML)		
	Leukemoid reaction	**CML**
Leukocyte count	Markedly elevated (>50,000/mm^3)	Markedly elevated (can be >100,000/mm^3)
Cause	Severe infection	*BCR::ABL1* fusion gene
LAP score	High	Low
Neutrophil precursors	More mature (metamyelocytes > myelocytes)	Less mature (metamyelocytes < myelocytes)
Absolute basophilia	Not present	Present
LAP = leukocyte alkaline phosphatase.		

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm caused by the *BCR-ABL* fusion gene. It is marked by a dramatic leukocytosis (often but not always >100,000/mm^3), absolute basophilia, and a preponderance of early immature neutrophil precursors (promyelocytes, myelocytes). The **leukocyte alkaline phosphatase** (LAP) score can help differentiate CML from leukemoid reaction. In CML the neutrophils are cytochemically and functionally abnormal, so the LAP score is usually **low**.

CML is often found on routine blood work in asymptomatic patients but may present with fatigue, weight loss, night sweats, or abdominal fullness (from splenomegaly). Thrombocytosis and anemia are common.

(Choice A) In patients with an elevated red blood cell count, the absence of measurable erythropoietin in urine may suggest polycythemia vera. This patient is anemic.

(Choice C) A positive acid-fast stain of the blood can be seen in disseminated tuberculosis (TB). Patients with disseminated TB can present with night sweats, fevers, and weight loss. However, disseminated TB is less likely to cause such a marked leukocytosis with immature neutrophil precursors.

(Choice D) The Coombs test is used to detect antibodies on the surface of red blood cells as is often seen in autoimmune hemolytic anemia (AIHA). AIHA is common in some hematologic malignances (eg, chronic lymphocytic leukemia). This patient more likely has anemia due to her underlying CML.

(Choice E) Malaria can be diagnosed using a Giemsa stain of the blood showing intraerythrocytic parasites. Although the patient recently traveled to Vietnam, her dramatic leukocytosis and cell differential would not be explained by malaria. It would also be uncommon for malaria manifestations to persist for several months.

(Choice F) Auer rods are seen in many forms of acute myeloid leukemia (AML). AML tends to present relatively acutely with manifestations related to pancytopenia such as bleeding or infection. In addition, myeloblasts would be expected on peripheral smear examination. This patient has a more indolent presentation with thrombocytosis and leukocytosis.

Educational objective:
Chronic myeloid leukemia (CML) is marked by dramatic leukocytosis, absolute basophilia, and a shift towards very early neutrophil precursor cells (promyelocytes, myelocytes). In CML, the leukocyte alkaline phosphatase score, a marker of neutrophil activity, typically is low.

Time spent:1 Seconds
QID:2885
Subject:
Medicine
System:
Hematology & Oncology (White blood cell disorders)

A 54-year-old man is brought to the emergency department with 2 days of severe diarrhea and 6 hours of abdominal pain. He is confused and lethargic. His daughter, who is at the bedside, notes that the patient has a history of hypertension and was recently treated for "strep throat." Temperature is 38.7 C (101.6 F), blood pressure is 92/58 mm Hg, pulse is 128/min, and respirations are 24/min. The patient appears agitated. The abdomen is mildly distended, and the patient winces with deep palpation of the left lower quadrant. Laboratory results are as follows:

Complete blood count	
Hemoglobin	13 g/dL
Platelets	398,000/mm^3
Leukocytes	44,800/mm^3
Neutrophils	24%
Bands	32%
Lymphocytes	15%
Promyelocytes	2%
Metamyelocytes	18%
Myelocytes	9%
Serum chemistry	
Sodium	132 mEq/L
Potassium	3.6 mEq/L
Chloride	98 mEq/L
Bicarbonate	18 mEq/L
Blood urea nitrogen	32 mg/dL
Creatinine	1.3 mg/dL

Intravenous fluids and antibiotics are administered. The next morning, the patient's temperature is still elevated. Repeat laboratory examination shows a leukocyte count of 52,000/mm^3 with a similar differential. The leukocyte alkaline phosphatase score is high. Which of the following is the likely cause of this patient's hematologic abnormalities?

A. Chronic lymphocytic leukemia
B. Chronic myeloid leukemia
C. Drug reaction
D. Leukemoid reaction
E. Myelodysplastic syndrome
F. Secondary polycythemia

Correct answer is
68% answered correctly

Explanation:

Comparison of leukemoid reaction & chronic myeloid leukemia (CML)		
	Leukemoid reaction	**CML**
Leukocyte count	Markedly elevated (>50,000/mm^3)	Markedly elevated (can be >100,000/mm^3)
Cause	Severe infection	*BCR::ABL1* fusion gene
LAP score	High	Low

Neutrophil precursors	More mature (metamyelocytes > myelocytes)	Less mature (metamyelocytes < myelocytes)
Absolute basophilia	Not present	Present
LAP = leukocyte alkaline phosphatase.		

This patient presents with manifestations of acute infectious diarrhea possibly due to *Clostridiodes difficile* (recent antibiotic use, severe diarrhea, high fever, left lower quadrant pain). His leukocyte count is dramatically elevated, with a predominance of **late neutrophil precursors** (metamyelocytes, bands) rather than early precursors (promyelocytes, myelocytes). This, combined with a **high leukocyte alkaline phosphatase** (LAP) score, suggests **leukemoid reaction** (LR), characterized by a leukocytosis of >50,000/mm^3. **Severe infections** can cause LR due to the mobilization of mature and immature leukocytes from the bone marrow. Given the severity of the infection, it may take >24 hours for clinical improvement with antibiotics.

LR must be differentiated from chronic myelogenous leukemia (CML), a myeloproliferative disorder that also presents with neutrophilia and dramatic leukocytosis. Unlike LR, CML is characterized by a low LAP score (due to cytochemically abnormal neutrophils) and a peripheral smear that features absolute basophilia and early neutrophil precursor cells **(Choice B)**.

(Choice A) Chronic lymphocytic leukemia is a lymphoproliferative disorder marked by lymphocytosis, not neutrophilia.

(Choice C) Drug reactions commonly present with rash and fever. A severe drug reaction, mediated by mast cells and basophils, can present with anaphylactic symptoms, angioedema, or hypotension. This patient's symptoms of acute, severe diarrhea, abdominal pain, and high fever are more consistent with infection.

(Choice E) Myelodysplastic syndrome often presents with infection in the setting of pancytopenia. It may progress to acute leukemia.

(Choice F) In secondary polycythemia, the red blood cell count is elevated, typically due to increased erythropoietin (EPO) from hypoxia or an EPO-secreting tumor. This patient's hemoglobin was slightly low.

Educational objective:
Leukemoid reaction (LR) occurs as a response to severe infection and is marked by leukocyte counts >50,000/mm^3. Compared to chronic myeloid leukemia, LR is characterized by the presence of a high alkaline phosphatase score, a greater proportion of late neutrophil precursors (metamyelocytes, bands), and a lack of absolute basophilia.

Time spent:1 Seconds
Subject:
Medicine

QID:2886
System:
Hematology & Oncology (White blood cell disorders)

A 65-year-old man is brought to the emergency department due to high fevers and confusion. He has had 2 days of cough productive of greenish sputum. He has a history of well-controlled type 2 diabetes mellitus and was treated for bronchitis twice in the last 4 months. The patient received the influenza vaccine this year. He has smoked a pack of cigarettes daily for the past 27 years and drinks alcohol occasionally. Temperature is 38.4 C (101.2 F), blood pressure is 118/74 mm Hg, pulse is 98/min, and respirations are 24/min. His pulse oximetry reading is 92% on room air. The patient is obese. His anterior cervical lymph nodes are enlarged and nonpainful. His lungs are clear to auscultation except for scattered rales at the right lung base. Abdominal examination reveals a palpable liver edge and spleen tip. Chest-x ray shows a developing right lower lobe infiltrate. Laboratory studies are as follows:

Hematocrit	32%
Platelets	120,000/mm^3
Leukocytes	42,800/mm^3
Neutrophils	10%
Bands	4%
Lymphocytes	85%
Monocytes	1%

Blood cultures are sent to the laboratory; antibiotics and supportive care are initiated. What is the best next step in management of this patient?

A. Bronchoscopy
B. Epstein-Barr virus serology
C. Flow cytometry of the peripheral blood
D. *JAK2* mutation testing
E. Lymph node biopsy
F. Serum protein electrophoresis

Correct answer is
35% answered correctly

Explanation:

Chronic lymphocytic leukemia	
Clinical features	• Lymphadenopathy (cervical, supraclavicular, axillary) • Hepatosplenomegaly • Mild thrombocytopenia & anemia • Often asymptomatic
Diagnosis	• Severe lymphocytosis & smudge cells • Flow cytometry • Lymph node & bone marrow biopsy not generally needed

Prognosis	• Median survival 10 years
	• Worse prognosis with:
	  ◦ Multiple chain lymphadenopathy
	  ◦ Hepatosplenomegaly
	  ◦ Anemia & thrombocytopenia

Complications	• Infection • Autoimmune hemolytic anemia • Secondary malignancies (eg, Richter syndrome)

This patient with a fever, productive cough, and right lower lobe infiltrate likely has bacterial pneumonia. Most bacterial infections cause a mild to moderate leukocytosis with a predominance of neutrophils. This patient's complete blood count demonstrates a **dramatic leukocytosis**, primarily with **lymphocytes**. In an elderly patient, severe lymphocytosis combined with hepatosplenomegaly, lymphadenopathy, and bicytopenia (anemia, thrombocytopenia) strongly suggests underlying **chronic lymphocytic leukemia** (CLL). Although patients with CLL have high white blood cell counts, their immune systems are abnormal; hypogammaglobulinemia and defects in cell signaling increase the risk and severity of **infections** (a major complication of CLL).

CLL is diagnosed by **flow cytometry** (showing a clonality of mature B cells).

(Choice A) Bronchoscopy with biopsy is sometimes used to determine the pathology of a lung mass, but it does not play a role in the diagnosis of CLL. This patient's lung infiltrate is likely pneumonia; bronchoscopy is not indicated at this time.

(Choice B) Epstein-Barr virus serology can be used to diagnose infectious mononucleosis (IM). IM typically affects young adults and presents with fever, lymphadenopathy, malaise, and pharyngitis. Although splenomegaly, lymphadenopathy, and lymphocytosis can occur with IM, leukocytosis is generally mild (12,000-18,000/mm^3) and cytopenias are rare.

(Choice D) The *JAK2* mutation is associated with myeloproliferative diseases, particularly polycythemia vera (PV). PV can lead to splenomegaly but usually causes an elevated hematocrit (>50%), thrombocytosis, and thrombotic complications.

(Choice E) Lymph node (LN) biopsy is not generally needed to diagnose CLL. Flow cytometry is the test of choice. LN biopsy is useful in diagnosing some lymphomas (eg, Hodgkin lymphoma, non-Hodgkin lymphoma).

(Choice F) Serum protein electrophoresis can detect elevated levels of monoclonal proteins. It is typically used to diagnose multiple myeloma (MM). MM often presents with anemia and bone pain; peripheral smear shows rouleaux formation (red blood cells that appear stacked) and leukopenia. This patient has dramatic leukocytosis.

Educational objective:
Infections are a common complication of chronic lymphocytic leukemia (CLL). CLL is diagnosed by flow cytometry (clonality of mature B cells).

Time spent:0 Seconds
Subject:
Medicine

QID:2887
System:
Hematology & Oncology (White blood cell disorders)

A 25-year-old woman comes to the physician with 6 weeks of dyspnea and fatigue. She has no other medical problems and takes no medications. She does not use tobacco, alcohol, or illicit drugs. There is no family history of asthma or blood disorders. Her blood pressure is 110/70 mm Hg, pulse is 96/min, and respirations are 12/min. Examination shows pallor, scleral icterus, mild jaundice, and splenomegaly. Laboratory results are as follows:

Hematocrit	20%
Leukocytes	10,000/μL
Platelets	180,000/μL
Total bilirubin	7 mg/dL
Direct bilirubin	1.4 mg/dL
Blood urea nitrogen	10 mg/dL
Serum creatinine	0.7 mg/dL
Serum lactate dehydrogenase	350 U/L (80–280 U/L)
Serum haptoglobin	30 mg/dL (30–220 mg/dL)
Reticulocyte count	8%

Peripheral blood smear shows spherocytes without central pallor. Direct Coombs test is positive. Based on these findings, which of the following is the most likely diagnosis?

A. Autoimmune hemolytic anemia
B. Glucose-6-phosphate dehydrogenase deficiency
C. Hereditary spherocytosis
D. Paroxysmal nocturnal hemoglobinuria
E. Sickle cell anemia

. Correct answer is
68% answered correctly

Explanation:

Causes of hemolysis	
Intravascular hemolysis	• Microangiopathic hemolytic anemia (eg, disseminated intravascular coagulation) • Transfusion reactions • Infections (eg, clostridial sepsis) • Paroxysmal nocturnal hemoglobinuria • Intravenous Rho(D) immunoglobulin infusion
Extravascular hemolysis	• Intrinsic RBC enzyme deficiencies (eg, G6PD) • Hemoglobinopathies (eg, sickle cell, thalassemia) • Membrane defects (eg, hereditary spherocytosis) • Hypersplenism, intravenous immunoglobulin infusion • Warm- or cold-agglutinin autoimmune hemolytic anemia (most cases) • Infections (eg, *Bartonella*, malaria)
G6PD = glucose-6-phosphate dehydrogenase; **RBC** = red blood cell.	

This patient's pallor, jaundice, splenomegaly, and laboratory findings are consistent with hemolytic anemia. The most likely diagnosis is **autoimmune hemolytic anemia (AIHA)**, which is due to **autoantibodies** to red blood cells (RBCs).

Hemolysis can occur intra- or extravascularly. Intravascular hemolysis is due to significant RBC structural damage resulting in RBC destruction within the intravascular space (eg, paroxysmal nocturnal hemoglobinuria, disseminated intravascular coagulation). The hemoglobin released from hemolyzed RBCs binds to haptoglobin, and the hemoglobin-haptoglobin complex is cleared by the liver. This leads to markedly reduced serum haptoglobin (to undetectable levels). RBC hemolysis also results in elevated indirect bilirubin levels (from heme breakdown) and raised serum lactate dehydrogenase (LDH) levels (released from RBCs).

In **extravascular hemolysis**, the RBCs are predominantly destroyed by phagocytes in the reticuloendothelial system (eg, lymph nodes, spleen). As a result, there is less hemoglobin release than in intravascular hemolysis, so laboratory results usually show normal to slightly low haptoglobin, slightly elevated LDH, and elevated indirect bilirubin. Extravascular hemolysis can be due to causes such as antibody-mediated RBC destruction (eg, most cases of AIHA) or intrinsic RBC enzyme (eg, glucose-6-phosphate dehydrogenase deficiency) or membrane (eg, hereditary spherocytosis) defects.

This patient's laboratory findings (anemia, indirect hyperbilirubinemia, low-normal haptoglobin, and slightly elevated LDH) all suggest extravascular hemolysis; her peripheral smear shows spherocytes without central pallor. These findings can be seen in AIHA as well as in hereditary spherocytosis. AIHA usually has a negative family history and **positive Coombs** test. Hereditary spherocytosis usually has a strong family history and a negative Coombs test. If the Coombs test is negative and there is still a high index of suspicion for AIHA, a micro-Coombs test can be performed to confirm the diagnosis. This patient most likely has warm-agglutinin (IgG autoantibody mediated-) AIHA from an autoimmune cause. AIHA usually causes extravascular hemolysis, although some degree of intravascular hemolysis can occur, especially with IgM-mediated AIHA.

(Choice B) Glucose-6-phosphate dehydrogenase deficiency is an X-linked hereditary cause of hemolytic anemia in which hemolytic episodes may be triggered by medications (eg, sulfa drugs). Peripheral blood smear may show cells with Heinz bodies.

(Choice C) Hereditary spherocytosis usually has a strong family history (most cases are autosomal dominant), positive eosin-5-maleimide (and osmotic fragility) test, and a negative Coombs test.

(Choice D) Paroxysmal nocturnal hemoglobinuria is caused by a defect in the cell membrane anchor that leads to complement-mediated hemolysis with a negative Coombs test but evidence of venous thrombosis and sometimes episodic intravascular hemolysis.

(Choice E) Sickle cell anemia is usually associated with a strong family history and sickle-shaped cells on peripheral blood smear. Splenomegaly may be seen in childhood, but autosplenectomy is a more common finding by adulthood.

Educational objective:
Autoimmune hemolytic anemia (AIHA) and hereditary spherocytosis (HS) can cause extravascular hemolytic anemia. A negative family history and positive Coombs test suggest AIHA; a positive family history and negative Coombs test suggest HS. The peripheral blood smear in both conditions may show spherocytes without central pallor.

A 66-year-old man comes to the office due to increasing pain in his left arm. The patient works as a furniture transporter and initially attributed the pain to a muscular strain, but it has slowly worsened and stopped responding to over-the-counter pain medications. The pain started 3 months ago and is mainly near the left elbow. He also notes back pain. He has not had fever or chills. His other medical problems include hypertension and hypercholesterolemia. The patient has never smoked. Temperature is 36.8 C (98.2 F), blood pressure is 132/86 mm Hg, pulse is 88/min, and respirations are 14/min. He appears comfortable. His mucous membranes are pale. There is no lymphadenopathy. Cardiopulmonary examination is normal. The abdomen is soft without organomegaly. The prostate is smooth, nontender, and moderately enlarged. Neurologic examination is unremarkable. Laboratory results are as follows:

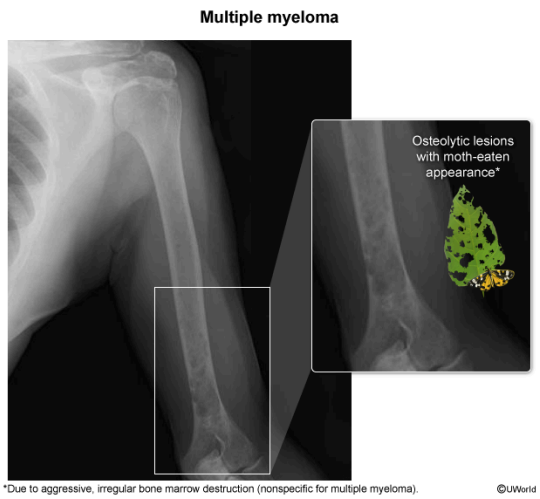
Complete blood count	
Hemoglobin	9.8 g/dL
Mean corpuscular volume	89 μm^3
Platelets	254,000/mm^3
Leukocytes	6,800/mm^3
Neutrophils	60%
Lymphocytes	32%
Monocytes	8%

X-ray of the left arm is shown in the exhibit. Which of the following tests would be the most useful next step in the management of this patient?

A. Blood cultures
B. Bone marrow biopsy
C. Bone scan
D. Prostate biopsy
E. Serum parathyroid hormone levels
F. Serum protein electrophoresis

. Correct answer is
54% answered correctly

Explanation:



This patient has back pain, normocytic anemia, and arm pain with an x-ray showing multiple **osteolytic** (lucent) **lesions**. In an elderly patient, this raises suspicion for **multiple myeloma** (MM).

MM is a plasma cell neoplasm. Pathology stems from bone marrow infiltration (fractures, hypercalcemia, anemia) and monoclonal protein production (renal insufficiency). **Serum protein electrophoresis** (SPEP) is a common **screening test** for MM that detects elevated serum monoclonal protein (**M-spike**). **Bone marrow biopsy**, a more invasive procedure, can then **confirm diagnosis** (>10% clonal plasma cells).

(Choice A) Blood cultures are useful for diagnosing infections. This patient has symptoms of bone pain and evidence of osteolytic lesions. He has not had fevers, chills, or other systemic symptoms. Infection is much less likely than malignancy.

(Choice B) Bone marrow biopsy is an invasive test and performed only after gathering more information with peripheral smear (rouleaux), serum free light chain analysis, SPEP, and urine protein electrophoresis.

(Choice C) Bone scans are not useful in the diagnosis of MM as they detect only osteoblastic activity (as is often seen in metastatic solid tumors). In MM, the lesions are osteoclastic (lytic), so whole body cross-sectional bone imaging (eg, low dose CT scan), is needed to identify bone involvement.

(Choice D) Prostate cancer can cause bone lesions, but they tend to be osteoblastic (sclerotic) not osteolytic. In a patient with osteolytic lesions alone, MM is far more likely.

(Choice E) Hyperparathyroidism can cause osteopenia with subsequent fractures but is unlikely to cause osteolytic lesions. Osteitis fibrosa cystica (eg, brown tumors of the long bones) is associated with hyperparathyroidism; however, it is very rare in the United States, lesions are typically well-defined (vs moth-eaten appearance), and other radiographic abnormalities are common (eg, subperiosteal bone resorption of the middle phalanx, highly specific for hyperparathyroidism). MM is far more common and more likely.

Educational objective:
Bone pain is a common presenting symptom in multiple myeloma (MM). In an elderly patient with evidence of osteolytic lesions on x-ray, MM should always be suspected. The screening tests of choice for MM are serum protein electrophoresis, urine protein electrophoresis, and free light chain analysis. Diagnosis can be confirmed with bone marrow biopsy.

Time spent:1 Seconds
Subject:
Medicine

QID:2889
System:
Hematology & Oncology (Plasma cell disorders)

A 67-year-old woman comes to the office due to progressive fatigue and anorexia over the last 6 months. She has lost 4 kg (8.8 lb), which she attributes to early satiety. She has had no abdominal pain, night sweats, or fevers. The patient's past medical history is significant for hypothyroidism, hypertension, and gout. She does not use tobacco, alcohol, or illicit drugs and is compliant with her medications. Temperature is 37.3 C (99.2 F), blood pressure is 128/82 mm Hg, and pulse is 88/min. The patient is slightly thin but well nourished. Mild mucosal pallor is present. There is no lymphadenopathy in the cervical or supraclavicular chains. Cardiopulmonary examination is normal. A spleen tip is palpable with deep exhalation. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Platelets	285,000/mm^3
Leukocytes	42,800 /mm^3

Florescence in situ hybridization reveals an abnormality in chromosome 22. Which of the following is the most important target in treating this patient's disease?

A. DNA methylation mutations
B. Folic acid metabolism
C. Retinoic acid receptor
D. Thymidine synthesis
E. Tyrosine kinase

Correct answer is
68% answered correctly

Explanation:

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder driven by the abnormal fusion gene *BCR-ABL* (due to a translocation between chromosomes 9 and 22). This gene causes **leukemogenesis** due to a constitutively active **tyrosine kinase**. First-line treatment for most CML patients involves **tyrosine kinase inhibitors** such as **imatinib**. Although these drugs are not curative, they often can induce long-term remission.

Patients with CML may present asymptomatically, although fatigue, night sweats, weight loss, and abdominal fullness (due to splenomegaly) are not uncommon. Patients may experience weight loss and early satiety from splenomegaly. Peripheral blood smear in CML reveals dramatic leukocytosis (often >100,000/mm^3) with absolute basophilia and a shift toward very early neutrophil precursors (promyelocytes, myelocytes).

(Choice A) DNA methylation mutations are found in many hematologic malignancies including acute myelogenous leukemia and certain myelodysplastic syndromes. Drugs are available to counter the effects of these mutations, but they are not currently used in CML.

(Choices B and D) Methotrexate alters folic acid metabolism and reduces the ability of the body to generate thymidine as folate is an important component of thymidine synthesis. Methotrexate is used in many autoimmune conditions and neoplasms but is not used in the treatment of CML.

(Choice C) The retinoic acid receptor is involved in the pathogenesis of acute promyelocytic leukemia (APML), a subtype of acute myeloid leukemia. All-trans retinoic acid is a crucial component of therapy for APML, which often presents with complications due to pancytopenia.

Educational objective:
Chronic myeloid leukemia (CML) is driven by a reciprocal translocation of chromosomes 9 and 22 forming the *BCR-ABL* fusion gene. This gene creates a constitutively active tyrosine kinase. Tyrosine kinase inhibitors such as imatinib are a key therapy in the treatment of CML.

Time spent:1 Seconds

Subject:
Medicine

QID:2894
System:
Hematology & Oncology (White blood cell disorders)

A 42-year-old woman comes to the office due to worsening abdominal pain and distension. The vague upper abdominal discomfort began 4 weeks ago, and her abdomen has become progressively distended over the past week. The patient also notes several months of generalized pruritus, which is worsened by water contact and is not relieved by over-the-counter emollients. She has no other medical conditions and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. Temperature is 36.5 C (97.7 F), blood pressure is 152/80 mm Hg, pulse is 88/min, and respirations are 16/min. Physical examination shows facial plethora and mild scleral icterus. The neck veins are flat, and heart and lung sounds are normal. The abdomen is distended with flank dullness to percussion, tender hepatomegaly, and splenomegaly. There is no extremity edema or skin rash. Laboratory results are as follows:

Complete blood count	
Hemoglobin	20.8 g/dL
Hematocrit	62%
Platelets	440,000/mm^3
Leukocytes	12,400/mm^3
Liver function studies	
Total bilirubin	4.3 mg/dL
Alkaline phosphatase	270 U/L
Aspartate aminotransferase (SGOT)	506 U/L
Alanine aminotransferase (SGPT)	614 U/L

Which of the following is the best next step in evaluation of this patient's abdominal pain?

A. Abdominal Doppler ultrasonography
B. Chronic hepatitis serology
C. Diagnostic paracentesis
D. MR cholangiopancreatography
E. Serum alpha-fetoprotein concentration
F. Ultrasound-guided liver biopsy

Correct answer is
46% answered correctly

Explanation:

Budd-Chiari syndrome	

Etiology	• Hepatic venous outflow obstruction
	• Usually due to:
	  ◦ Myeloproliferative disorder (eg, PV)
	  ◦ Malignancy (eg, hepatocellular carcinoma)
	  ◦ Oral contraception use/pregnancy

Manifestations	• Acute
	  ◦ Jaundice, hepatic encephalopathy, variceal bleeding
	  ◦ Prolonged INR/PTT; elevated transaminases
	• Subacute/chronic
	  ◦ Vague, progressive abdominal pain
	  ◦ Hepatomegaly, splenomegaly, ascites
	  ◦ Mild/moderate elevation in bilirubin, transaminases

Diagnosis	• Abdominal Doppler ultrasonography: ↓ hepatic vein flow • Investigation for underlying disorders (eg, *JAK2* testing for PV)
PV = polycythemia vera.	

This patient's aquagenic pruritus, facial plethora, and dramatically elevated hematocrit raise strong suspicion for **polycythemia vera (PV)**, a chronic myeloproliferative disorder marked by elevated red blood cell mass. Although PV is often discovered incidentally on routine laboratory testing, patients may have **aquagenic pruritus** (itching worse with water), erythromelalgia (burning in feet/hands), transient vision disturbances (from hyperviscosity), or complications related to **thrombosis**/hemorrhage. The etiology of some of these findings is unclear, but improvement in pruritus and erythromelalgia with aspirin may reflect a causative role for prostaglandins (which are pruritogenic).

Risk of venous and arterial thrombosis is significantly increased in PV due to increased blood viscosity and abnormalities in platelet and leukocyte function. One classic thrombotic complication is **Budd-Chiari syndrome**, a disorder marked by hepatic venous outflow obstruction (usually due to hepatic vein thrombosis). Manifestations may be acute, subacute, or chronic; subacute cases often present with progressive **abdominal discomfort**, **ascites** (eg, abdominal distension, flank dullness), and **hepatosplenomegaly** (this may also be caused by PV directly). Mild/moderate elevations in liver transaminases, bilirubin, and alkaline phosphatase also commonly occur.

The diagnosis of Budd-Chiari syndrome is established with noninvasive imaging such as **abdominal Doppler ultrasonography**, which typically shows abnormal hepatic blood flow, hepatomegaly, splenomegaly, and ascites. Patients with suspected PV (as in this case) should also undergo blood testing for the *JAK2* V617F mutation, which is almost always positive.

(Choice B) Chronic hepatitis B or C virus infection often leads to cirrhosis, which frequently causes ascites, hepatosplenomegaly, and elevated bilirubin/transaminases. However, significant polycythemia, aquagenic pruritis, and facial plethora would be atypical.

(Choice C) Diagnostic paracentesis can help identify spontaneous bacterial peritonitis, which usually presents with abdominal pain, fever, and hepatic encephalopathy. Almost all cases occur in those with underlying advanced cirrhosis; polycythemia, aquagenic pruritis, and facial plethora indicate an alternate diagnosis.

(Choice D) MR cholangiopancreatography can identify biliary tree or pancreatic head lesions. Although biliary obstruction can cause elevated transaminases, bilirubin, and alkaline phosphatase, it would not account for the aquagenic pruritis, facial plethora, and polycythemia.

(Choice E) Approximately 50% of patients with hepatocellular carcinoma have elevated serum alpha-fetoprotein levels. Although hepatocellular carcinoma can present with abdominal pain, mild/moderate polycythemia (due to ectopic erythropoietin production), and decompensated cirrhosis, most cases arise in those with chronic viral hepatitis or alcohol abuse. In addition, the presence of aquagenic pruritis, severe polycythemia (HCT > 60%), and facial plethora make PV far more likely.

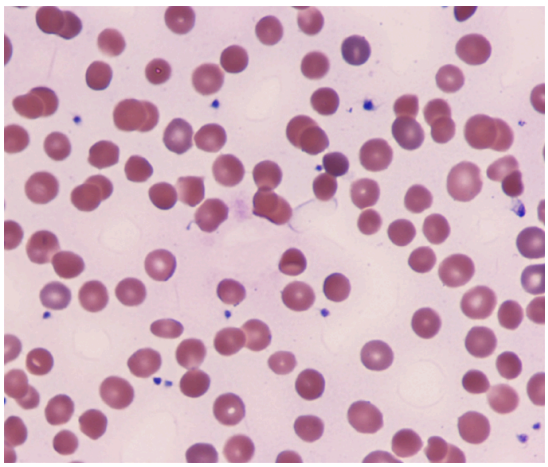
(Choice F) Ultrasound-guided liver biopsy is generally indicated when patients have cirrhosis from unclear causes or a liver lesion that cannot be diagnosed with imaging. This patient needs abdominal imaging prior to considering a biopsy.

Educational objective:
Budd-Chiari syndrome, a condition marked by obstruction of hepatic venous outflow, often presents with subacute manifestations such as vague, progressive abdominal pain, ascites, and hepatosplenomegaly. Polycythemia vera, a chronic myeloproliferative neoplasm associated with increased red blood cell mass, is particularly likely to cause Budd-Chiari syndrome.

Time spent:1 Seconds
Subject:
Medicine

QID:2988
System:
Hematology & Oncology (Red blood cell disorders)

A 20-year-old man from northern Europe comes to the emergency department with a 2-month history of intermittent right upper quadrant pain. The patient's medical history is unremarkable, and he considers himself healthy. His mother had her gallbladder removed at a young age. Abdominal ultrasound reveals cholelithiasis. Laboratory results show a hemoglobin level of 10.2 g/dL. Peripheral blood smear is shown in the image below.



This patient most likely has which of the following additional laboratory findings?

A. Absence of CD55 in red blood cell membranes
B. High hemoglobin A2 and hemoglobin F levels
C. High mean corpuscular hemoglobin concentration
D. High mean corpuscular volume
E. Low serum iron and ferritin levels

68% answered correctly

Explanation:

Hereditary spherocytosis	
Epidemiology	• Usually autosomal dominant
Clinical presentation	• Hemolytic anemia • Jaundice • Splenomegaly
Laboratory findings	• ↑ MCHC • Negative Coombs test • Spherocytes on peripheral smear • ↑ Osmotic fragility on acidified glycerol lysis test • Abnormal eosin-5-maleimide binding test

Treatment	• Folic acid supplementation • Blood transfusion • Splenectomy
MCHC = mean corpuscular hemoglobin concentration.	

This patient is anemic and has spherocytes (small, round, hyperchromic red blood cells [RBCs] without central pallor) on peripheral smear, which are indicative of **hereditary spherocytosis** (HS). HS is usually an **autosomal dominant** disorder and is most common in northern Europeans. A defect in RBC membrane proteins (eg, spectrin, ankyrin) results in spherocytes that are less deformable than normal biconcave RBCs and are more prone to splenic sequestration.

Depending on the extent of hemolysis, patients can have the classic triad of **hemolytic anemia**, jaundice, and splenomegaly (generally seen with severe hemolysis). **Pigment gallstones** can develop from excess bilirubin and cause right upper quadrant pain, as seen in this patient. Laboratory studies usually show **elevated mean corpuscular hemoglobin concentration** due to membrane loss and RBC dehydration. Other findings include **reticulocytosis**, normal to elevated red cell distribution width due to various RBC forms (eg, reticulocytes, spherocytes, normal RBCs), and low to normal mean corpuscular volume **(Choice D)**.

Diagnosis is clinical but can be confirmed with specific tests (eg, osmotic fragility test, eosin-5-maleimide binding test). Treatment is generally supportive (eg, folic acid, transfusions for severe anemia); in severe cases, **splenectomy** may be considered to improve anemia and reduce gallstone risk.

(Choice A) The CD55 molecule helps protect cells from complement-mediated destruction, and its absence leads to the hemolytic anemia seen in paroxysmal nocturnal hemoglobinuria. This condition typically presents with red urine and normal RBC morphology on blood smear.

(Choice B) Hemoglobin A2 levels are increased in patients with beta thalassemia trait. Hemoglobin F levels are increased in patients with sickle cell anemia, beta thalassemia, congenital aplastic anemia, and hereditary persistence of fetal hemoglobin. These conditions do not cause spherocytes on peripheral smear.

(Choice E) Iron deficiency anemia presents with low serum iron, low serum ferritin, and peripheral smear showing microcytic and hypochromic RBCs.

Educational objective:
Hereditary spherocytosis is usually an autosomal dominant disorder characterized by hemolytic anemia, jaundice, splenomegaly, and spherocytes on peripheral blood smear. Mean corpuscular hemoglobin concentration is elevated due to red blood cell dehydration and membrane loss. Pigment gallstones are a common complication.

A 58-year-old man comes to the office due to 2 months of exertional shortness of breath and easy fatigability. The patient has no chronic medical problems and takes no medications. He eats a balanced diet. He does not use tobacco, alcohol, or recreational drugs. Vital signs are within normal limits. Physical examination shows conjunctival pallor and areas of depigmentation on the arms suggestive of vitiligo. The tongue appears shiny. The spleen is not palpable. The remainder of the examination is normal. Laboratory results are as follows:

Complete blood count

Hemoglobin	7.5 g/dL
Mean corpuscular volume	110 μm^3
Platelets	135,000/mm^3
Leukocytes	4,100/mm^3

Which of the following is the most likely cause of this patient's current symptoms?

A. Autoantibodies to intrinsic factor
B. Autoimmune (Hashimoto) thyroiditis
C. Dietary folic acid deficiency
D. Dietary vitamin B_{12} deficiency
E. Replacement of bone marrow with fat cells

. Correct answer is
71% answered correctly

Explanation:

Common causes of macrocytic anemia*
• Folate deficiency • Vitamin B_{12} deficiency • Myelodysplastic syndromes • Acute myeloid leukemias • Drug-induced (eg, hydroxyurea, zidovudine, chemotherapy agents) • Liver disease • Alcohol use disorder • Hypothyroidism
*Mean corpuscular volume >100 μm^3.

Macrocytic anemia, mild thrombocytopenia/leukopenia, and glossitis (smooth, shiny tongue) indicate likely **vitamin B_{12} deficiency**. The leading cause is **pernicious anemia**, due to **antibodies against intrinsic factor** (carrier-protein crucial for vitamin B_{12} absorption). Most cases occur in **older patients** with other autoimmune conditions (eg, **vitiligo**, autoimmune thyroid disease).

Vitamin B_{12} is a crucial cofactor for DNA synthesis, particularly in rapidly dividing cells (eg, hematologic, gastrointestinal). Therefore, significant vitamin B_{12} deficiency often causes:

- **Megaloblastic changes** (eg, macrocytosis, hypersegmented neutrophils) due to reduced rates of nuclear division relative to cytoplasmic maturation (nuclear-cytoplasmic desynchrony). Macrocytic erythrocytes are at greater risk for hemolysis, leading to **anemia**; increased rates of apoptosis frequently results in **mild thrombocytopenia and leukopenia**.
- **Glossitis** due to impaired replication of tongue epithelial cells.

Because vitamin B_{12} is also required for myelin sheath maintenance, many (but not all) patients with clinically significant B_{12} deficiency also have neuropsychiatric findings (sensory ataxia, mood changes). The diagnosis of pernicious anemia can be confirmed by the detection of anti–intrinsic factor antibodies; parenteral vitamin B_{12} supplementation is generally curative.

(Choice B) Hypothyroidism from autoimmune thyroiditis usually causes normocytic, normochromic anemia (due to bone marrow hypoproliferation). Occasionally, mild macrocytic anemia can occur, but no megaloblastic changes or other signs of vitamin B_{12} deficiency (eg, glossitis) would be present. Most cases arise in young women.

(Choice C) Nutritional folate deficiency, which can also cause megaloblastic anemia, is rare in developed countries due to grain fortification with folate, although folate body stores are lower than those of vitamin B_{12} and can be depleted in a few months when nutrition is poor (eg, alcohol use disorder). This patient eats a balanced diet and is unlikely to have folate deficiency.

(Choice D) Dietary vitamin B_{12} deficiency is uncommon in those who eat a balanced diet because the vitamin is found in a wide range of animal proteins (eg, meat, dairy, eggs) and total body stores are generally sufficient for >1 year (total stores are 2-5 mg and daily requirement is ~2 µg/day). However, patients with long-standing poor nutrition (eg, alcohol use disorder) or vegan dietary habits may be at risk.

(Choice E) Aplastic anemia is associated with the destruction of hematopoietic stem cells, leading to the replacement of bone marrow with fat. Although pancytopenia is common, macrocytosis is rarely seen and glossitis would be atypical.

Educational objective:
Pernicious anemia, associated with auto-antibodies against intrinsic factor, is the most common cause of vitamin B_{12} deficiency. It occurs most often in older adults with other autoimmune conditions. Manifestations include megaloblastic anemia, atrophic glossitis (smooth, shiny tongue), and/or neurologic abnormalities (eg, paresthesia, subacute combined degeneration).

A 55-year-old male presents with face and arm swelling that he says is worst when he wakes in the morning. He also notes a 10 pound unintentional weight loss over the past three months, plus new-onset exertional dyspnea. His past medical history is significant for hypertension, for which he takes hydrochlorothiazide. He has smoked cigarettes for the past 40 years and drinks alcohol occasionally. On physical examination, he is afebrile and his vital signs are within normal limits. His face is plethoric and dark-appearing. The veins on the anterior chest wall appear engorged. His abdomen is soft, non-tender, and non-distended, and there is no organomegaly. The lower extremities are non-edematous. What is the most appropriate next step in the management of this patient?

A. Echocardiogram
B. Doppler ultrasound of the upper extremities
C. Chest x-ray
D. Urine for 24-hour protein excretion
E. Serum albumin level

Correct answer is
79% answered correctly

Explanation:

This patient's signs and symptoms are consistent with superior vena cava (SVC) syndrome, a condition where obstruction of the SVC impedes venous return from the head, neck and arms to the heart. Signs and symptoms include dyspnea, venous congestion, and swelling of the head, neck and arms. Malignancy is the most common cause of obstruction (i.e. lung cancer, non-Hodgkin lymphoma), accounting for >60% of cases. This patient's 40 year smoking history and recent 10 pound weight loss make lung cancer a likely diagnosis. Chest x-ray **(Choice C)** can identify the cause of SVC syndrome in >80% of cases. Abnormalities on chest x-ray warrant follow-up with chest CT and histology to determine the tumor type and to guide therapy.

(Choice A) Echocardiogram is not part of the work-up for SVC syndrome. Echocardiography can be helpful in suspected cardiac tamponade, which presents with Beck's triad of jugular venous distention, distant heart sounds and hypotension. Tamponade does not cause arm or face swelling or engorgement of the anterior chest wall veins.

(Choice B) Unexplained unilateral arm swelling warrants a Doppler to rule out DVT. However, simultaneous swelling of the face and bilateral arms indicates venous obstruction in the SVC, which upper extremity Doppler would not demonstrate.

(Choices D & E) Measurement of the 24-hour urinary protein excretion can help assess for nephrotic syndrome, and measurement of the serum albumin level can help assess for liver disease. These conditions can cause generalized edema, but not edema isolated to the upper half of the body.

Educational objective:
Malignancy is the most common cause of SVC syndrome. Lung cancer (particularly small cell lung cancer) and NHL are often implicated. Other possible causes include fibrosing mediastinitis (secondary to histoplasmosis or Tb infection) or thrombosis secondary to indwelling central venous devices. When the history and physical examination are suggestive, chest x-ray is warranted.

Time spent:0 Seconds **QID**:3508

Subject:
Medicine

System:
Hematology & Oncology (Principles of oncology)

A 45-year-old woman comes to the emergency department with left leg pain and swelling that has worsened over the last 2 days. The patient has no fevers, chills, dyspnea, or chest pain and has had no trauma to the left leg. Her medical history includes rheumatoid arthritis and gastroesophageal reflux disease, for which she takes low-dose methotrexate, folic acid, and omeprazole. The patient has smoked a pack of cigarettes daily for 10 years and does not consume alcohol. Temperature is 37 C (98.6 F), blood pressure is 130/80 mm Hg, pulse is 70/min, and respirations are 14/min. BMI is 30 kg/m^2. The left leg is swollen (>4 cm) compared to the right and is warm and tender on palpation. Pitting edema is present. Her legs are shown in the image below.

Which of the following is the most appropriate next step in management of this patient?

A. Aspirin
B. Blood cultures followed by antibiotics
C. Chest CT angiogram
D. Compression ultrasonography
E. D-dimer test
F. Empiric anticoagulation

Correct answer is
54% answered correctly

Explanation:

Modified Wells criteria for pretest probability of deep venous thrombosis	
Score 1 point for each feature present	• Previously documented DVT • Active cancer • Recent immobilization of the legs • Recently bedridden >3 days • Localized tenderness along vein distribution • Swollen leg • Calf swelling >3 cm compared to other leg • Pitting edema

	• Collateral superficial nonvaricose veins • Alternate diagnosis more likely (−2 points)
Total score for clinical probability	• 0 points = Low probability • 1 or 2 points = Moderate probability • ≥3 points = High probability
DVT = deep venous thrombosis.	

This patient with left leg pain and marked asymmetric swelling likely has a **deep venous thrombosis (DVT)**. Rheumatoid arthritis (RA) itself is a risk factor, regardless of whether or not it is associated with immobilization. Other common risk factors include family history of DVT, trauma, **hypercoagulable state** (eg, underlying malignancy), and medications (eg, oral contraceptives).

The diagnosis of DVT is based on history and physical examination findings combined with laboratory results and imaging. The modified **Wells score** is a widely used risk assessment tool for DVT. Patients with a score ≥2 (eg, pitting edema, calf swelling >3 cm compared to the other leg) are more likely to have DVT. In such patients, **compression ultrasonography** is the preferred initial test as it can be performed quickly in most emergency departments.

Patients with clinical evidence of pulmonary embolus (eg, pleuritic chest pain, dyspnea, tachypnea, tachycardia) should be started on anticoagulation if there are no contraindications (eg, active bleeding) while undergoing diagnostic evaluation (eg, chest CT angiogram) **(Choice C)**. In contrast, patients with features of DVT only, as in this case, should have DVT confirmed by imaging prior to starting anticoagulation as anticoagulation itself has risks **(Choice F)**.

(Choice A) Anticoagulation is the preferred treatment for patients with confirmed DVT. Aspirin is used in patients with peripheral artery disease, which can cause atypical leg pain (without swelling or warmth) that is often bilateral and exacerbated by exertion.

(Choice B) Blood cultures and empiric antibiotic therapy would be appropriate in patients with cellulitis, but such patients would generally also have fever (or other systemic symptoms), extremity redness, and an elevated white blood cell count. Marked asymmetric swelling is also more suggestive of a DVT.

(Choice E) In patients with low pretest probability based on the Wells score, a negative D-dimer is useful for excluding DVT. However, D-dimer levels are not specific for DVT, and an elevated level alone is not sufficient to establish the diagnosis. In patients with moderate or high pretest probability (as in this patient), compression ultrasonography is the best next step.

Educational objective:
Noninvasive evaluation with compression ultrasonography is recommended as an initial test in patients with moderate or high probability of deep venous thrombosis.

Time spent:1 Seconds
Subject:
Medicine

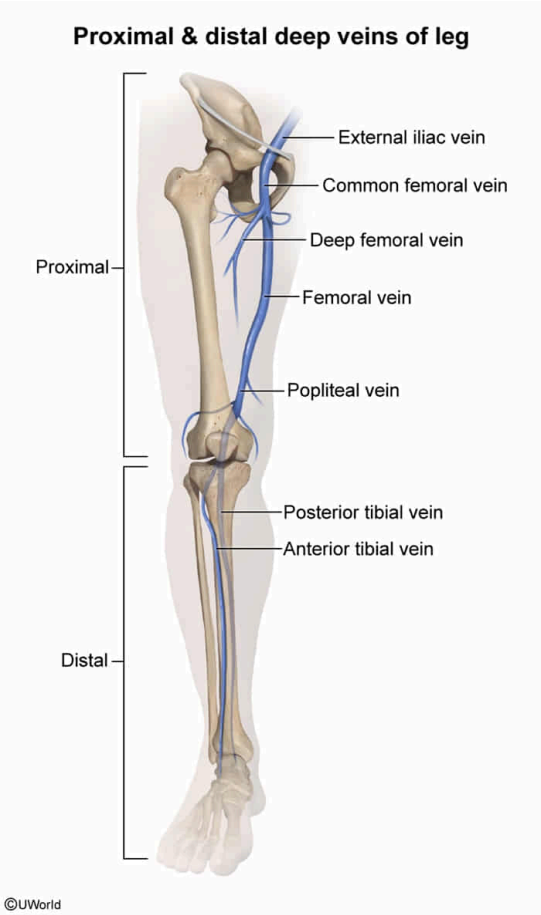
QID:3596
System:
Hematology & Oncology (Hemostasis and thrombosis)

A 66-year-old man comes to the emergency department with acute onset of severe chest pain and shortness of breath. The pain is in the right upper chest and is aggravated by deep breathing and coughing. Medical history is significant for hypertension and obstructive sleep apnea. The patient quit smoking 10 years ago and drinks beer on weekends. Blood pressure is 110/70 mm Hg, pulse is 116/min and regular, and respirations are 22/min. BMI is 30 kg/m^2. Normal vesicular breath sounds are heard on auscultation of the chest. Cardiac auscultation reveals tachycardia and an accentuated S2. Chest x-ray is unremarkable. ECG shows sinus tachycardia. CT angiogram of the chest reveals an embolus in the right pulmonary artery. Which of the following is the most likely origin of this embolus?

A. Calf vein
B. Femoral vein
C. Renal vein
D. Right atrium
E. Upper extremity vein

. Correct answer is
53% answered correctly

Explanation:



This patient's clinical presentation (eg, acute chest pain worse with inspiration, tachycardia, S2 suggestive of pulmonary hypertension) with CT angiogram findings of a thrombus in the right pulmonary artery is diagnostic of **pulmonary**

embolus (PE). The deep veins of the lower extremities are the most frequent source. Lower extremity deep vein thrombosis (DVT) is divided into 2 categories:

- **Proximal**/thigh (eg, iliac, **femoral**, **popliteal**): These DVTs are the source of **>90% of acute PEs**, probably due to their large caliber and proximity to the lungs.
- Distal/calf: Although most DVTs occur in the calf vein, distal/calf DVTs are less likely than proximal/thigh DVTs to embolize to the lungs and cause PE and they are more likely to spontaneously resolve **(Choice A)**.

(Choice C) Thrombi originating from the renal veins are most common in patients with nephrotic syndrome. The prevalence of PE in patients with nephrotic syndrome is 10%-30%.

(Choice D) Thrombi originating in the right atrium are more common in patients with intracardiac devices (eg, pacemaker) and are less likely to occur spontaneously.

(Choice E) Spontaneous upper extremity DVT is generally uncommon (1%-4%) and even less likely to cause PE. Common risk factors for upper extremity DVT include prothrombotic state, indwelling catheter, and anatomical venous obstruction (eg, cervical rib, bony overgrowth after clavicular fracture).

Educational objective:
The proximal deep leg veins are the most common source of symptomatic pulmonary embolism. Other less common sources of emboli include the calf veins, renal veins, pelvic veins, upper extremity veins, and right heart.

Time spent:0 Seconds	**QID**:3597
Subject:	**System:**
Medicine	Hematology & Oncology (Hemostasis and thrombosis)

A 25-year-old African American man is admitted to the hospital due to sudden-onset back pain, dark urine, and a day of fatigue. Four days ago, the patient began taking trimethoprim-sulfamethoxazole for right arm cellulitis. Yesterday he was unable to go to work due to fatigue and weakness. Medical history is otherwise unremarkable. Physical examination shows conjunctival pallor and improving cellulitis. Laboratory results are as follows:

Hemoglobin	7.5 g/dL
Hematology	
Mean corpuscular hemoglobin concentration	32% Hb/cell
Haptoglobin	15 mg/dL (normal: 30-200)
Liver function studies	
Total bilirubin	3.5 mg/dL
Direct bilirubin	0.8 mg/dL
Lactate dehydrogenase	700 U/L

Peripheral smear shows bite cells. Glucose-6-phosphate dehydrogenase activity assay is sent on admission and returns within normal limits. Which of the following is the most likely cause of this patient's hemolysis?

A. Galactokinase deficiency
B. Glucose-6-phosphate dehydrogenase deficiency
C. Hereditary spherocytosis
D. Pyruvate kinase deficiency
E. Sickle cell disease

Correct answer is
61% answered correctly

Explanation:

Glucose-6-phosphate dehydrogenase deficiency	
Epidemiology	• Hemolytic anemia due to oxidative stress (infection, sulfa drugs, fava beans) • X-linked: Asian, African, or Middle Eastern descent
Manifestations	• Pallor & fatigue • Dark urine, jaundice & icterus • Abdominal/back pain
Laboratory findings	• Hemolysis: ↓ hemoglobin, ↓ haptoglobin, ↑ bilirubin & LDH, ↑ reticulocytes • Peripheral smear: bite cells & Heinz bodies • Negative Coombs test • ↓ G6PD activity level (may be normal during attack)
Management	• Remove or treat responsible agent/condition • Provide supportive care
G6PD = glucose-6-phosphate dehydrogenase; **LDH** = lactate dehydrogenase.	

This patient developed hemolytic anemia after receiving trimethoprim-sulfamethoxazole, raising strong suspicion for **glucose-6-phosphate dehydrogenase (G6PD) deficiency**. This X-linked, inherited disorder is seen in ~10% of **Black men** but also occurs in those of Mediterranean, Asian, and Middle Eastern descent. Patients are generally asymptomatic but develop hemolysis when exposed to **oxidative stressors** such as infection, medications (eg, **trimethoprim-sulfamethoxazole**, nitrofurantoin, primaquine), or certain foods (eg, fava beans).

Hemolysis generally manifests with pallor and fatigue (due to anemia), jaundice (due to elevated bilirubin) and dark urine (due to hemoglobinuria), and back/abdominal pain. Laboratory results will show low hemoglobin, **elevated indirect bilirubin**, elevated lactate dehydrogenase, and **decreased haptoglobin**. Peripheral blood smear typically reveals Heinz bodies (oxidized/precipitated hemoglobin) and bite cells (bite-shaped membrane defects due to removal of Heinz bodies by splenic macrophages). Coombs testing will be negative, unlike antibody-mediated forms of hemolysis.

G6PD activity testing can be normal (**low sensitivity**) in acute hemolytic episodes because older erythrocytes (lowest G6PD activity) have been hemolyzed and young erythrocytes/reticulocytes (higher G6PD activity) are disproportionally elevated. Therefore, in such settings, this test cannot be used to rule out G6PD deficiency; repeat testing should be done at 3 months to confirm the diagnosis in those whose initial test was negative. No intervention is generally required other than removing or treating the inciting oxidative stress.

(Choice A) Galactokinase deficiency does not cause hemolytic anemia. The classic manifestation of this condition is bilateral cataract development.

(Choice C) Hereditary spherocytosis is a genetic disorder associated with chronic hemolytic anemia due to erythrocyte membrane defects. However, mean corpuscular hemoglobin concentration will be >36 g/dL, and blood smear will show spherocytes.

(Choice D) Pyruvate kinase deficiency is an autosomal recessive disorder that causes chronic hemolysis, hepatosplenomegaly, skin ulcers, and pigmented gallstones. Unlike with G6PD deficiency, hemolysis is constant, so there is no relationship to inciting events (eg, sulfa drug exposure).

(Choice E) Sickle cell crisis is associated with worsened hemolytic anemia and acute pain. Peripheral blood smear will show sickle cells or Howell-Jolly bodies.

Educational objective:
Glucose-6-phosphate dehydrogenase (G6PD) deficiency causes episodic hemolytic anemia after oxidative insults (eg, sulfa drugs, primaquine, infection, fava beans). Laboratory studies show hemolytic anemia (eg, elevated lactate dehydrogenase/bilirubin, low haptoglobin), and peripheral blood smear typically demonstrates bite cells and Heinz bodies. Diagnosis is made by G6PD activity level, but sensitivity is low in acute hemolytic crises; therefore, this test cannot be relied on to rule out the condition in the acute setting.

Time spent:1 Seconds
Subject:
Medicine

QID:3609
System:
Hematology & Oncology (Red blood cell disorders)

A 25-year-old African American man is admitted to the hospital due to sudden-onset back pain, dark urine, and a day of fatigue. Four days ago, the patient began taking trimethoprim-sulfamethoxazole for right arm cellulitis. Yesterday he was unable to go to work due to fatigue and weakness. Medical history is otherwise unremarkable. Physical examination shows conjunctival pallor and improving cellulitis. Laboratory results are as follows:

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Mean corpuscular hemoglobin concentration	32% Hb/cell
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E. Sickle cell disease

Correct answer is
61% answered correctly

Explanation:

Glucose-6-phosphate dehydrogenase deficiency	
Epidemiology	• Hemolytic anemia due to oxidative stress (infection, sulfa drugs, fava beans) • X-linked: Asian, African, or Middle Eastern descent
Manifestations	• Pallor & fatigue • Dark urine, jaundice & icterus • Abdominal/back pain
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Time spent:1 Seconds
Subject:
Medicine

QID:3609
System:
Hematology & Oncology (Red blood cell disorders)

A 70-year-old man comes to the office due to 6 months of progressive fatigue and dyspnea. He has had no fever, night sweats, or weight loss. The patient's medical history is significant for benign prostatic hyperplasia, hypertension, and mechanical aortic valve replacement for severe aortic stenosis. The patient currently takes warfarin, tamsulosin, and amlodipine. He does not drink alcohol. Temperature is 36.4 C (97.5 F), blood pressure is 150/99 mm Hg, and pulse is 68/min. BMI is 27 kg/m^2. The patient appears well nourished and fit. No scleral icterus is present, but the mucosa is pale. There is no jugular venous distension or lymphadenopathy. Cardiac examination reveals a normal S1 and a mechanical S2. Pulmonary examination is normal. Both the liver and the spleen are palpable. The remainder of the examination shows no abnormalities. Laboratory results are as follows:

Complete blood count
- Hematocrit 26%
- Reticulocytes 10%
- Platelets 90,000/mm^3
- Leukocytes 7,500/mm^3

Serum chemistry
- Creatinine 1.2 mg/dL

Coagulation studies
- INR 3

Which of the following is the best next step in management?

A. ADAMTS-13 assay
B. Bone marrow biopsy
C. Colonoscopy
D. Echocardiogram
E. Liver biopsy

. Correct answer is
37% answered correctly

Explanation:

This patient with a mechanical aortic valve developed symptomatic anemia and reticulocytosis, raising strong suspicion for **traumatic macrovascular hemolysis**. Most cases arise in the setting of a dysfunctional **mechanical** or severely calcified **aortic valve**; high pressure gradients across the irregular valve cause shearing of passing erythrocytes, leading to **intravascular hemolysis**. Damaged erythrocytes that are not lysed in the intravascular space are generally destroyed by splenic macrophages, leading to concurrent extravascular hemolysis.

Mechanical aortic valves often cause mild, asymptomatic hemolysis. However, valve deterioration can trigger **progressive symptomatic anemia** (eg, fatigue, dyspnea with exertion) with signs of erythrocyte lysis (eg, jaundice, dark urine) and **reticulocytosis**. **Thrombocytopenia** can also occur because platelets may be damaged as they pass through the rigid valve opening. Hepatosplenomegaly can develop as the fragmented erythrocytes are cleared in the macrophages and monocytes within the liver and spleen. Peripheral blood smear generally shows schistocytes (helmet cells). A **transthoracic echocardiogram** should be performed to visualize valve function and determine valvular pressure gradients.

(Choice A) ADAMTS-13, a plasma protease that cleaves ultralarge von Willebrand fibers, is deficient in thrombotic thrombocytopenic purpura (TTP). Patients with TTP frequently have acute (not chronic) anemia due to microangiopathic hemolysis. Severe thrombocytopenia (<10,000/mm^3) is also present due to platelet consumption in the microvasculature. Most patients also have altered mental status or renal insufficiency.

(Choice B) Bone marrow suppression (eg, tumor infiltration) can cause chronic anemia and thrombocytopenia. However, significant reticulocytosis is uncommon because the bone marrow cannot efficiently generate cells.

(Choice C) Colon cancer is a common cause of chronic anemia in older individuals who have not undergone screening colonoscopy. Reticulocytosis would be unusual (it is more common with acute, rather than chronic, blood loss anemia), and splenomegaly and thrombocytopenia are not typically present.

(Choice E) Cirrhosis can cause hepatosplenomegaly with thrombocytopenia (splenic platelet trapping), as well as anemia (eg, bleeding varices, chronic inflammation). However, this patient has no risk factors for cirrhosis (eg, alcohol use, hepatitis); his elevated INR likely reflects therapeutic warfarin use rather than liver disease; and his mechanical valve makes traumatic hemolysis much more likely. Finally, because liver biopsy is an invasive procedure, noninvasive tests (eg, echocardiogram evaluating valve function) are generally performed first.

Educational objective:
A mechanical or severely calcified aortic valve can cause hemolytic anemia due to erythrocyte shearing. Patients also frequently have mildly low platelets due to concurrent mechanical platelet injury. An echocardiogram should be performed to assess the valvular function.

Time spent:0 Seconds
Subject:
Medicine

QID:3610
System:
Hematology & Oncology (Red blood cell disorders)

A 25-year-old woman comes to the office due to heavy menses. Over the past few months, the patient's menstrual periods have lasted 7 days rather than the usual 3 days. In addition, her menstruation has been unusually heavy and has, at times, bled through her clothing while at work. The patient is an active volleyball player but has not been able to play recently due to increasing fatigue; frequent, diffuse myalgias; and bilateral pain in her wrists that requires icing after practice. She has also noticed that her forearms become easily bruised in areas where the ball hits. The patient takes no medications and does not use tobacco, alcohol, or illicit drugs. Temperature is 37 C (98.6 F), blood pressure is 116/76 mm Hg, pulse is 76/min, and respirations are 16/min. There are scattered petechiae across the body with a few large ecchymoses on the forearms. The remainder of the physical examination is normal. Laboratory results are as follows:

Complete blood count
- Hematocrit 37%
- Platelets 24,000/mm^3
- Leukocytes 11,000/mm^3

Coagulation studies
- PT 12 sec
- Activated PTT 38 sec

Peripheral blood smear shows normal and large platelets. Which of the following is the best next step in evaluation of this patient?

A. Antinuclear antibody screen
B. Ascorbic acid level test
C. Factor VIII assay
D. Hemoglobin electrophoresis
E. Platelet aggregation test
F. Von Willebrand antigen level test

Correct answer is
33% answered correctly

Explanation:

Immune thrombocytopenic purpura	
Epidemiology	• Commonly acquired form of thrombocytopenia • Autoantibody formation • Often recent viral infection or comorbidity (eg, HIV, HCV, CLL)
Manifestations	• Frequently asymptomatic • Mucocutaneous bleeding (eg, menorrhagia, epistaxis) • Ecchymoses, petechiae, purpura • Severe hemorrhage is rare
Diagnosis	• Diagnosis of exclusion • Normal coagulation tests, platelet morphology (peripheral smear) • HIV, HCV testing (commonly induces ITP)
Treatment	• Observation if no bleeding & platelets >30,000/mm^3 • Corticosteroids if platelets <30,000/mm^3

	• IVIG & platelet transfusion if hemorrhage

CLL = chronic lymphocytic leukemia; **HCV** = hepatitis C virus; **ITP** = immune thrombocytopenic purpura; **IVIG** = intravenous immunoglobulin.

Immune thrombocytopenia (ITP) is an acquired disorder marked by the formation of autoantibodies to platelet surface glycoproteins, which increases platelet clearance in the spleen and inhibits megakaryocytosis. In ITP, platelet counts fall to **<100,000/mm^3**, leading to prolonged skin/mucosal bleeding (eg, menstrual, nasal), ecchymosis, and petechiae.

ITP is a **diagnosis of exclusion**; therefore, other causes of thrombocytopenia (eg, drug-induced thrombocytopenia, liver disease, hypersplenism, microangiopathic disorders, bone marrow abnormalities) must be ruled out. In ITP, leukocyte count, erythrocyte count, and **coagulation studies are normal**; peripheral blood smear usually shows normal platelet morphology (both normal-sized and large platelets may be seen due to increased platelet turnover).

ITP is categorized as either primary (no discernible cause) or secondary (due to an underlying condition). HIV and hepatitis C are the most common secondary causes, so testing for these 2 conditions is generally performed. Additional testing is warranted when specific signs or symptoms of another disorder are present. This patient's myalgias and arthralgias raise concern for an autoimmune disease (eg, systemic lupus erythematosus); therefore, **antinuclear antibody testing** is advisable.

(Choice B) Ascorbic acid (vitamin C) deficiency causes impaired collagen synthesis and can lead to ecchymosis and palpable purpura. However, most cases occur in severely malnourished individuals or those who use alcohol or illicit drugs.

(Choice C) Factor VIII deficiency can cause similar bleeding symptoms but is associated with prolonged PTT. Hemophilia A, an X-linked disorder (seen only in males), causes severe factor VIII deficiency.

(Choice D) Hemoglobin electrophoresis is used to diagnose thalassemia, a genetic hemoglobin disorder associated with anemia, microcytosis, and target cells. Hemoglobin disorders do not usually cause thrombocytopenia.

(Choice E) Platelet aggregation testing evaluates for rare disorders of platelet function and is generally indicated in those who have normal platelet count and prolonged bleeding times. This patient's thrombocytopenia makes ITP far more likely; platelet aggregation testing would not be indicated.

(Choice F) Von Willebrand disease (vWD) is associated with impaired platelet aggregation, which occasionally causes bruising and prolonged mucosal bleeding. However, platelet count and PT are normal; PTT is sometimes prolonged due to increased destruction of factor VIII.

Educational objective:
Immune thrombocytopenia (ITP) is an autoimmune disorder associated with isolated thrombocytopenia. Although most cases are primary, a minority of individuals have ITP due to an underlying condition (eg, HIV, hepatitis C). Testing for HIV and hepatitis C virus is recommended for all patients with ITP; additional testing is needed when signs and symptoms of other disorders (eg, systemic lupus erythematosus) are present.

Time spent:2 Seconds
Subject:
Medicine

QID:2251
System:
Hematology & Oncology (Platelet disorders)

A 43-year-old man is being evaluated for erectile dysfunction, which has been progressive over the past year. He has no other symptoms except some fatigue that he attributes to his intense work schedule. The patient drinks 1-2 beers every day after work and has a 20-pack-year smoking history. He does not use recreational drugs or take over-the-counter medications. Vital signs are normal. BMI is 29 kg/m^2. Skin examination shows brownish skin pigmentation, most pronounced over the face and both arms. The abdomen is soft and nontender without organomegaly. Cardiopulmonary examination shows no abnormalities, and there is no peripheral edema. Laboratory results are as follows:

Hemoglobin	14 g/dL
Platelets	200,000/mm^3
Leukocytes	7,500/mm^3
Blood urea nitrogen	14 mg/dL
Creatinine	0.8 mg/dL
Fasting glucose	130 mg/dL
Aspartate aminotransferase	78 U/L
Alanine aminotransferase	80 U/L

If untreated, this patient is at increased risk for developing which of the following complications?

A. Gastric adenocarcinoma
B. Hepatocellular carcinoma
C. Hypotensive crisis
D. Nephrotic syndrome
E. Pancreatic cancer
F. Skin cancer

Correct answer is
63% answered correctly

Explanation:

Clinical manifestations of hereditary hemochromatosis	
Skin	Hyperpigmentation (bronze diabetes)
Musculoskeletal	Arthralgia, arthropathy & chondrocalcinosis
Gastrointestinal	Elevated hepatic enzymes with hepatomegaly (early), cirrhosis (later) & increased risk for hepatocellular carcinoma
Endocrine	Diabetes mellitus, secondary hypogonadism & hypothyroidism
Cardiac	Restrictive or dilated cardiomyopathy & conduction abnormalities
Infections	Increased susceptibility to *Listeria*, *Vibrio vulnificus* & *Yersinia enterocolitica*

This patient's presentation is most consistent with **hereditary hemochromatosis** (HH). The increased total body iron leads to deposits in various organs (eg, liver, pancreas), resulting in multisystem organ damage. Disease progression typically requires decades of increased iron deposition. Consequently, patients tend to present in their 30s to 50s, with women presenting later due to therapeutic iron loss through menstruation.

Most patients with HH are diagnosed early in the disease due to **elevated liver enzymes** on routine laboratory studies. However, continued iron deposition can cause hepatic fibrosis and cirrhosis, **skin pigmentation** (sun-exposed areas, scars, genitalia), **diabetes mellitus** ("bronze diabetes"), arthropathy, and hypogonadism (diminished libido, erectile dysfunction [ED]). Patients with HH have an approximate 20-fold increased risk for **hepatocellular cancer** (HCC), accounting for 45% of deaths in HH patients.

The initial evaluation of HH commonly shows elevated iron studies. Diagnosis can be confirmed by genetic analysis of *HFE* mutations. Serial phlebotomy to deplete excess iron stores can significantly reduce the risk for cirrhosis and HCC.

(Choice A) Gastric adenocarcinoma is rarely associated with Leser-Trélat sign (sudden development of seborrheic keratoses) or acanthosis nigricans (thickened, hyperpigmented, velvety skin patches over the neck and folds). In this patient, the distribution of hyperpigmentation and lack of skin thickening are not consistent with acanthosis nigricans. In addition, the combination of ED, skin pigmentation, hyperglycemia, and liver function test abnormalities makes HH more likely.

(Choice C) Hypotensive crisis can complicate Addison disease (primary adrenal insufficiency). Hyperpigmentation (due to increased ACTH leading to increased melanocyte-stimulating hormone) is common; however, Addison disease is associated with hypoglycemia, not hyperglycemia.

(Choice D) Primary systemic amyloidosis, which commonly presents with fatigue, hepatomegaly, and petechiae/ecchymosis on the face, can be complicated by nephrotic syndrome. However, it is usually not associated with ED or hyperglycemia.

(Choice E) Pancreatic cancer can be associated with chronic pancreatitis and certain genetic syndromes (eg, Peutz-Jeghers syndrome), but not HH.

(Choice F) Patients with genetic disorders such as xeroderma pigmentosum and albinism are at increased risk for skin cancer. HH does not confer increased risk.

Educational objective:
Hereditary hemochromatosis should be considered in patients who have elevated liver enzymes, diabetes mellitus, and skin hyperpigmentation. It can progress to cirrhosis and is associated with a significantly increased risk for hepatocellular carcinoma.

A 55-year-old man comes to the office due to fatigue for the past month. He has also had occasional heartburn but no chronic abdominal pain. Medical history is significant for hepatomegaly due to fatty liver. He has been drinking 3-4 shots of alcohol per day for several years. He does not smoke. Physical examination reveals pallor of skin and mucous membranes, and mild hepatomegaly. Laboratory results are as follows:

Hemoglobin	8.5 g/dL
Leukocytes	8,000/mm^3
Mean corpuscular volume	110 fL
Platelets	150,000/mm^3
Blood glucose	118 mg/dL
Blood urea nitrogen	16 mg/dL
Creatinine	1.0 mg/dL

What is the most likely cause of anemia in this patient?

A. Vitamin B12 deficiency
B. Folate deficiency
C. Chronic blood loss from peptic ulcer
D. Anemia of chronic disease
E. Thiamine deficiency

Correct answer is
73% answered correctly

Explanation:

This patient's heavy alcohol use, pancytopenia, and significant macrocytosis likely has megaloblastic anemia due to **nutritional folate deficiency**. Folate is an essential dietary nutrient found in leafy vegetables and fortified grains; because it has relatively limited total body stores, consumption of an unbalanced or nutrient-poor diet (as is common in those with **alcohol use disorder)** frequently results in folate deficiency within 5-10 weeks. Alcohol also directly hastens folate deficiency by reducing folate absorption in the small intestine, impairing uptake/storage in the liver, and increasing urinary excretion.

Although many cases are asymptomatic, patients often develop clinically significant megaloblastic anemia with **macrocytosis** (mean corpuscular volume [MCV] often **>110 μm^3**) and **mild thrombocytopenia/leukopenia**. Alcohol may also cause other hematologic abnormalities such as microcytic anemia due to gastritis or bleeding varices (iron deficiency anemia) or normocytic anemia due to direct toxic effects on the bone marrow.

(Choice A) Vitamin B12 deficiency also causes megaloblastic anemia. Although patients with heavy alcohol use can develop vitamin B12 deficiency, nutritional folate deficiency arises far more quickly (due to smaller total body stores). In addition, vitamin B12 deficiency is rare in patients with alcohol use disorder who do not have chronic pancreatitis; most cases of vitamin B12 deficiency arise in older individuals with disorders of the stomach (eg, pernicious anemia, atrophic gastritis) or small intestine that impair absorption.

(Choice C) Chronic blood loss would cause iron deficiency or microcytic (MCV <80 μm^3) anemia.

(Choice D) Anemia of chronic disease usually causes normochromic, normocytic anemia.

(Choice E) Thiamine deficiency is common in alcoholics, however it is not associated with megaloblastic anemia; rather it is associated with Wernicke encephalopathy.

Educational objective:
Heavy alcohol use is a common cause of nutritional folate deficiency in the United States and would cause megaloblastic anemia.

Time spent:1 Seconds

QID:3930

Subject:
Medicine

System:
Hematology & Oncology (Red blood cell disorders)

A 65-year-old woman comes to the office due to a month of back pain. The pain is primarily in her lumbar and thoracic spine and is partially relieved with acetaminophen. It is worse with activity and has limited her ability to take restorative yoga classes. The patient has a history of hypertension, type 2 diabetes mellitus, and osteopenia. She takes over-the-counter calcium and vitamin D supplements in addition to prescription medications. The patient had her yearly physical examination 4 months ago; physical and laboratory examinations were normal at that time. Temperature is 36.6 C (97.8 F), blood pressure is 148/82 mm Hg, and pulse is 94/min. The patient is thin but appears well. Mucous membranes are moist. There is no lymphadenopathy in the cervical or supraclavicular chains. Cardiopulmonary and abdominal examinations are normal. There is no focal tenderness over the spine. Muscle strength is 5/5 in all 4 extremities. Laboratory results are as follows:

Complete blood count

Hemoglobin	10.2 g/dL
Platelets	220,000/mm^3
Leukocytes	8,800/mm^3

Serum chemistry

Sodium	138 mEq/L
Potassium	4.2 mEq/L
Chloride	102 mEq/L
Bicarbonate	26 mEq/L
Blood urea nitrogen	30 mg/dL
Creatinine	2.5 mg/dL
Calcium	10.9 mg/dL
Glucose	118 mg/dL

Urine dipstick is negative and urine sediment is bland except for a few granular casts. Which of the following is the most likely cause of this patient's current condition?

A. Acetaminophen toxicity
B. Diabetes mellitus
C. Monoclonal protein
D. Primary hyperparathyroidism
E. Systemic lupus erythematosus
F. Vitamin D toxicity

Correct answer is
66% answered correctly

Explanation:

Multiple myeloma (MM) is a plasma cell neoplasm. Patients with MM often present with constitutional symptoms (fatigue, weight loss) or **bone pain** (back, chest). MM is characterized by the proliferation of neoplastic cells in the bone marrow (bone destruction, **hypercalcemia, anemia**) and the excessive production of a single immunoglobulin (**monoclonal protein**). The latter can accumulate at high levels in the serum and deposit in the renal tubules. This can result in **renal insufficiency**, often with a bland urinalysis (urine dipstick protein typically detects albumin, not immunoglobulins) that may show evidence of granular casts. The monoclonal protein can also damage the glomeruli (amyloidosis, monoclonal immunoglobulin deposition disease), leading to nephrotic syndrome.

(Choice A) Acetaminophen toxicity may occur at high doses. However, it typically affects the liver (hepatitis, jaundice) and would not account for this patient's hypercalcemia or anemia.

(Choice B) Diabetic nephropathy usually develops over many years and is associated with albuminuria. With normal laboratory studies 4 months ago and a bland urinalysis, this patient is unlikely to have diabetic nephropathy.

(Choice D) Primary hyperparathyroidism can cause hypercalcemia. However, most patients are asymptomatic or are diagnosed after developing calcium nephrolithiasis. This patient who has hypercalcemia associated with bone pain and anemia is more likely to have multiple myeloma.

(Choice E) Systemic lupus erythematosus typically causes glomerular injury resulting in proteinuria and hematuria, often with an increase in creatinine. This patient has a bland urinalysis, making lupus nephritis unlikely.

(Choice F) Vitamin D toxicity tends to occur only at exceedingly high doses and is associated with vomiting, confusion, polyuria, and polydipsia. Anemia and renal failure would be uncommon.

Educational objective:
Multiple myeloma is a plasma cell neoplasm. It is characterized by the excessive production of monoclonal protein that can accumulate in the kidneys and cause renal insufficiency. Approximately 50% of patients with multiple myeloma have renal insufficiency at diagnosis.

Time spent:1 Seconds
QID:3943
Subject:
Medicine
System:
Hematology & Oncology (Plasma cell disorders)

A 64-year-old woman comes to the emergency department due to headache and nausea over the past 2 days. Medical history is significant for advanced chronic kidney disease due to diabetic nephropathy and hypertension. She started receiving an erythropoiesis-stimulating agent and iron therapy 3 weeks ago for anemia due to chronic kidney disease. Blood pressure is 210/121 mm Hg and pulse is 76/min. Muscle strength, gait, and sensory examinations are unremarkable. There are no heart murmurs. The lungs are clear to auscultation. Trace bilateral edema is present and is unchanged from her previous visit. The skin is normal. Ophthalmoscopic examination shows bilateral retinal hemorrhages. Laboratory results are as follows:

	Today	**3 weeks ago**
Complete blood count		
Hemoglobin	11 g/dL	8.3 g/dL
Platelets	240,000/mm^3	234,000/mm^3
Leukocytes	6,300/mm^3	7,800/mm^3
Serum chemistry		
Potassium	5.0 mEq/L	4.9 mEq/L
Bicarbonate	22 mEq/L	22 mEq/L
Blood urea nitrogen	36 mg/dL	34 mg/dL
Creatinine	4.1 mg/dL	4.0 mg/dL
Calcium	8.0 mg/dL	8.1 mg/dL

Which of the following is the most likely cause of this patient's current condition?

A. Cerebellar stroke
B. Cerebral venous sinus thrombosis
C. Medication adverse effect
D. Pheochromocytoma
E. Tertiary hyperparathyroidism

Correct answer is
68% answered correctly

Explanation:

This patient with advanced **chronic kidney disease** (CKD) and new-onset nausea and headache has retinal hemorrhages and a significantly elevated blood pressure consistent with **hypertensive emergency**. Hypertension is common in CKD patients and can be due to a variety of causes that include medication nonadherence; sodium and water retention; increased activity of the renin-angiotensin and sympathetic nervous systems; and an **adverse effect** of **erythropoiesis-stimulating agents** (ESAs) (eg, epoetin, darbepoetin).

Up to 30% of patients receiving an ESA for CKD-induced anemia develop new or worsening **hypertension**, which typically occurs **2-8 weeks** after treatment

initiation. Hypertension is generally mild but can be severe, as in this patient. The mechanism by which ESAs cause hypertension appears to be independent of increased blood volume and likely involves **systemic vasoconstriction** caused by:

- Activation of erythropoietin receptors on vascular smooth muscle cells
- Heightened sensitivity of alpha receptors
- Depletion of endothelium-derived nitric oxide

The risk of ESA-induced hypertension is increased by large doses and a **rapidly rising hemoglobin** soon after ESA administration, as in this patient whose hemoglobin increased from 8.3 to 11 g/dL in 3 weeks. Following acute treatment of hypertension, subsequent ESA doses should be decreased with a **goal of slowly increasing hemoglobin**.

(Choice A) An acute hypertensive response is common with stroke. Cerebellar stroke can present with headache and nausea and/or vomiting; however, it is unlikely in the presence of a normal neurologic examination (eg, no ataxia or other gait disturbance).

(Choice B) Cerebral venous sinus thrombosis most commonly affects young women with hypercoagulability risk factors (eg, use of oral contraceptives) and typically causes a headache with or without nausea and/or vomiting. Papilledema (not retinal hemorrhages) is common due to increased intracranial hypertension; systemic hypertension is not a typical feature.

(Choice D) Although hypertensive emergency due to a pheochromocytoma may present with headache and retinal hemorrhages, signs and symptoms of a hyperadrenergic state (eg, sinus tachycardia, palpitations, tremor, diaphoresis) are also expected.

(Choice E) Tertiary hyperparathyroidism represents progression of the secondary hyperparathyroidism typically present with CKD such that parathyroid hormone secretion is no longer inhibited by serum calcium level. Hypercalcemia is present and may cause mild hypertension (due to vasoconstriction), but hypertensive emergency would be extraordinarily rare. This patient's serum calcium level is low-normal.

Educational objective:
Hypertension is a common adverse effect of erythropoiesis-stimulating agents. Patients who receive large doses or experience a rapid rise in hemoglobin concentration are at greatest risk.

Time spent:1 Seconds	**QID**:3978
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 66-year-old man comes to the office due to several weeks of severe constipation and increasing back pain. The patient notes that he has always had regular bowel movements; however, for the last 2 months, he has required over-the-counter laxatives to produce any stool. During this period, he has also had increasing pain in his lower back. He has had no trauma to that area. There is no radiation down the legs, bowel incontinence, or lower extremity weakness. The patient takes lisinopril for hypertension and ibuprofen as needed for back pain. He does not use tobacco or alcohol. Temperature is 36.1 C (97 F), blood pressure is 134/80 mm Hg, and pulse is 78/min. Mucosal pallor is present. He is anicteric. Cardiopulmonary and abdominal examinations are normal. Rectal examination reveals a smooth, nonenlarged prostate. The stool is negative for occult blood. Strength and reflexes are intact in his lower extremities. Laboratory results are as follows:

Complete blood count

Hemoglobin	9.6 g/dL
Platelets	260,000/mm^3
Leukocytes	7,500/mm^3

Serum chemistry

Sodium	140 mEq/L
Potassium	4.4 mEq/L
Blood urea nitrogen	28 mg/dL
Creatinine	2.2 mg/dL
Calcium	11.4 mg/dL
Glucose	100 mg/dL

Which of the following is the best explanation for this patient's constipation?

A. Electrolyte disturbance
B. Hormonal disturbances
C. Irritable bowel syndrome
D. Mechanical obstruction
E. Medication side effect
F. Neurologic dysfunction

Correct answer is
68% answered correctly

Explanation:

Multiple myeloma	
Pathophysiology	• Plasma cell neoplasm produces **monoclonal** paraprotein (immunoglobulin)
Manifestations	• Bone pain, fractures • Constitutional symptoms (weight loss, fatigue) • Recurrent infections
Laboratory	• Normocytic anemia • Renal insufficiency • Hypercalcemia (constipation, muscle weakness) • Monoclonal paraproteinemia **(M-spike)**

Radiology	• **Osteolytic lesions**/osteopenia (osteoclast activation)

This patient with constipation, back pain, and laboratory evidence of anemia, renal insufficiency, and hypercalcemia likely has **multiple myeloma** (MM). MM is a plasma cell neoplasm that commonly presents with manifestations related to bone marrow infiltration (bone pain, fractures, hypercalcemia, anemia) or elevations in serum monoclonal protein (**renal insufficiency**). At the time of diagnosis, approximately 25% of patients with MM have **hypercalcemia**. Typically, this is a result of osteolytic bone destruction by the neoplastic plasma cells. Although hypercalcemia may be asymptomatic with a calcium level <12 mg/dL, fatigue, **constipation**, and depression are common. This patient's constipation is likely a result of hypercalcemia.

Patients with suspected MM should have serum/urine protein electrophoresis (M-spike), a peripheral blood smear (rouleaux), and a serum free light chain analysis. If these screening tests suggest MM, diagnosis can be confirmed by bone marrow biopsy.

(Choice B) Hormonal causes of constipation include hypothyroidism and hyperparathyroidism (causing hypercalcemia). However, in an elderly patient, the cluster of renal insufficiency, anemia, and hypercalcemia are far more commonly associated with MM.

(Choice C) Irritable bowel syndrome (IBS) is associated with abdominal pain and altered bowel habits. The laboratory findings in this patient would not be consistent with IBS.

(Choice D) Mechanical causes of constipation are usually associated with pain and bloating. If severe, nausea and vomiting may result. This patient's examination (normal abdominal/prostate/occult blood examination) and laboratory findings make a mechanical cause less likely.

(Choice E) Ibuprofen and lisinopril do not commonly cause constipation.

(Choice F) Many neurologic conditions can affect colonic transit resulting in constipation. However, given the patient's laboratory findings, including hypercalcemia, this would be less likely.

Educational objective:
Hypercalcemia is common in patients with multiple myeloma. It is caused by osteolytic bone destruction. Fatigue, constipation, and depression are common symptoms of mild hypercalcemia.

Time spent:0 Seconds
Subject:
Medicine

QID:4013
System:
Hematology & Oncology (Plasma cell disorders)

A 36-year-old man comes to the office due to progressive fatigability. Medical history is significant for infiltrative pulmonary tuberculosis diagnosed 2 months ago. His current treatment includes isoniazid, rifampin, ethambutol, and pyrazinamide. Laboratory results are as follows:

Hemoglobin	7 g/dL
Mean corpuscular volume	77 μm^3
Mean corpuscular hemoglobin concentration (MCHC)	30 Hb/cell
Erythrocyte sedimentation rate	17 mm/hr
Iron, serum	180 µg/dL
Total iron binding capacity (TIBC)	280 µg/dL (normal: 300-360 µg/dL)

Microscopy reveals 2 populations of red blood cells: hypochromic and normochromic. Which of the following is the next best step in the management of this patient?

A. Bone marrow biopsy
B. Iron preparations
C. Folic acid
D. Folic acid and vitamin B12
E. Pyridoxine

73% answered correctly

Explanation:

The most likely diagnosis in this patient is **acquired sideroblastic anemia**. Sideroblastic anemias consist of different types of anemias characterized by defects in heme synthesis (eg, in mitochondria) and ring sideroblasts (nucleated erythroblasts with mitochondrial iron granules surrounding the nucleus). They can be congenital (presenting in children or adolescents) or acquired (most common). Although acquired sideroblastic anemias may be related to clonal abnormalities (eg,

myelodysplastic syndrome), they are frequently due to reversible etiologies (eg, **alcohol**, malnutrition, medications) that lead to **pyridoxine**-dependent impairment in the early steps of protoporphyrin synthesis within mitochondria.

This patient is on **isoniazid** (INH), a well-known pyridoxine (vitamin B6) antagonist that can cause acquired sideroblastic anemia. It frequently manifests as **microcytic** hypochromic anemia, simulating iron deficiency anemia.

- As can sometimes be seen with iron deficiency anemia, usually 2 groups of red blood cells (RBCs) can be demonstrated on microscopy: hypochromic and normochromic (**"dimorphic" RBC population**), likely reflecting the defective heme synthesis.
- Unlike iron deficiency anemia, iron studies typically reveal **increased serum iron** concentration and normal or decreased total iron binding capacity due to mitochondrial mishandling of iron (explaining the mitochondrial iron granules seen in ring sideroblasts); in contrast, iron deficiency anemia is characterized by decreased serum iron concentration and high total iron binding capacity.

In this patient with an easily identifiable cause of vitamin B6 deficiency (ie, INH), administration of **pyridoxine** is the most reasonable next step. Bone marrow sampling can confirm the diagnosis by demonstrating **ring sideroblasts** (a specific finding in sideroblastic anemia), but it is not necessary in this patient **(Choice A)**.

(Choices C and D) Folic acid or the combination of folic acid with vitamin B12 is employed in patients with macrocytic anemia (which would cause an elevated mean corpuscular volume).

Educational objective:
Sideroblastic anemia usually manifests as microcytic/hypochromic anemia simulating iron-deficiency anemia, but iron studies reveal elevated serum iron level and normal or decreased total iron binding capacity. In patients with an identifiable cause of vitamin B6 deficiency (alcohol, medications), the administration of pyridoxine can easily correct the problem.

Time spent:1 Seconds

QID:4037

Subject:
Medicine

System:
Hematology & Oncology (Red blood cell disorders)

An 18-year-old woman comes to the office to establish medical care. The patient had been seeing her pediatrician for annual evaluations and reports no history of serious medical illnesses. She has no symptoms. The patient does not use tobacco, alcohol, or recreational substances. She consumes a balanced diet and exercises regularly. Menses have been irregular and heavy since menarche at age 12. Family history is insignificant. Vital signs are within normal limits. BMI is 24.5 kg/m^2. Physical examination shows no abnormalities. Laboratory results are as follows:

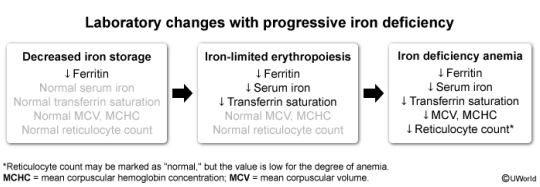
Complete blood count	
Hemoglobin	10.1 g/dL
Mean corpuscular volume	82 µm^3
Mean corpuscular hemoglobin concentration	28%
Reticulocytes	1.5%
Platelets	380,000/mm^3
Leukocytes	7,500/mm^3
Serum chemistry	
Sodium	136 mEq/L
Potassium	4 mEq/L
Creatinine	0.6 mg/dL
Glucose	80 mg/dL

Hemoglobin was 12.2 g/dL a year ago. Which of the following is the best next step in diagnosis of this patient's condition?

A. Antiglobulin testing
B. Bone marrow biopsy
C. Hemoglobin electrophoresis
D. Serum folate level
E. Serum iron studies

Correct answer is
79% answered correctly

Explanation:



This patient has **normocytic anemia** (normal mean corpuscular volume [MCV]), which has a broad differential diagnosis. It is most commonly associated with chronic hematologic or nonhematologic (eg, chronic kidney disease, hypothyroidism, malignancy) disease. However, early blood loss and early stages of nutrient deficiencies (eg, vitamin B_{12}, iron) can also result in normocytic

anemia. **Reticulocyte count** measurement can be helpful in distinguishing between anemia etiologies. A **low** or (as in this case) **inappropriately normal reticulocyte count** suggests disrupted or rate-limited **red blood cell production** (eg, nutrient deficiency, bone marrow disorders).

Given this patient's ongoing blood loss (eg, menometrorrhagia), **iron deficiency** is the most likely cause of her anemia. Although iron deficiency is classically associated with microcytosis (MCV <80 μm^3), low MCV is a late indicator seen in long-standing iron deficiency. In contrast, the **earliest** abnormalities include low indicators of **iron stores** (eg, serum ferritin levels, transferrin/total iron-binding capacity), followed by a decrease in hemoglobin. Therefore, in this patient with probable iron deficiency, measurement of **serum iron markers** is indicated and likely to confirm the diagnosis.

(Choice A) Antiglobulin testing is positive in patients with autoimmune hemolytic anemia, as well as in some patients with hemolytic transfusion reactions and drug-induced hemolytic anemia. These disorders present with normocytic anemia, but the reticulocyte count is usually elevated.

(Choice B) Bone marrow biopsy can be used to assess iron stores, but noninvasive tests (ie, serum iron studies) are typically performed first. Biopsy is also used in the evaluation of intrinsic bone marrow disorders (eg, myelodysplasia), but these disorders are much less common than iron deficiency, especially in young patients.

(Choice C) Hemoglobin electrophoresis can be used to identify sickle cell trait, sickle cell anemia, and thalassemia. These disorders usually present with significant microcytosis. In addition, this patient's prior normal hemoglobin measurement makes hemoglobinopathy less likely.

(Choice D) Serum folate and vitamin B_{12} levels are typically used in the evaluation of macrocytic anemia. Early stages of folate and vitamin B_{12} deficiency can occasionally present with normocytic anemia, but in a young woman with heavy menses, blood loss resulting in iron deficiency is much more likely.

Educational objective:
In early or mild iron deficiency, measures of iron stores (eg, serum ferritin, transferrin/total iron-binding capacity) decrease before measurable changes in red cell indices (eg, mean corpuscular volume [MCV]) are apparent. As iron deficiency progresses, hemoglobin may drop; low MCV is a late indicator seen in long-standing deficiency.

Time spent:1 Seconds
QID:4069
Subject:
Medicine
System:
Hematology & Oncology (Red blood cell disorders)

A 62-year-old man comes to the office due to several months of fatigue. The patient has no chest pain, vomiting, diarrhea, weight loss, or back pain. Review of systems is significant for occasional leg cramps. He takes lisinopril for hypertension and atorvastatin for hyperlipidemia. The patient no longer smokes cigarettes but has a 30-pack-year history. He does not consume alcohol. Blood pressure is 132/80 mm Hg and pulse is 95/min. Conjunctiva are pale. Cardiopulmonary auscultation reveals clear lungs and a soft 2/6 ejection murmur at the right upper sternal border. The abdomen is soft and nontender without palpable masses. There are no skin rashes or peripheral edema. Laboratory results are as follows:

Complete blood count	
Hemoglobin	7.7 g/dL
Mean corpuscular volume	72 fL
Platelets	180,000/mm^3
Leukocytes	8,200/mm^3
Serum chemistry	
Blood urea nitrogen	12 mg/dL
Creatinine	0.8 mg/dL
Blood, plasma, and serum	
Ferritin, serum	7 ng/mL

Which of the following is the most appropriate next step in management of this patient?

A. Bone marrow biopsy
B. Discontinuation of atorvastatin
C. Endoscopic evaluation
D. Serum C-reactive protein
E. Serum erythropoietin level
F. Serum free monoclonal light chains

Correct answer is
73% answered correctly

Explanation:

This patient has clinical findings (fatigue, pallor, ejection murmur) consistent with **anemia** and laboratory evidence (low mean corpuscular volume and ferritin) of **iron deficiency**.

Iron is derived from dietary sources (eg, animal meat) and is mostly absorbed in the duodenum. Body iron is distributed to red blood cells (hemoglobin), other iron-containing proteins (eg, myoglobin), and ferritin/hemosiderin in the reticuloendothelial system. In developed countries, iron deficiency rarely stems

from dietary or absorption inadequacies. Most cases are due to overt or occult **blood loss**.

History and physical examination can often identify an overt source of bleeding (eg, menorrhagia); otherwise, referral to a gastroenterologist for **endoscopic evaluation** (eg, colonoscopy, esophagogastroduodenoscopy) is usually required (particularly in those age >50) as patients may have gastritis, telangiectasia, or **malignancy** (eg, colon cancer).

(Choice A) Although bone marrow biopsy is considered the gold standard for assessing iron stores, less invasive testing (eg, ferritin) has largely supplanted this diagnostic modality. Bone marrow biopsy is used primarily to evaluate for hematologic malignancies (eg, myelodysplastic syndrome) and stem cell abnormalities (eg, aplastic anemia).

(Choice B) Atorvastatin may cause hepatotoxicity and myopathy but is not associated with iron deficiency anemia.

(Choice D) C-reactive protein is usually elevated in infection or inflammatory conditions. Patients with these illnesses often have anemia of chronic disease due to poor iron utilization and impaired erythrocytosis. Anemia of chronic disease is usually associated with normal or high ferritin levels.

(Choice E) Erythropoietin (EPO) stimulates erythrocytosis. Low levels of EPO can be seen in many chronic diseases (eg, renal insufficiency). EPO is not often measured, and conditions that result in low EPO are usually associated with anemia of chronic disease (normal or high ferritin levels).

(Choice F) Monoclonal light chains can be elevated in plasma cell disorders such as multiple myeloma. Although anemia is common, it is usually normocytic and normochromic (not microcytic).

Educational objective:
Gastrointestinal blood loss is the most common occult cause of iron deficiency anemia, especially in patients age >50. Referral to a gastroenterologist for endoscopy is usually required.

Time spent:1 Seconds	**QID**:4081
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 32-year-old woman comes to the office for a regularly scheduled follow-up visit. She has mild fatigue but no other symptoms. Medical history is significant for generalized seizures controlled with chronic phenytoin therapy. Her last seizure was 6 months ago. She does not use tobacco, alcohol, or illicit drugs. She is afebrile and vital signs are within normal limits. Examination shows mild gingival hyperplasia and pallor. There is no jaundice or lymphadenopathy. Cardiopulmonary examination is normal. The abdomen is soft and nontender with no hepatosplenomegaly. Laboratory results are as follows:

Complete blood count	
Hemoglobin	10.8 g/dL
Mean corpuscular volume	105 μm^3
Platelets	180,000/mm^3
Leukocytes	7,800/mm^3
Neutrophils	68%
Bands	1%
Lymphocytes	25%
Monocytes	6%

Supplementation with which of the following could have prevented this patient's condition?

A. Folic acid
B. Iron
C. Vitamin B_1
D. Vitamin B_6
E. Vitamin B_{12}

Correct answer is
76% answered correctly

Explanation:

This patient with a history of seizure disorder is being treated with **phenytoin**, an antiepileptic with several common adverse effects, including:

- **Folic acid deficiency:** Phenytoin impairs folic acid absorption in the jejunum, which often results in folic acid deficiency over weeks or months. Because folate (tetrahydrofolate) is required for purine and thymidine synthesis, deficiency impairs DNA synthesis, particularly in cells that undergo rapid turnover (eg, hematologic cells). This often leads to **megaloblastic anemia** (eg, macrocytosis, hypersegmented neutrophils).
- **Gingival overgrowth/hyperplasia:** Phenytoin has several effects on the gingival mucosa but is thought to reduce folic acid use in the extracellular matrix of the gums, leading to impaired collagenase activity and a subsequent buildup of gingival matrix.

These adverse effects can usually be prevented with oral **folic acid supplementation**. Because phenytoin also disrupts bone and mineral metabolism (leading to reduced bone density), calcium and vitamin D supplementation are also generally administered.

Other medications that commonly cause megaloblastic anemia include methotrexate, trimethoprim, and pyrimethamine due to disruptions in dihydrofolate reductase (the enzyme that mediates tetrahydrofolate production).

(Choice B) Iron deficiency causes microcytic anemia and does not enhance gingival growth.

(Choice C) Vitamin B_1 (thiamine) deficiency can occur in those who use excess alcohol; it causes Wernicke encephalopathy, which is characterized by gait dysfunction, confusion, and oculomotor palsy. Macrocytic anemia is atypical.

(Choice D) Vitamin B_6 (pyridoxine) deficiency is associated with peripheral neuropathy, not macrocytic anemia. Pyridoxine deficiency often occurs as a consequence of isoniazid therapy for tuberculosis; high risk patients are given pyridoxine supplementation to prevent this adverse effect.

(Choice E) Vitamin B_{12} deficiency also causes megaloblastic anemia but is not associated with gingival hyperplasia or phenytoin use.

Educational objective:
Phenytoin commonly causes megaloblastic anemia and gingival hyperplasia due to impaired folic acid absorption in the jejunum. Supplementation with folic acid prevents these adverse effects. Calcium and vitamin D supplementation are also usually given to counter alterations in bone mineral metabolism that impair bone density.

Time spent:0 Seconds	**QID**:4147
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 35-year-old man with aplastic anemia undergoes bone marrow transplantation. The donor is an HLA-matched sibling. Two weeks after the procedure, he develops a maculopapular pruritic rash that is predominantly found on his face, hands, and feet. He also complains of diarrhea. The stool is positive for occult blood. Liver function tests are abnormal. Which of the following is the most likely pathophysiologic mechanism of this patient's condition?

A. Activation of the donor T lymphocytes
B. Activation of the donor B-lymphocytes
C. Activation of the host T lymphocytes
D. Virus-induced lymphocyte proliferation
E. Depression of the donor myelopoiesis

Correct answer is
60% answered correctly

Explanation:

The clinical scenario described is typical for acute graft-versus-host disease (GVHD), which is common after bone marrow transplantation. Up to 50% of patients with bone marrow transplantation from matched siblings develop the disease. The target organs for GVHD are the skin (maculopapular rash involving palms, soles, and face that may generalize is typical), intestine (blood-positive diarrhea), and liver (abnormal liver function tests and jaundice). The basic pathophysiologic mechanism involved is recognition of host major and minor HLA-antigens by donor T-cells and consequent cell-mediated immune response.

(Choice B) The donor B-lymphocytes have less importance in the development of GVHD.

(Choices C and E) Activation of the host T lymphocytes mediates the rejection of the graft, thereby resulting in the depression of myelopoiesis. Failure to generate blood cells manifests as severe neutropenia for several consecutive days and increased risk of infection. Graft rejection may occur in up to 20% of high-risk patients.

(Choice D) Virus-induced lymphocyte proliferation due to Epstein-Barr virus is the mechanism responsible for the development of immunoblastic lymphoma in patients who underwent bone marrow transplantation.

Educational Objective:
GVHD is caused by recognition of host major and minor HLA-antigens by donor T-cells and consequent cell-mediated immune response. The organs that are typically affected include the skin, intestine, and liver.

Time spent:0 Seconds
QID:4151
Subject:
Medicine
System:
Hematology & Oncology (Principles of oncology)

A 43-year-old woman comes to the emergency department with abdominal pain and dark urine. Physical examination shows right upper-quadrant tenderness without guarding or rebound. Laboratory results are as follows:

Hemoglobin	8.9 g/dL
Platelets	134,000/mm^3
Total bilirubin	6.3 mg/dL
Lactate dehydrogenase	740 U/L
Haptoglobin	30 mg/dL (50–150 mg/dL)

Further workup, including MRI of the abdomen, shows hepatic vein thrombosis. Which of the following is the most likely diagnosis?

A. Acute intermittent porphyria
B. Aplastic anemia
C. G6PD deficiency
D. Hereditary spherocytosis
E. Paroxysmal nocturnal hemoglobinuria

Correct answer is
45% answered correctly

Explanation:

Clinical features of paroxysmal nocturnal hemoglobinuria	
Clinical manifestations	• Hemolysis → fatigue • Cytopenias (impaired hematopoiesis) • Venous thrombosis (intraabdominal, cerebral veins)
Work-up	• Complete blood count (hypoplastic/aplastic anemia, thrombocytopenia, leukopenia) • Elevated lactate dehydrogenase and low haptoglobin (hemolysis) • Indirect hyperbilirubinemia • Urinalysis (hemoglobinuria) • Flow cytometry (absence of CD55 & CD59)
Treatment	• Iron & folate supplementation • Eculizumab (monoclonal antibody that inhibits complement activation)

The most likely diagnosis in this case is **paroxysmal nocturnal hemoglobinuria** (PNH). PNH is a clonal stem cell disorder characterized by **intravascular and extravascular hemolysis** and hemoglobinuria. The disease is due to an acquired genetic defect that results in lack of the glycosylphosphatidylinositol anchor, which connects proteins, including CD55 and CD59, to the cell surface. These proteins normally inhibit the activation of complement on red blood cells, but their absence allows the complement **membrane attack complex** to form and results in hemolysis.

On average, patients have manifestations in the third decade of life resulting from one of the following:

- **Hemolysis** leading to hemoglobinuria
- **Cytopenias** - fatigue and dyspnea from anemia
- **Hypercoagulable** state (eg, portal vein thrombosis, hepatic vein thrombosis)

This patient's anemia and low haptoglobin accompanied by elevated bilirubin and lactate dehydrogenase (LDH) are all consistent with intravascular hemolysis. The key to the diagnosis is the patient's hepatic vein thrombosis **in conjunction** with these signs of hemolysis. The pathophysiology of thrombosis is unclear but may be related to release of procoagulant molecules as a result of hemolysis and possibly to changes in complement levels. Unusual sites of thrombosis may be noted, and cerebral and intraabdominal vein involvement is classic. Abdominal pain may be due to severe hemolysis, thrombosis, or effects on smooth muscle.

Flow cytometry tests are used to confirm the diagnosis by assessing for the absence of the CD55 and CD59 proteins on the surface of the red blood cells.

(Choice A) Acute intermittent porphyria may also present with abdominal pain and dark red/brown urine. However, the pigmented urine is due to porphyrins and/or porphyrin precursors (not hemoglobinuria), and hematologic abnormalities and thromboembolism are rare.

(Choice B) The elevated LDH and bilirubin accompanied by the low haptoglobin make a hemolytic anemia much more likely than an aplastic anemia.

(Choice C) G6PD deficiency can cause hemolytic anemia but is more common in male patients, particularly those of African descent. Patients are generally asymptomatic when there is no anemia, but disease can be triggered by medications or infections. Venous thrombosis is unlikely.

(Choice D) Symptomatic hereditary spherocytosis would likely have led to some symptoms in this patient before age 43, and it is not usually associated with venous thromboses.

Educational objective:
Paroxysmal nocturnal hemoglobinuria should be suspected in patients who have a combination of hemolytic anemia, cytopenias, and hypercoagulable state (intraabdominal or cerebral venous thrombosis). Flow cytometry tests are used to confirm the diagnosis by assessing for absence of the CD55 and CD59 proteins on the surface of red blood cells.

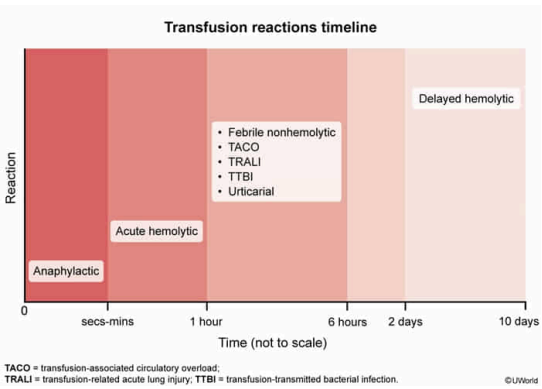
Time spent:1 Seconds	**QID**:2258
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 55-year-old man is hospitalized after a massive hemorrhage from a duodenal ulcer. The bleeding is stopped with endoscopic manipulation. The patient receives 2 L of intravenous fluids, followed by 2 units of packed red blood cells. Two hours after the transfusion is started, he develops chills and malaise. Temperature is 38.7 C (101.7 F), blood pressure is 120/76 mm Hg, pulse is 100/min, and respirations are 20/min. The transfusion is stopped, and the patient is given acetaminophen. Direct antiglobulin and plasma-free hemoglobin level tests are negative. Urinalysis is within normal limits. The symptoms resolve within 6 hours of transfusion discontinuation. Which of the following is the best procedure for preventing this type of transfusion reaction?

A. Careful cross-matching of blood
B. Infusing calcium gluconate
C. Premedicating with diphenhydramine
D. Using a leukoreduced blood product
E. Warming the blood product

58% answered correctly

Explanation:



Febrile nonhemolytic transfusion reaction (FNHTR), the **most common** adverse transfusion reaction, is a **benign** occurrence caused by cytokine release from leukocytes within the donor blood product.

During preparation of blood products, whole blood is separated into red blood cells and plasma. However, small amounts of **leukocyte** debris remain in the red cell concentrate. During blood storage, these leukocytes can **release cytokines**, which when transfused can cause

transient fever, **chills**, and **malaise** within **1-6 hours** of transfusion initiation. Management includes transfusion cessation (to exclude other serious reactions) and antipyretic administration.

Risk of recurrent FNHTR is high after a first episode, and **prevention** is best achieved by using leukoreduced blood products for future transfusions. **Leukoreduction** involves filtering out most of the leukocytes after blood collection but before blood storage, thereby minimizing cytokine production within the packed red blood cell product. Leukoreduction also reduces the risk of human leukocyte antigen alloimmunization and transmission of cytomegalovirus (which typically resides in leukocytes). Many facilities empirically leukoreduce all blood products, but this process is not universal.

(Choice A) Careful cross-matching of blood prevents acute hemolytic transfusion reaction (AHTR), which is caused by mismatched donor and recipient blood. Symptoms include chills, flank pain, and gross hematuria within an hour of transfusion. Unlike this patient, those with AHTR have a positive direct antiglobulin (Coombs) test, increased plasma-free hemoglobin, and hemoglobinuria.

(Choices B and E) Citrate, which binds ionized calcium, is the main anticoagulant used for blood product storage and can cause hypocalcemia if a massive transfusion is required (eg, cardiac surgery). Calcium gluconate infusion is used to prevent or treat severe hypocalcemia. Similarly, warming the blood product is recommended during rapid, massive transfusion to prevent hypothermia and arrhythmia.

(Choice C) Premedication with antipyretics or antihistamines (eg, diphenhydramine), which was previously used in some centers, has been found not to reduce the incidence of FNHTR in several studies.

Educational objective:
Febrile nonhemolytic transfusion reaction (FNHTR) is the most common adverse reaction and is caused by release of cytokines from leukocytes in the stored blood product. Symptoms develop within 1-6 hours and include transient fever, chills, and malaise. Leukoreduction of donor blood helps prevent FNHTR.

Time spent:0 Seconds
QID:4160
Subject:
Medicine
System:
Hematology & Oncology (Transfusion medicine)

A 59-year-old woman comes to the emergency department due to right leg swelling and pain for 3 days. The patient was started on hemodialysis 2 months ago for end-stage renal disease from poorly controlled hypertension and type 2 diabetes mellitus. Duplex ultrasound shows a right popliteal vein thrombosis. The patient is started on intravenous heparin infusion and admitted to the medical floor. On the third day of hospitalization, the right leg is more swollen and painful. Repeat ultrasound shows an extension of thrombus to the right femoral vein. Laboratory results are as follows:

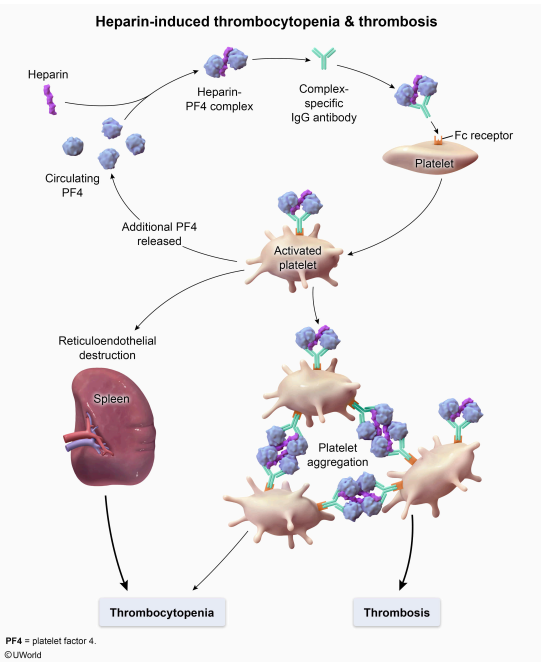
Hemoglobin	14.0 g/dL
Platelets	50,000/mm^3
Leukocytes	7,500/mm^3
Activated partial thromboplastin time	70 seconds

Which of the following is the most likely cause of this patient's worsening condition?

A. Antibody-mediated platelet activation
B. Decreased bone marrow platelet production
C. Disseminated intravascular coagulation
D. Nonimmune platelet aggregation
E. Platelet sequestration and redistribution

Correct answer is
64% answered correctly

Explanation:



This patient with thrombocytopenia and thrombus progression 3 days into heparin therapy likely has **type 2 heparin-induced thrombocytopenia** (HIT). Heparin induces a conformational change to a platelet surface protein (platelet factor 4 [PF4]), which exposes a neoantigen. In patients with type 2 HIT, the immune system responds by forming an IgG autoantibody (**HIT antibody**) that then coats the surface of platelets and forms complexes (heparin-PF4-HIT antibody), resulting in:

- **Thrombocytopenia** - the reticuloendothelial system (largely the spleen) removes antibody-coated platelets, causing a mild to moderate thrombocytopenia (rarely

<20,000/mm^3).
- **Arterial and venous thrombus** - HIT antibodies **activate platelets**, resulting in platelet aggregation and the release of procoagulant factors. The risk of thrombus is as high as 50% in untreated HIT.

Although type 2 HIT usually manifests with a >50% drop in platelets **5-10 days** after the initiation of heparin, it can occur **earlier** (sometimes <1 day) in patients **previously exposed**. Patients with end-stage renal disease typically receive unfractionated heparin with hemodialysis to prevent blood clots in the dialysis tubing and dialyzer; therefore, this patient who recently started hemodialysis has likely had heparin exposure. If HIT is suspected, all heparin products should be discontinued immediately, and an alternate anticoagulant (eg, argatroban, fondaparinux) should be initiated.

Heparin works by binding antithrombin, which inactivates factor Xa; this **prolongs activated partial thromboplastin time**.

(Choice B) Impaired bone marrow platelet production is seen with malignant infiltration or myelodysplastic syndrome. Typically, the other cell lines are also affected (eg, leukocytosis, pancytopenia).

(Choice C) Acute disseminated intravascular coagulation is usually characterized by bleeding, end-organ dysfunction (renal, pulmonary, liver), and shock. Trauma, infection, and malignancy are the most common causes, and patients tend to be acutely ill. In this patient on heparin with thrombocytopenia and thrombus progression alone, HIT is far more likely.

(Choice D) Type 1 HIT is marked by nonimmune-mediated platelet aggregation. It results in mild thrombocytopenia (platelets rarely <100,000/mm^3), usually within 2 days of heparin initiation. Type 1 HIT does not cause thrombosis or ill effects. Therefore, no intervention is required for type 1 HIT; the thrombocytopenia resolves without cessation of heparin.

(Choice E) Splenomegaly may cause platelet sequestration and redistribution. It is associated with thrombocytopenia but does not increase thrombus risk.

Educational objective:
In type 2 heparin-induced thrombocytopenia (HIT), heparin induces a conformational change in a platelet surface protein which exposes a neoantigen. Antibodies are formed and bind to the surface of platelets, resulting in platelet activation, thrombocytopenia, and a prothrombotic state. Type 2 HIT typically occurs 5-10 days after heparin initiation but may occur sooner in patients previously exposed to heparin.

Time spent:1 Seconds	**QID**:4316
Subject:	**System:**
Medicine	Hematology & Oncology (Hemostasis and thrombosis)

A 72-year-old man comes to the office due to severe fatigue. He says that 5 months ago he was able to climb 4 flights of stairs without shortness of breath, but now he has to rest after 2 flights. His appetite has decreased, but he has not had any abdominal discomfort or black stool. Physical examination reveals firm, enlarged cervical, inguinal and supraclavicular lymph nodes. A soft II/VI grade systolic murmur is heard along the left sternal border. Abdomen is soft and nontender. His liver span is 10 cm and the spleen is palpated 4 cm below the left costal margin. His blood hemoglobin level is 7.1 mg/dL. Which of the following is the most likely cause of this patient's anemia?

A. Iron deficiency
B. Folate deficiency
C. Cobalamin deficiency
D. Glucose-6-phosphate dehydrogenase deficiency
E. Red blood cell membrane defect
F. Hemoglobinopathy
G. Bone marrow infiltration
H. Intravascular hemolysis
I. Erythropoietin deficiency
J. Bone marrow aplasia

Correct answer is
64% answered correctly

Explanation:

The numerous causes of **anemia** may be divided into 3 categories:

- Decreased red blood cell (RBC) production (eg, bone marrow infiltration)
- Increased RBC destruction (eg, hemolysis)
- Blood loss

The patient in this vignette has several signs and symptoms suggestive of a lymphoproliferative disorder, most likely lymphoma, including generalized lymphadenopathy, splenomegaly, and constitutional symptoms (eg, fatigue). The anemia of lymphoproliferative disorders, such as leukemia and lymphoma, is due to the replacement of RBC

progenitor cells with cancer cells in the **bone marrow**. Treatment of the malignancy may improve the patient's anemia, though many chemotherapeutic agents are myelosuppressive.

(Choices A, B, and C) Iron deficiency, folate deficiency, and cobalamin deficiency are not associated with lymphadenopathy or splenomegaly.

(Choices D, E, and F) Glucose-6-phosphate dehydrogenase (G6PD) deficiency, hereditary spherocytosis, and hemoglobinopathies (sickle cell disease and thalassemias) are not associated with lymphadenopathy.

(Choice H) Intravascular hemolysis refers to the breaking down of RBCs in the blood vessels. Schistocytes are seen on the peripheral blood smear. Common causes include shearing secondary to prosthetic valves, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and paroxysmal nocturnal hemoglobinuria (PNH). Of note, the spleen and reticuloendothelial system are considered extravascular. Therefore, autoimmune hemolytic anemia in patients with chronic lymphocytic leukemia (CLL) is extravascular!

(Choice I) Erythropoietin deficiency is due to decreased erythropoietin production, most often in patients with renal failure.

(Choice J) Bone marrow aplasia is seen in aplastic anemia. Splenomegaly is very unlikely to occur with aplastic anemia; its presence suggests an alternate diagnosis.

Educational objective:
Anemia can be due to decreased red blood cell (RBC) production, increased RBC destruction, and frank blood loss. The anemia of lymphoproliferative disorders is due to bone marrow infiltration with cancerous cells.

Time spent:0 Seconds

Subject:
Medicine

QID:4329
System:
Hematology & Oncology (White blood cell disorders)

A 54-year-old man comes to the office due to several months of increased fatigability. He drinks 2-3 cans of beer on the weekends and rarely eats meat. Physical examination reveals pale conjunctivae and hyperdynamic carotid pulses. Hemoglobin level is 7.7 g/dL, leukocytes are 4,500/mm^3, and platelets are 170,000/mm^3. Folic acid therapy is initiated. Four weeks later the patient's hemoglobin level is 9.1 mg/dL, but he has new tingling in his toes. Which of the following is a likely cause of this patient's current symptoms?

A. Drug toxicity
B. Iron deficiency
C. Vitamin deficiency
D. Glucose intolerance
E. Extramedullary hematopoiesis
F. Autoimmune hemolysis
G. Factitious disorder

Correct answer is
93% answered correctly

Explanation:

This patient with anemia was treated empirically for folate deficiency in the setting of heavy alcohol use. He now has worsening neurologic symptoms, consistent with untreated, coexisting **cobalamin (vitamin B12) deficiency**, possibly due to limited meat intake or to pernicious anemia.

Both folate and cobalamin (vitamin B12) deficiency can result in a macrocytic, megaloblastic anemia. Folate supplementation is often given to patients with heavy alcohol use; cobalamin supplementation is not routinely administered because, in these patients, cobalamin deficiency is rare in the absence of chronic pancreatitis. However, cobalamin deficiency can develop with limited animal protein (eg, meat) intake or with advanced age due to decreased intrinsic factor (eg, pernicious anemia) and subsequent malabsorption of vitamin B12. In advanced stages, cobalamin deficiency can result in **peripheral neuropathy** (eg, tingling) or posterior column defects due to defective myelin synthesis.

Because both folate and cobalamin are cofactors in the conversion of homocysteine to methionine, **folate supplementation** can improve the anemia of cobalamin deficiency. However, because cobalamin is used in other processes as well, **neurologic deficits can be precipitated** or worsened when folic acid is given without cobalamin supplementation. Therefore, it is important to consider cobalamin deficiency prior to starting folic acid replacement.

(Choice A) Several drugs, including many cancer chemotherapy agents, cause peripheral neuropathy. The most commonly implicated agents are vincristine, cisplatin, and the taxanes (docetaxel and paclitaxel). Other drugs that cause

peripheral neuropathy include phenytoin, isoniazid, amiodarone, and hydralazine. There is no evidence that this patient is taking any of these drugs.

(Choice B) Iron deficiency is not associated with peripheral neuropathy, nor does the associated anemia improve with folate supplementation.

(Choice D) Peripheral neuropathy is a common complication of diabetes due to small vessel changes from hyperglycemia. There is nothing in this vignette to suggest that this patient has diabetes mellitus.

(Choice E) Extramedullary hematopoiesis refers to red blood cell (RBC) production outside of the bone marrow. It can occur in hematologic malignancies, chronic anemias (eg, thalassemias and sickle cell anemia), or myelofibrosis, or it may be idiopathic. Extramedullary hematopoiesis is not associated with peripheral neuropathy.

(Choice F) Autoimmune hemolysis occurs when an IgG autoantibody binds to the RBC membrane and promotes removal of the RBC from circulation in the spleen's reticuloendothelial system. The direct Coombs test will be positive. Autoimmune hemolysis is not associated with peripheral neuropathy nor does it improve with folate supplementation.

(Choice G) Factitious disorder is the deliberate production or feigning of symptoms in order to assume a sick role. This vignette does not describe any factors that would raise suspicion for factitious disorder (eg, atypical or dramatic presentation, long medical record, vague historical details, or complex knowledge of medicine).

Educational objective:
Folate and cobalamin deficiency both result in megaloblastic, macrocytic anemia. Folate supplementation can improve the anemia of either disorder but will not improve the neurologic changes of cobalamin deficiency. It is important to distinguish between the two prior to initiating therapy.

Time spent:46 Seconds	**QID**:4330
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 12-year-old African American boy is brought to the emergency department with back pain, abdominal pain, and dark urine that began earlier this morning. The patient has never had symptoms like these before. Two days ago, he developed fever, runny nose, and cough, for which he took ibuprofen. Temperature is 37 C (98.6 F), blood pressure is 110/60 mm Hg, and pulse is 100/min. The patient appears tired and has scleral icterus. There is clear rhinorrhea. Lung examination is unremarkable. Heart sounds are normal. Abdominal examination reveals mild, diffuse tenderness with palpation, but no rebound tenderness or rigidity. There is no rash. Hemoglobin is 8.2 g/dL. Peripheral blood smear reveals bite cells and red blood cell inclusions on crystal violet staining. Which of the following is the most likely cause of this patient's condition?

A. Acute intermittent porphyria
B. Glucose-6-phosphate dehydrogenase deficiency
C. Hereditary spherocytosis
D. Paroxysmal nocturnal hemoglobinuria
E. Sickle cell disease
F. Thalassemia minor

Correct answer is
81% answered correctly

Explanation:

This patient's upper respiratory infection (eg, fever, rhinorrhea, cough) followed a few days later by hemolytic anemia (eg, dark urine, scleral icterus, back/abdominal pain), raises strong suspicion for **glucose-6-phosphate dehydrogenase (G6PD) deficiency**. G6PD is an enzyme that generates NADPH, a cofactor required to make glutathione. Without glutathione, oxidative metabolites (eg, superoxide anion, hydrogen peroxide) accumulate in erythrocytes and denature/precipitate hemoglobin into **Heinz bodies** (dark red erythrocyte inclusions), which reduce erythrocyte flexibility and lead to red cell damage (bite cells) and lysis in the reticuloendothelial system.

Although G6PD deficiency is often clinically silent at baseline, patients can develop **episodes of hemolytic anemia** following exposure to **oxidative triggers** such as **infection** (activated leukocytes release

reactive oxygen species), medications (eg, trimethoprim-sulfamethoxazole, nitrofurantoin), or certain foods (eg, fava beans). G6PD deficiency is X-linked and affects approximately 10% of **black men** in the United States; it is also commonly seen in those of Mediterranean, Middle Eastern, and Asian descent.

(Choice A) Acute intermittent porphyria is an autosomal dominant disorder due to a partial deficiency of a heme biosynthetic enzyme. Patients are largely asymptomatic but may develop episodes of abdominal pain, peripheral neuropathy, and dark red urine. Anemia and bite cells are not typically seen.

(Choice C) Hereditary spherocytosis is an autosomal dominant disorder of proteins (eg, spectrin) that provide scaffolding for red blood cells. In this disease, erythrocytes are rigid and get trapped in the fenestrations of the spleen's red pulp, leading to chronic hemolysis and splenomegaly. Peripheral blood smear shows spherocytes and increased reticulocytes.

(Choice D) Paroxysmal nocturnal hemoglobinuria is a hematopoietic stem cell disease characterized by episodes of complement-mediated hemolysis, which may be triggered by stress or infection. Most patients have fatigue, dark urine, and dyspnea; blood smear shows reticulocytosis; bite cells and Heinz bodies would not be present.

(Choice E) Sickle cell crises can be triggered by infection but are usually associated with significant pain. Furthermore, peripheral blood smear would show sickle cells.

(Choice F) Thalassemia minor is caused by mutations to 1 beta or 2 alpha globin chains. Patients are generally asymptomatic, but peripheral blood smear shows microcytic target cells. It is not associated with acute hemolytic anemia.

Educational objective:
Glucose-6-phosphate dehydrogenase deficiency is an X-linked disorder commonly seen in African American men. It is characterized by episodic hemolysis in response to oxidants, drugs, infections, or certain foods (eg, fava beans). Heinz bodies and bite cells are characteristically seen on peripheral blood smear.

Time spent:1 Seconds

QID:4331

Subject:
Medicine

System:
Hematology & Oncology (Red blood cell disorders)

A 23-year-old man comes to the emergency department due to severe abdominal pain and fatigue. He has had nausea and vomiting for several hours and is unable to eat. He took ibuprofen but has had no pain relief. The patient has a history of anemia and dark brown urine that has not been evaluated because he tries "to avoid going to the doctor." Review of systems is otherwise negative, and he has no known medical conditions. He emigrated from Scotland during childhood but has not traveled outside the United States since. Temperature is 38.8 C (101.8 F), blood pressure is 120/80 mm Hg, pulse is 102/min, and respirations are 16/min. There is tenderness in the right upper quadrant of the abdomen that is exacerbated by deep inspiration. Splenomegaly and jaundice are present. There are no peritoneal signs. The remainder of the examination is normal. Laboratory results are as follows:

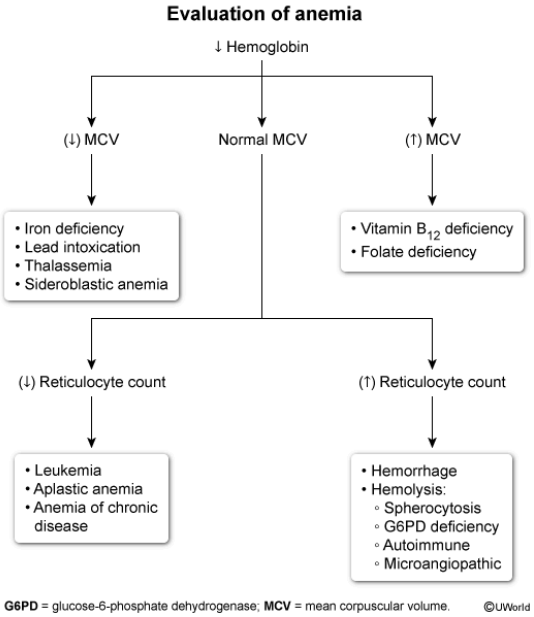
Complete blood count	
Leukocytes	13,800/mm^3
Hemoglobin	10 g/dL
Mean corpuscular volume	88 μm^3
Mean corpuscular hemoglobin concentration	46% Hb/cell
Reticulocytes	12%
Platelets	350,000/mm^3
Liver function studies	
Total bilirubin	2.3 mg/dL
Direct bilirubin	0.5 mg/dL
Aspartate aminotransferase (SGOT)	32 U/L
Alanine aminotransferase (SGPT)	34 U/L
Lipase	12 U/L (normal: 10-140)
Hematology	
Blood type	A positive
Serum lactate dehydrogenase	1,000 U/L
Coombs test	negative

Which of the following is the most likely primary cause of this patient's anemia?

A. Acute hemorrhage
B. Autoimmune hemolysis
C. Genetic red blood cell defect
D. Malignant bone marrow infiltration
E. Medication side effect
F. Viral suppression
G. Vitamin deficiency

Correct answer is
75% answered correctly

Explanation:



This patient has **hemolytic anemia**, jaundice, and **splenomegaly**, the classic triad of **hereditary spherocytosis** (HS). HS is an inherited deficiency of red blood cell (RBC) scaffolding proteins (eg, spectrin, ankyrin). Sphere-shaped RBCs are more fragile and get trapped in splenic fenestrations. The anemia is generally normocytic with associated reticulocytosis in response to hemolysis. **Increased mean corpuscular hemoglobin concentration** occurs due to membrane loss and RBC dehydration.

Chronic hemolysis causes high hemoglobin turnover and excess bilirubin that overwhelms conjugation and elimination from the body. The resulting hyperbilirubinemia manifests as **jaundice**, dark urine, and pigment (calcium bilirubinate) gallstones. This patient has classic symptoms of **acute cholecystitis** (fever, right upper quadrant pain, positive Murphy sign, leukocytosis) due to **pigment gallstones**.

In addition to a cholecystectomy for acute gallbladder inflammation, patients need folate supplementation because chronic hemolysis consumes folate. Many patients also require a splenectomy to minimize hemolysis and reduce gallstone risk.

(Choice A) Acute gastrointestinal hemorrhage is a rare complication of cholecystitis. This patient's normal blood pressure and prolonged history of dark urine make acute blood loss unlikely.

(Choice B) Autoimmune hemolytic anemia can present with normocytic anemia, reticulocytosis, jaundice, and splenomegaly. However, the negative Coombs test in this patient makes an autoimmune process unlikely.

(Choices D and F) Leukemia and viral infections can cause anemia by suppressing erythropoiesis. These etiologies are unlikely because this patient's reticulocytosis reflects a robust bone marrow response to anemia.

(Choice E) Drug-induced immune hemolytic anemia is a rare complication of ibuprofen and would cause a positive Coombs test. Frequent ibuprofen use can cause gastric ulcers and epigastric pain, but this patient's right upper quadrant abdominal pain and laboratory results suggest acute cholecystitis from HS.

(Choice G) Folate deficiency is a complication of chronic hemolytic anemia and can cause a secondary megaloblastic anemia. This patient's mean corpuscular volume is normal.

Educational objective:
Hereditary spherocytosis is an inherited defect in the red blood cell membrane that presents with hemolytic anemia, jaundice, and splenomegaly. Acute cholecystitis from pigmented gallstones is a common complication.

Time spent:1 Seconds
Subject:
Medicine

QID:4333
System:
Hematology & Oncology (Red blood cell disorders)

A 35-year-old man is brought to the emergency department by his roommate, who says that the patient has been acting strangely for 2 days. The patient has spent most of the time in his room and has not eaten much. He has not noted headaches, focal weakness, or sensory symptoms. Medical history is significant for untreated HIV and hepatitis C infections. Temperature is 37.9 C (100.2 F), blood pressure is 140/86 mm Hg, pulse is 96/min, and respirations are 16/min. Mild scleral icterus is present. The oropharynx is normal and there is no nuchal rigidity. Examination of the chest and abdomen is unremarkable. Neurologic examination shows no focal deficits. Laboratory results are as follows:

Complete blood count	
Hemoglobin	7.6 g/dL
Mean corpuscular volume	85 μm^3
Reticulocytes	8.1%
Platelets	26,000/mm^3
Leukocytes	4,500/mm^3
Serum chemistry	
Blood urea nitrogen	30 mg/dL
Creatinine	2.2 mg/dL
Calcium	9.4 mg/dL
Glucose	98 mg/dL
Total bilirubin	3.2 mg/dL
Indirect bilirubin	2.2 mg/dL
Alkaline phosphatase	108 U/L
Aspartate aminotransferase (SGOT)	62 U/L
Alanine aminotransferase (SGPT)	64 U/L

CT scan of the head with and without contrast reveals no abnormalities. Which of the following is the best next step in evaluation of this patient?

A. Bone marrow biopsy
B. Flow cytometry of peripheral blood
C. Liver biopsy
D. Peripheral blood smear
E. Right upper quadrant ultrasonography

Correct answer is
54% answered correctly

Explanation:

Thrombotic thrombocytopenic purpura	
Pathophysiology	• ↓ ADAMTS13 level → uncleaved vWF multimers → platelet trapping & activation • Acquired (autoantibody) or hereditary
Clinical features	• Hemolytic anemia (↑ LDH, ↓ haptoglobin) with schistocytes • Thrombocytopenia (↑ bleeding time, normal PT/PTT) Sometimes with: • Renal failure • Neurologic manifestations • Fever
Management	• Plasma exchange • Glucocorticoids • Rituximab

	• Caplacizumab
LDH = lactate dehydrogenase; **vWF** = von Willebrand factor.	

Thrombotic thrombocytopenic purpura (TTP) is marked by **small vessel thrombi** that consume platelets, shear red blood cells, and cause end organ damage (primarily renal and CNS). This patient has several manifestations of the classic TTP **pentad**, which includes:

- Thrombocytopenia.
- **Microangiopathic hemolytic anemia** (MAHA).
- Renal insufficiency.
- Neurologic changes (eg, acting "strangely").
- Fever (not always present).

TTP is usually due to an acquired **autoantibody** to ADAMTS13, a protease that cleaves von Willebrand factor (vWF) off the endothelial surface. As ADAMTS13 levels fall (due to the antibody), vWF multimer accumulation on the endothelial wall traps platelets at areas of high shearing force (eg, small arterioles, capillaries), leading to thrombus formation.

Most cases arise in middle age and are idiopathic; however, chronic infections (eg, **HIV**), malignancy, or certain medications can increase the risk for TTP. Diagnosis is based on clinical and laboratory data. Thrombocytopenia (platelet count <30,000/mm^3) and MAHA (eg, increased levels of indirect bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase, and reticulocytes) should always raise suspicion. A peripheral blood smear showing intravascular hemolysis (eg, **schistocytes**, helmet cells, triangle cells) supports the diagnosis

TTP must be **treated urgently** with **plasma exchange**. Patients should also receive high-dose **glucocorticoids** and **rituximab** to suppress autoantibody production by B cells. Caplacizumab (monoclonal antibody that blocks the vWF binding site for the ADAMTS13-autoantibody) is frequently added for severe disease.

(Choice A) Bone marrow biopsy is useful in unknown causes of anemia and thrombocytopenia. This patient has evidence of intravascular hemolysis and end organ damage, making TTP most likely.

(Choice B) Flow cytometry can evaluate for paroxysmal nocturnal hemoglobinuria, which can cause hemolysis but not neurologic changes; hemoglobinuria and dyspnea are common, and thrombocytopenia and renal failure are also less likely. Flow cytometry can assess CD4 cell count, which would be useful in this patient with HIV; however, urgent TTP management takes precedence.

(Choices C and E) Cirrhosis (eg, from hepatitis C) may cause acute confusion (eg, encephalopathy). However, this patient's mild AST and ALT elevations, indirect hyperbilirubinemia, and significant anemia likely reflect intravascular hemolysis due to TTP, not intrinsic liver pathology requiring ultrasonography or liver biopsy. Indirect (vs direct) hyperbilirubinemia also makes gallbladder disease (evaluated by right upper quadrant ultrasonography) less likely.

Educational objective:
Thrombotic thrombocytopenic purpura should be suspected in patients with thrombocytopenia and intravascular hemolytic anemia. Neurologic changes and renal failure may be present at diagnosis. Peripheral blood smear will show intravascular hemolysis (eg, schistocytes).

Time spent:2 Seconds
Subject:
Medicine

QID:4338
System:
Hematology & Oncology (Platelet disorders)

A 45-year-old, previously healthy man is brought to the emergency department due to headache and confusion for 2 days. He has no focal weakness or sensory symptoms. The patient has no significant medical history and takes no medications. He does not use tobacco, alcohol, or recreational drugs. Temperature is 37.9 C (100.2 F), blood pressure is 140/86 mm Hg, pulse is 96/min, and respirations are 16/min. Mild icterus is present. The neck is supple and with no rigidity. Cardiopulmonary and abdominal examinations are normal. Neurologic examination shows no focal deficits. Laboratory results are as follows:

Complete blood count	
Hemoglobin	8.4 g/dL
Platelets	44,000/mm^3
Leukocytes	5,500/mm^3
Serum chemistry	
Blood urea nitrogen	30 mg/dL
Creatinine	2.2 mg/dL
Calcium	10 mg/dL
Glucose	98 mg/dL

Peripheral blood smear shows many fragmented red blood cells. PT is normal. Which of the following is the most appropriate next step in management of this patient?

A. Cryoprecipitate infusion
B. Hemodialysis
C. MRI of the brain
D. Packed red blood cell transfusion
E. Plasma exchange
F. Platelet transfusion
G. Urine drug screen
H. Whole blood transfusion

47% answered correctly

Explanation:

Thrombotic thrombocytopenic purpura	
Pathophysiology	• ↓ ADAMTS13 level → uncleaved vWF multimers → platelet trapping & activation • Acquired (autoantibody) or hereditary
Clinical features	• Hemolytic anemia (↑ LDH, ↓ haptoglobin) with schistocytes • Thrombocytopenia (↑ bleeding time, normal PT/PTT) Sometimes with: • Renal failure • Neurologic manifestations • Fever
Management	• Plasma exchange • Glucocorticoids • Rituximab • Caplacizumab
LDH = lactate dehydrogenase; **vWF** = von Willebrand factor.	

This patient likely has **thrombotic thrombocytopenic purpura** (TTP), a life-threatening thrombotic microangiopathy that classically causes a **pentad** of manifestations:

- Thrombocytopenia
- Microangiopathic hemolytic anemia (MAHA)
- Renal insufficiency
- Neurologic changes (eg, headache, confusion, coma, stroke)
- Fever

However, most patients **do not have all 5** manifestations at the time of diagnosis. Cases are most common in previously healthy individuals in middle age who are female, black, pregnant, or obese.

Immune TTP is caused by **autoantibodies** against the plasma protease **ADAMTS13**. Low levels of ADAMTS13 lead to the accumulation of long chains of von Willebrand factor on the endothelial wall, which traps platelets and generates thrombi in areas of high shearing force (eg, arterioles, capillaries). Patients with TTP will have MAHA (eg, **schistocytes**) on peripheral blood smear; **coagulation studies** are generally **normal** (in contrast to those with disseminated intravascular coagulation). Although purpura often occurs in the setting of severe thrombocytopenia, it is not always present in patients with TTP and is not required for the diagnosis.

TTP is life threatening and must be treated with emergency **plasma exchange** (PEX), which removes the patient's plasma and replaces it with donor plasma. This replenishes ADAMTS13 and removes the autoantibodies. Without emergency PEX, mortality is approximately 90%.

TTP is closely related to hemolytic uremic syndrome (HUS). Both cause MAHA and thrombocytopenia. Unlike TTP, HUS is typically associated with *Escherichia coli* O157:H7 infection and is primarily a disorder of the renal system; neurologic findings and fever are uncommon.

(Choice A) Cryoprecipitate contains clotting factors, fibrinogen, and von Willebrand factor. It is often used in patients with DIC. This patient's PT is normal, making DIC unlikely.

(Choice B) This patient's renal insufficiency is mild. Hemodialysis would not be required. In contrast to PEX, hemodialysis does not eliminate the autoantibodies against ADAMTS13 or replenish ADAMTS13.

(Choice C) This patient has headache and confusion but no focal neurologic deficits. If there were concern for intracranial bleeding (given thrombocytopenia), a noncontrast CT scan of the head could be ordered. MRI of the brain is expensive and time consuming and would not be a useful next step.

(Choices D and H) Red blood cell transfusions are considered for life-threatening bleeding or a hemoglobin level <7 g/dL (and possibly higher in patients with coronary artery disease).

(Choice F) Nothing in this patient's clinical and laboratory findings suggests he has severe bleeding. Platelets should not be transfused in TTP unless an invasive procedure or significant bleeding occurs.

(Choice G) Urine drug screens are often useful in patients with confusion. However, given this patient's anemia, thrombocytopenia, and evidence of intravascular hemolysis, TTP is likely. Emergency PEX is necessary.

Educational objective:
Thrombotic thrombocytopenic purpura (TTP) is caused by autoantibodies to the plasma protease ADAMTS13 and is marked by microangiopathic hemolytic anemia and thrombocytopenia. TTP is life threatening and requires emergency treatment with plasma exchange.

Time spent:1 Seconds
Subject:
Medicine

QID:4339
System:
Hematology & Oncology (Platelet disorders)

A 26-year-old woman comes to the office due to progressive tiredness. The patient has no known chronic medical conditions and takes no medications. Her menstrual periods are regular, and bleeding lasts 3 days. The patient does not use tobacco, alcohol, or illicit drugs. Examination shows no abnormalities. Complete blood count is as follows:

Hemoglobin	10.1 g/dL
Mean corpuscular hemoglobin concentration	32% Hb/cell
Mean corpuscular volume	70 μm^3
Platelets	200,000/mm^3
Leukocytes	7,500/mm^3
Neutrophils	58%
Eosinophils	2%
Lymphocytes	35%
Monocytes	5%

Fecal occult blood test is negative. Iron therapy is initiated. When the patient returns 6 weeks later, her laboratory findings are unchanged. Which of the following is the most likely cause of this patient's condition?

- A. Bone marrow aplasia [1%]
- B. Bone marrow infiltration [3%]
- C. Circulating anti–red blood cell antibodies [5%]
- D. Cobalamin deficiency
- E. Erythropoietin deficiency [6%]
- F. Folic acid deficiency [1%]
- ✔ G. Hemoglobin defect [57%]
- ✘ H. Hereditary red blood cell membrane defect [6%]
- I. Iron deficiency [10%]
- J. Red blood cell enzyme deficiency [4%]
- K. Traumatic hemolysis

Incorrect. Correct answer is G
56% answered correctly

Explanation:

Iron deficiency anemia & thalassemias			
Parameter	**Iron deficiency anemia**	**α-Thalassemia minor**	**β-Thalassemia minor**
MCV	↓	↓	↓
RDW	↑	Normal	Normal
RBCs	↓	Normal/↑	Normal/↑
Peripheral smear	Microcytosis, hypochromia	Target cells	Target cells
Serum iron studies	↓ Iron & ferritin ↑ TIBC	Normal/↑ iron & ferritin (RBC turnover)	Normal/↑ iron & ferritin (RBC turnover)
Response to iron supplementation	↑ Hemoglobin	No improvement	No improvement
Hemoglobin electrophoresis	Normal	Normal	↑ Hemoglobin A_2

MCV = mean corpuscular volume; **RBCs** = red blood cells; **RDW** = red blood cell distribution width; **TIBC** = total iron-binding capacity.

The 2 most common causes of **microcytic anemia**, iron deficiency and thalassemia minor, have similar laboratory (eg, low mean corpuscular volume [MCV], low mean corpuscular hemoglobin concentration [MCHC]) and peripheral blood smear (eg, target cells, hypochromia) findings. Differentiation requires iron studies, but empiric iron supplementation is sometimes prescribed. Lack of improvement in hemoglobin levels within 4 weeks makes iron deficiency unlikely **(Choice I)**. Therefore, this patient likely has **thalassemia**, a genetic disorder with **hemoglobin defects**.

Hemoglobin A, the major form of hemoglobin in children and adults, contains 2 alpha-globins and 2 beta-globins. Transcription of the 4 alpha-globin and 2 beta-globin genes is tightly regulated (eg, specific ratio of alpha-/beta-globin production). In thalassemia, mutations or deletions to ≥1 of these genes alter the ratio of alpha-/beta-globin synthesis. Precipitation of excess unpaired globin chains results in erythrocyte toxicity in the bone marrow (ineffective hematopoiesis) and bloodstream (hemolysis).

Thalassemia severity depends on the number of globin chains affected. Defects in 1 or 2 of the alpha-globin chains (alpha-thalassemia minima or minor) or 1 of the beta-globin chains (beta-thalassemia minor) often cause minimal symptoms. Thalassemia minor is associated with mild/moderate **reductions in hematocrit** (>28%) and **low MCV** (55-75 μm^3).

(Choices A and B) Aplastic anemia (multipotent hematopoietic stem cell injury) and bone marrow infiltration (eg, myelofibrosis, metastatic cancer) are usually associated with pancytopenia and normocytic or macrocytic erythrocytes.

(Choices C and K) Circulating antibodies to erythrocyte membranes and traumatic hemolysis (eg, erythrocyte shearing on artificial heart valves) can cause hemolytic anemia, usually associated with normocytic anemia and, sometimes, manifestations of hyperbilirubinemia (eg, icterus).

(Choices D and F) Cobalamin (vitamin B_{12}) or folate deficiency leads to macrocytic anemia and hypersegmented neutrophils.

(Choice E) Erythropoietin promotes erythrocyte differentiation and maturation. Deficiency, most commonly seen in renal failure, is associated with normocytic anemia.

(Choice H) Hereditary spherocytosis is associated with hemolytic anemia due to an erythrocyte membrane defect. MCV is low (small erythrocyte size from the membrane defect), but MCHC is elevated (>36% Hb/cell) due to the increased hemoglobin:cell membrane ratio.

(Choice J) Deficiency in erythrocyte glucose-6-phosphate dehydrogenase leads to oxidative injury and subsequent hemolytic anemia. MCV and MCHC are usually normal.

Educational objective:
The 2 most common causes of microcytic anemia, iron deficiency and thalassemia, are differentiated by iron studies. Thalassemia is a hemoglobin defect caused by alterations to ≥1 of the hemoglobin globin subunits. Thalassemia minor is minimally symptomatic.

Time spent:3 Seconds
Subject:
Medicine

QID:4343
System:
Hematology & Oncology (Red blood cell disorders)

A 23-year-old man comes to the emergency department due to sudden-onset fatigue and dark urine. The patient was recently diagnosed with dermatitis herpetiformis. He began treatment with dapsone and a gluten-free diet 3 days ago. This morning, the patient felt weak and had difficulty getting out of bed. His urine also appeared dark. Temperature is 36.8 C (98.2 F), blood pressure is 130/76 mm Hg, pulse is 88/min, and respirations are 14/min. The patient appears tired. Examination shows scleral icterus and pale lips. There is a papular rash along the scalp, elbows, and knees with overlying excoriation. Laboratory evaluation reveals the following:

Complete blood count

Hemoglobin	8.5 g/dL
Reticulocytes	7%
Platelets	160,000/mm^3

Urinalysis

Blood	moderate
Red blood cells	0/hpf

Which of the following is the most likely mechanism for this patient's urinary findings?

- A. Autoantibody production [12%]
- B. Complement activation [7%]
- ✗ C. Immune complex deposition [12%]
- D. Interstitial leukocyte infiltration [3%]
- ✓ E. Oxidative injury [64%]

Incorrect. Correct answer is **E**
64% answered correctly

Explanation:

This patient developed hemolytic anemia (eg, low hemoglobin, reticulocytosis, icterus) after taking dapsone, likely indicating underlying **glucose-6-phosphate dehydrogenase (G6PD) deficiency**. In this condition, erythrocytes are unable to generate sufficient NADPH to counter **oxidative injury** (eg, superoxide anions) from certain medications (eg, **dapsone**, trimethoprim-sulfamethoxazole, primaquine), infections, or

foods (eg, fava beans). This results in periods of **hemolytic anemia**, whereby lysed erythrocytes release heme into the circulation, leading to:

- **Hyperbilirubinemia** - heme is catabolized to bilirubin, which causes scleral icterus and jaundice
- **Hemoglobinuria** – heme is excreted in the kidneys, which causes dark-colored urine and a false-positive urine dipstick for blood (the heme in hemoglobin causes a positive urine dipstick test, but no erythrocytes are seen on urine microscopy)

(Choice A) Antibody-mediated hemolysis is seen with warm or cold agglutinin disease. Certain medications can also cause immune-mediated hemolysis, but most cases are linked to cephalosporins, penicillins, and nonsteroidal antiinflammatory drugs. In contrast, dapsone is classically linked with G6PD exacerbations.

(Choice B) Complement activation contributes to hemolytic uremic syndrome, which is associated with microangiopathic hemolytic anemia, thrombocytopenia, and acute renal injury. Urinalysis typically shows hematuria and proteinuria. This patient's platelets are normal and no red blood cells are present in the urine.

(Choice C) Immune complex deposition causes membranous glomerulonephritis, leading to hematuria with dysmorphic red cells on urinalysis. Most cases are caused by chronic infection (eg, hepatitis B or C), rheumatic disease (eg, systemic lupus erythematosus), or monoclonal gammopathy (eg, multiple myeloma).

(Choice D) Interstitial leukocyte infiltration is seen in acute interstitial nephritis, which can be associated with antibiotics (eg, trimethoprim-sulfamethoxazole). However, urinalysis typically shows erythrocytes, leukocytes, and white cell casts. Furthermore, patients frequently have rash, fever, and/or peripheral eosinophilia.

Educational objective:
Glucose-6-phosphate dehydrogenase deficiency causes hemolytic anemia due to oxidative injury to red blood cells. Hemolytic episodes can be precipitated by infection or medications, especially dapsone, antimalarials, and nitrofurantoin.

Time spent:7 Seconds	**QID**:4347
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell

A 74-year-old man comes to the office due to 3 months of "problems of old age." He has daily temporal headaches and feels quite fatigued. Intermittently, the patient's ears ring and his eyes become blurry. Both feet feel as if someone is "sticking them with electric pins." The patient used to smoke cigarettes but now uses vaporized nicotine. His medical history is unremarkable. Temperature is 36.6 C (97.8 F), blood pressure is 128/74 mm Hg, and pulse is 88/min. He is well appearing. There is moderate cervical lymphadenopathy. Cardiopulmonary examination is normal. Hepatosplenomegaly is present. Funduscopy shows dilated, segmented, and tortuous retinal veins. There are sensory deficits in his feet, but reflexes and strength are intact. Laboratory results are as follows:

Complete blood count

Hemoglobin	9.6 g/dL
Platelets	136,000/mm^3
Leukocytes	6,200/mm^3

Serum chemistry

Glucose	108 mg/dL
Sodium	141 mEq/L
Potassium	3.6 mEq/L
Blood urea nitrogen	18 mg/dL
Creatinine	0.9 mg/dL

Serum protein electrophoresis reveals a sharp IgM spike. Which of the following is the most likely diagnosis for this patient?

- ○ A. Chronic lymphocytic leukemia [1%]
- ○ B. Monoclonal gammopathy of undetermined significance [15%]
- ○ C. Multiple myeloma [18%]
- ✗ ◉ D. Non-Hodgkin lymphoma
- ✓ ○ E. Waldenstrom macroglobulinemia [64%]

Incorrect. Correct answer is **E**
63% answered correctly

Explanation:

Waldenström macroglobulinemia vs multiple myeloma		
	Waldenström macroglobulinemia	**Multiple myeloma**
Major manifestations	• Hyperviscosity syndrome • Neuropathy • Bleeding • Hepatosplenomegaly • Lymphadenopathy	• Osteolytic lesions/fractures • Anemia • Hypercalcemia • Renal insufficiency
Monoclonal antibody	• IgM	• IgG, IgA, light chains
Peripheral smear	• Rouleaux	• Rouleaux
Bone marrow biopsy	• >10% clonal B cells	• >10% clonal plasma cells

Waldenstrom macroglobulinemia (WM) is a lymphoplasmocytic malignancy characterized by the excessive production of **monoclonal IgM antibody**. Clinical manifestations of WM stem from elevated serum IgM (hyperviscosity syndrome, neuropathy, cryoglobulinemia) and neoplastic infiltration of tissue (hepatosplenomegaly, lymphadenopathy, cytopenias). Peripheral blood smear may show rouleaux formation (or erythrocyte agglutination) due to elevated serum protein. Serum protein electrophoresis (SPEP) is an important screening study; patients with WM have a monoclonal spike (**M-spike**) of IgM. Diagnosis is then confirmed by bone marrow biopsy showing **>10% clonal B cells** with specific cytogenetic features.

This patient presents with manifestations of **hyperviscosity syndrome** (diplopia, tinnitus, headache, dilated/segmented funduscopic findings), **neuropathy** (electric sensation), and evidence of **infiltrative** disease (hepatosplenomegaly, anemia, thrombocytopenia), suggesting WM.

(Choice A) A minority of patients with chronic lymphocytic leukemia (CLL) have high levels of monoclonal IgM. However, patients with CLL tend to have a dramatic lymphocytic predominant leukocytosis (often >100,000/mm^3) on complete blood count.

(Choice B) Patients with monoclonal gammopathy of undetermined significance (MGUS) also have M spikes, but they are most commonly due to IgA, IgG, or IgD (IgM is seen in 15% of cases). MGUS is marked by smaller M spikes (<3 g/dL), bone marrow biopsy with <10% monoclonal plasma cells, and, unlike this patient, no end-organ effects (no anemia, hepatosplenomegaly, lymphadenopathy, or systemic symptoms).

(Choice C) Multiple myeloma (MM) is also a plasma cell neoplasm that produces a monoclonal antibody spike by SPEP; however, patients with MM rarely (<0.5%) produce monoclonal IgM. MM is typically characterized by monoclonal IgG, IgA, or light chains. In addition, patients with MM tend to present with bone pain rather than hyperviscosity, neuropathy, and tissue infiltration.

(Choice D) Non-Hodgkin lymphoma (NHL) usually presents with lymphadenopathy, splenomegaly, and B symptoms (fevers, night sweats, weight loss). SPEP tends not to show monoclonal spikes with NHL. In addition, hyperviscosity syndrome is not a feature of this disease.

Educational objective:
Waldenstrom macroglobulinemia (WM) is a lymphoplasmocytic neoplasm characterized by excessive monoclonal IgM, end-organ damage, and >10% clonal lymphocytes by bone marrow biopsy. Hyperviscosity syndrome, neuropathy, and cryoglobulinemia are common consequences of elevated serum IgM in patients with WM.

Time spent:1 Seconds
Subject:
Medicine

QID:2597
System:
Hematology & Oncology (Miscellaneous)

A 42-year-old woman is evaluated for chronic abdominal pain and fatigue. Her pain is epigastric, burning, and sometimes awakens her from sleep. She has no recent weight loss, nausea, or vomiting. Her diet consists primarily of fruits and vegetables. The patient also complains of a "strange appetite" for paper and ice that she has never had before. Upper gastrointestinal endoscopy shows duodenal erythema and an ulcer on the anterior wall of the duodenal bulb but is otherwise normal. Her unusual appetite is most directly related to which of the following?

- ✔ ○ A. Chronic bleeding [83%]
- ○ B. *Helicobacter pylori* infection [5%]
- ○ C. Lactose intolerance
- ○ D. Oral leukoplakia
- ✘ ◉ E. Reflux esophagitis
- ○ F. Vitamin B12 deficiency [9%]

Incorrect. Correct answer is **A**
83% answered correctly

Explanation:

Pica is an appetite for items other than food, such as paper products, clay, or dirt. It is a behavioral symptom that occasionally develops in iron deficiency anemia. Pagophagia is pica for ice and is quite specific for iron deficiency. It may be present before anemia develops and responds rapidly to iron supplementation. Pica may also be a manifestation of psychiatric disease; these patients may eat very odd items, including light bulbs or hair. This patient has a low-iron diet and likely chronic gastrointestinal bleeding from the ulcer, which has led to iron deficiency and pica.

(Choice B) *Helicobacter pylori* infection is the most common cause of peptic ulcer in the developed world and likely accounts for this patient's ulcer. However, it is the depletion of iron from chronic bleeding, not the *H pylori* infection itself, that causes pica.

(Choice C) Lactose intolerance is a common cause of gastrointestinal symptoms, but it does not lead to bleeding and does not cause iron deficiency or pica.

(Choice D) Oral leukoplakia is a precancerous white patch or plaque on the oral mucosa. Approximately 1%-20% of plaques will progress to cancer within 10 years. Oral leukoplakia is not associated with iron deficiency anemia or pica.

(Choice E) Reflux esophagitis can cause low-grade bleeding and iron deficiency if present for a prolonged period. It is a much less common cause of iron deficiency than peptic ulcer.

(Choice F) Vitamin B12 (cobalamin) deficiency can occur in the setting of chronic gastritis due to decreased production of intrinsic factor. Vitamin B12 deficiency can cause anemia, but it is not associated with ulcers and does not cause pica (iron is a mineral, not a vitamin).

Educational objective:
Pica is an appetite for nonnutritive substances such as ice, clay, dirt, and paper products. Pica, especially for ice, can be indicative of iron deficiency.

Time spent:1 Seconds
QID:4348
Subject:
Medicine
System:
Hematology & Oncology (Red blood cell disorders)

A 56-year-old man comes to the office due to fatigue. He has a 20-year history of diabetes mellitus treated with daily insulin therapy. The patient also has end-stage renal disease and receives hemodialysis 3 times a week. He has been receiving erythropoietin therapy for anemia (pretreatment hemoglobin: 8.0 g/dL). Physical examination shows pale conjunctiva. Laboratory results are as follows:

Hemoglobin	9.2 g/dL
Mean corpuscular volume	77 μm^3
Mean corpuscular hemoglobin concentration	30% hemoglobin/cell
White blood cell count	7,000/mm^3
Platelets	150,000/mm^3
Hemoglobin A1c	7.5%
Erythrocyte sedimentation rate	15 mm/hr

Which of the following is the most appropriate intervention to improve this patient's symptoms?

A. Blood transfusion
B. Change erythropoietin to darbepoetin
C. Folic acid supplementation
D. Iron supplementation
E. Tighter blood glucose control

Correct answer is
78% answered correctly

Explanation:

Patients with advanced chronic kidney disease and end-stage renal disease frequently develop a hypoproliferative (normochromic, normocytic) anemia due to decreased erythropoietin production by the failing kidneys. The primary treatment is **erythropoiesis-stimulating agents** (ESAs), such as erythropoietin or darbepoetin, which increase production of red blood cells in the bone marrow. Goal hemoglobin is typically 10-11.5 g/dL.

However, this patient has a **hypochromic** (low mean corpuscular hemoglobin concentration) and **microcytic** (low mean corpuscular volume) **anemia** that has not responded to ESA therapy. This suggests concurrent **iron deficiency**, which is the most common cause of

inadequate response to ESAs in patients on dialysis. Iron stores can be rapidly depleted during hematopoiesis after ESA administration, especially in chronically ill patients whose iron stores may already be low. Iron stores should therefore be evaluated prior to starting ESAs and frequently thereafter. The treatment of choice for iron deficiency in patients on dialysis is **intravenous iron**.

(Choice A) Blood transfusions are associated with significant complications (eg, volume overload, transfusion reactions) and should be used only for more severe anemia that cannot be corrected by other means. Iron supplementation in this patient is likely to restore responsiveness to ESAs and correct his anemia.

(Choice B) Darbepoetin is an ESA with a longer half-life than erythropoietin and can be dosed less frequently; however, they both have the same effects on hematopoiesis. Both require sufficient iron stores to induce red blood cell production.

(Choice C) Folic acid supplementation is beneficial for folate deficiency and hereditary spherocytosis. Folate deficiency causes a macrocytic anemia, not a microcytic anemia as seen in this patient.

(Choice E) Tight blood glucose control decreases the incidence of microvascular complications of diabetes (eg, retinopathy, neuropathy, nephropathy). Although improved glucose control could reduce this patient's risk of renal complications, it will not help his anemia.

Educational objective:
Anemia of chronic kidney disease is due to erythropoietin deficiency; treatment is with erythropoiesis-stimulating agents (ESAs) (eg, erythropoietin, darbepoetin). Iron deficiency is the most common cause of inadequate response to ESAs in patients on dialysis.

Time spent:1 Seconds

QID:4349

Subject:
Medicine

System:
Hematology & Oncology (Red blood cell disorders)

A 54-year-old woman comes to the office due to fatigue. She also notes a tingling sensation in her feet and light-headedness and palpitations during moderate physical activity. The patient has no chronic health conditions and takes no medication regularly. She has never had surgery. The patient eats a balanced diet and does not use tobacco, alcohol, or recreational drugs. Vital signs are within normal limits. Physical examination shows pale conjunctivae and a shiny tongue. Ankle reflexes are decreased bilaterally. Laboratory results are as follows:

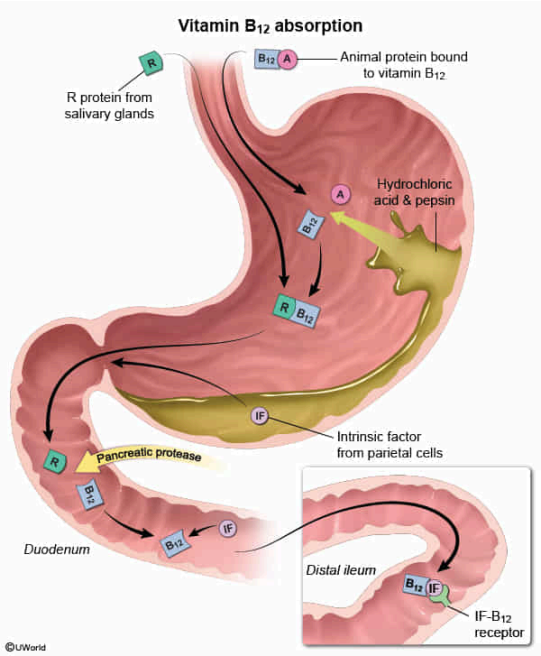
Complete blood count	
Hemoglobin	7.6 g/dL
Mean corpuscular volume	120 μm^3
Mean corpuscular hemoglobin concentration	36% Hb/cell
Platelets	160,000/mm^3
Leukocytes	4,900/mm^3

This patient is at greatest risk for which of the following long-term complications?

A. Acute myeloid leukemia
B. Aortic aneurysm
C. Cirrhosis
D. Gastric cancer
E. Glomerulonephritis
F. T-cell lymphoma

Correct answer is
63% answered correctly

Explanation:



This patient's symptomatic anemia (light-headedness, palpitations) with macrocytosis (eg, mean corpuscular volume [MCV] >100 μm^3), glossitis (smooth tongue), and lower extremity neurologic findings (paresthesia, diminished reflexes) suggests **vitamin B_{12} deficiency**. Vitamin B_{12} absorption relies on the salivary glands (R-protein), stomach (intrinsic factor, gastric acid), pancreas (proteases), and ileum (absorption). Although damage to any of

these structures can impair uptake, the most common cause of vitamin B_{12} deficiency is **pernicious anemia**.

Pernicious anemia is marked by antibody-mediated destruction of **intrinsic factor**, a protein carrier produced by gastric parietal cells and required for vitamin B_{12} absorption. Antibodies also directly target gastric parietal cells, leading to atrophy of the acid/pepsin-producing parts of the stomach. Over time, the atrophic gastric mucosa undergoes **intestinal-type metaplasia**, which dramatically increases the risk of **gastric cancer**. Therefore, patients with pernicious anemia require esophagogastroduodenoscopy at initial diagnosis and with any suspicious symptoms (eg, positive fecal occult blood test, mid-epigastric abdominal pain).

(Choice A) Risk of acute myeloid leukemia is increased with certain hematologic malignancies (eg, myelofibrosis). Although myelofibrosis can cause symptomatic anemia, severe macrocytosis (eg, MCV >115 μm^3) is uncommon, the other cell lines are often abnormal (eg, thrombocytopenia or leukocytosis), and peripheral neuropathy is not generally seen.

(Choice B) Aortic aneurysm can be a complication of syphilis. Although tabes dorsalis (a form of neurosyphilis) can be associated with lower extremity paresthesia (posterior column damage), most patients have sensory ataxia and lancinating pains. Macrocytic anemia would be atypical.

(Choice C) Cirrhosis is a common complication of chronic hepatitis C virus infection, which may cause symptomatic hemolytic anemia and peripheral neuropathy due to mixed cryoglobulinemia. However, macrocytic anemia and a smooth tongue would be atypical. In addition, patients with mixed cryoglobulinemia generally have systemic manifestations (eg, weakness, fatigue, arthralgia).

(Choice E) Glomerulonephritis is a common consequence of systemic lupus erythematosus (SLE). Although SLE can be associated with anemia and paresthesia (due to peripheral neuropathy), macrocytosis is uncommon and the peripheral neuropathy is usually asymmetric.

(Choice F) Risk of T-cell lymphoma is increased with human T-lymphotropic virus type 1. Patients generally develop progressive leg weakness and spasticity with upper motor neuron signs (eg, hyperreflexia, clonus, Babinski reflex). Macrocytic anemia and diminished reflexes are not typically seen. Vitamin B_{12} deficiency can cause hyperreflexia or hyporeflexia (eg, subacute combined degeneration, peripheral neuropathy).

Educational objective:
Vitamin B_{12} deficiency often presents with macrocytic anemia and/or neurologic manifestations (eg, paresthesia, subacute combined degeneration). Most cases are seen in older individuals with pernicious anemia, marked by antibody-mediated destruction of intrinsic factor and gastric parietal cells. Damage to the stomach results in gastric atrophy and increases the risk of gastric cancer.

Time spent:1 Seconds	**QID**:4356
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 42-year-old woman comes to the physician with bilateral knee pain that severely limits her mobility. She also complains of diffuse morning joint stiffness that takes several hours to improve. She has been taking over-the-counter ibuprofen and aspirin but has experienced little relief of symptoms. She has no other medical problems and does not use tobacco, alcohol, or illicit drugs. Her vital signs are within normal limits. Physical examination shows tenderness and swelling of multiple metacarpophalangeal joints, as well as both wrists and knees. Laboratory results are as follows:

Hemoglobin	8.4 g/dL
Serum iron	30 µg/dL (normal 50-150 µg/dL)
Total iron-binding capacity	230 µg/dL (normal 250-460 µg/dL)
Ferritin	300 ng/mL (normal 15-200 ng/mL)

Which of the following is the most appropriate next step in management of this patient's anemia?

A. Cyanocobalamin supplementation
B. Erythropoietin
C. Folic acid supplementation
D. Iron supplementation
E. Methotrexate
F. Packed red blood cell transfusion
G. Splenectomy

Correct answer is
69% answered correctly

Explanation:

Iron studies in microcytic anemia					
	MCV	**Iron**	**Ferritin**	**Transferrin (TIBC)**	**Transferrin saturation (iron/TIBC)**
Iron deficiency	↓	↓	↓	↑	↓
Thalassemia	↓↓	Normal/↑	Normal/↑	Normal/↓	Normal/↑
Anemia of chronic disease (inflammation)	Normal/↓	↓	Normal/↑	↓	Normal/↓
MCV = mean corpuscular volume; **TIBC** = total iron binding capacity.					

This patient has inflammatory arthritis, which is most consistent with early rheumatoid arthritis. She has moderate anemia with low serum iron and total iron-binding capacity (TIBC) consistent with **anemia of chronic disease** (ACD). Other characteristic laboratory findings of ACD include normochromic normocytic red blood cells, mildly decreased transferrin saturation, and normal to elevated ferritin. In contrast, iron-deficiency anemia features elevated TIBC and low ferritin. Erythropoietin levels are variable, but ACD patients usually have a low reticulocyte count relative to anemia severity, suggesting impaired red blood cell production. ACD pathophysiology is thought to involve iron trapping within macrophages, leading to reduced serum iron concentrations and **poor iron availability** for hemoglobin synthesis. Decreased erythropoietin production and poor marrow response to erythropoietin may also play a role.

ACD is commonly associated with chronic inflammatory diseases (eg, infections, cancer, autoimmune disorders) but can also be observed in heart disease, diabetes mellitus, and acute inflammation. Treating the underlying inflammatory disorder will often improve the anemia. Common agents used in rheumatoid arthritis treatment include methotrexate, hydroxychloroquine, and tumor necrosis factor inhibitors (eg, infliximab, etanercept). Erythropoietin or darbepoetin treatment may benefit ACD patients unresponsive to underlying inflammatory disorder treatment **(Choice B)**. Packed red blood cell transfusions are rarely required but can be considered after all other treatment interventions have failed **(Choice F)**.

(Choice D) Serum iron concentrations are low in ACD patients. However, iron supplementation is not beneficial due to impaired iron utilization in ACD.

(Choices A and C) B-complex vitamins (pyridoxine, folic acid, cyanocobalamin, nicotinic acid) are not deficient in ACD; supplementation will not improve the anemia of ACD.

(Choice G) Hereditary spherocytosis is treated via splenectomy; this can be occasionally used for treating immune thrombocytopenic purpura and chronic idiopathic myelofibrosis with refractory anemia. However, splenectomy will not improve this patient's anemia.

Educational objective:
Anemia of chronic disease is a disorder of iron utilization that most commonly occurs in the setting of chronic inflammation. It is characterized by a normocytic anemia with decreased serum iron, decreased total iron-binding capacity, decreased iron saturation, and normal/elevated serum ferritin. Treating the underlying inflammatory disorder will often improve the anemia.

Time spent:1 Seconds	**QID**:4358
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 21-year-old man comes to the office due to recent irritability and aggressive behavior. He is a star college football linebacker and is training for his senior season. The patient does not use tobacco or alcohol. His mother has diabetes and his father has basal cell skin cancer. Blood pressure is 132/84 mm Hg and pulse is 62/min. The patient is muscular and well appearing. There is no lymphadenopathy in the cervical or supraclavicular chains. Cardiopulmonary examination is normal. Mild gynecomastia is present. The abdomen is soft and nontender. Liver span is 8 cm, and the spleen is not palpable. Laboratory results are as follows:

Hematocrit	58%
Platelets	175,000/mm^3
Leukocytes	7800/mm^3
Erythrocyte sedimentation rate	15 mm/h

Which of the following is the best single explanation for this patient's presentation?

A. Anabolic steroid abuse
B. Autologous blood transfusion
C. Erythropoietin abuse
D. Intensive exercise schedule
E. Polycythemia vera

.. Correct answer is
89% answered correctly

Explanation:

Clinical features of androgen abuse	
Types of androgens	• Exogenous (eg, testosterone replacement therapy) • Synthetic (eg, stanozolol, nandrolone) • Androgen precursors (eg, DHEA)

Side effects/ clinical presentation	• **Reproductive**
	  ◦ **Men:** decreased testicular function & sperm production, gynecomastia
	  ◦ **Women:** acne, hirsutism, voice deepening, menstrual irregularities
	• **Cardiovascular:** left ventricular hypertrophy, possible ↓ HDL & ↑ LDL
	• **Psychiatric:** aggressive behavior (men), mood disturbances

	• **Hematologic:** polycythemia, possible hypercoagulability
DHEA = dehydroepiandrostenedione.	

Androgen abuse is common amongst high-performance athletes. Androgens are **anabolic**; they increase muscle mass and maximum voluntary strength. They are taken directly (natural or synthetic androgens) or induced to rise indirectly (estrogen blockers, androgen precursors, gonadotropins). Adverse effects are common. In men, androgen abuse can cause testicular atrophy, reduced spermatogenesis, **gynecomastia**, **mood disturbances**, and **aggressive** behavior. In women, androgens can cause acne, hirsutism, deepening of the voice, and menstrual irregularities. Laboratory findings include **erythrocytosis**, hepatotoxicity, and dyslipidemia. The mechanism for erythrocytosis in androgen abuse remains unclear, but increases in hematocrit and hemoglobin are dose dependent. This patient is likely abusing androgens in preparation for his upcoming football season.

(Choice B) An autologous blood transfusion involves removing blood several weeks before a competitive event and then transfusing the blood back into the athlete prior to the event. The net effect is increased hematocrit, oxygen-carrying capacity, and performance. However, this process typically does not cause gynecomastia or mood changes, as seen in this patient.

(Choice C) Self-injection of erythropoietin (EPO) stimulates the bone marrow to produce more red blood cells, thereby increasing the hematocrit. Gynecomastia, aggression, and mood changes are atypical in EPO abuse; they are much more common with androgens. EPO is primarily abused by athletes participating in endurance sports.

(Choice D) An intensive exercise schedule usually increases muscle mass, improves muscle function, and enhances exercise capacity. Erythrocytosis is not a typical consequence of a strenuous exercise regimen.

(Choice E) Polycythemia vera (PV) is a chronic myeloproliferative disorder that causes erythrocytosis. It is often asymptomatic, but aquagenic pruritus (itching after a warm bath or shower), bleeding, transient neurologic symptoms, and erythromelalgia (burning cyanosis of the hands or feet) are common presenting symptoms. Gynecomastia, irritability, and aggression are more suggestive of androgen abuse than PV.

Educational objective:
Competitive athletes using exogenous androgens, autologous blood transfusions, or erythropoietin to enhance athletic performance can develop an elevated hematocrit. Clinical findings suggesting exogenous androgens include gynecomastia, testicular atrophy, mood disturbances, and hepatotoxicity.

A 17-year-old girl comes to the emergency department due to a nosebleed that began an hour ago after she was hit in the face by a basketball. She pinched the nostrils for about 20 minutes in an attempt to stop the bleeding, but the hemorrhage continued after pressure was removed. The patient has a history of heavy, painful menses and takes scheduled ibuprofen for the first few days of her period. Her last period was a week ago. Temperature is 37.2 C (99 F). Examination shows clear lung fields with normal S1 and S2. The liver span measures 8 cm along the midclavicular line, and the spleen is not palpable. Scattered ecchymoses are present on both legs and arms. Laboratory results are as follows:

Hematocrit	36%
Platelets	9,000/mm^3
Leukocytes	5,500/mm^3
Neutrophils	60%
Eosinophils	1%
Lymphocytes	32%
Monocytes	7%
Fibrinogen	250 mg/dL (normal: 150-350 mg/dL)
PT	13 sec

Which of the following is the most likely cause of this patient's condition?

A. Blocked production of thromboxane A2
B. Bone marrow infiltration by malignant cells
C. Decreased circulating von Willebrand protein
D. Deficient ADAMTS13 activity
E. Hyperactivation of coagulation and fibrinolysis
F. Platelet autoantibody productior

Correct answer is
52% answered correctly

Explanation:

Immune thrombocytopenia	
Etiology	• Platelet autoantibodies • Preceding viral infection
Clinical findings	• Petechiae, ecchymosis • Mucosal bleeding (eg, epistaxis, hematuria)
Laboratory findings	• Isolated thrombocytopenia <100,000/mm^3 • Few platelets (size normal to large) on peripheral smear

Treatment	• Children ◦ Observe if cutaneous symptoms only ◦ Glucocorticoids, IVIG, or anti-D if bleeding • Adults ◦ Observation if cutaneous symptoms AND platelets ≥30,000/mm^3 ◦ Glucocorticoids, IVIG, or anti-D if bleeding or platelets <30,000/mm^3
IVIG = intravenous immunoglobulin.	

This patient has bleeding episodes and **isolated thrombocytopenia**, likely due to **immune thrombocytopenia** (ITP). ITP is an autoimmune disorder in which IgG **autoantibodies** against platelet membrane glycoproteins cause increased platelet destruction and inhibition of platelet production. Presentation is most common in healthy children (age 2-5) or adolescents with petechiae, ecchymoses, and **mucosal bleeding** (eg, epistaxis, heavy menses). Other than bruising, physical examination is generally unremarkable. Patients have a **normal liver span** (eg, 6-12 cm at midclavicular line) and **nonpalpable spleen**.

Although ITP is a common cause of isolated thrombocytopenia (ie, normal hematocrit and leukocytes), it is a diagnosis of exclusion. Prolonged bleeding warrants workup with coagulation tests (PT, PTT, fibrinogen), which are normal in patients with ITP. Observation alone is sufficient for mild ITP (cutaneous manifestations) in children, whereas glucocorticoids, anti-D immune globulin (if Rh-positive and Coombs-negative), or intravenous immunoglobulin is the treatment for bleeding. Hormonal therapy may also be considered in patients with heavy menses.

(Choice A) Nonsteroidal anti-inflammatories (eg, ibuprofen) block production of thromboxane A2, which can impair platelet function but would not result in the severe thrombocytopenia seen in this patient.

(Choice B) Malignant infiltration of the bone marrow, as seen in leukemia, typically results in pancytopenia. It is unlikely in this patient with isolated thrombocytopenia and no hepatosplenomegaly.

(Choice C) Decreased von Willebrand factor can present in adolescent girls with heavy menstrual bleeding. Although platelet function is affected, platelet count is typically normal.

(Choice D) ADAMTS13 is deficient in thrombocytopenic purpura, which is characterized by thrombocytopenia and microangiopathic hemolytic anemia (not seen in this patient).

(Choice E) Disseminated intravascular coagulation is associated with hyperactivation of coagulation and fibrinolysis. Patients typically have thrombocytopenia, microangiopathic hemolytic anemia, low levels of clotting factors (fibrinogen, factors V and VIII), and prolonged PT and PTT.

Educational objective:
Immune thrombocytopenia is an autoimmune disorder with increased platelet destruction and inhibition of platelet production due to IgG autoantibodies against platelet membrane glycoproteins. Patients may have mucocutaneous bleeding with isolated thrombocytopenia and no hepatosplenomegaly.

A 34-year-old man is brought to the emergency room after being involved in a motor vehicle collision. He suffered blunt abdominal trauma and bilateral femur fractures. Medical history is unremarkable. Blood pressure is 80/40 mm Hg and pulse is 110/min. He receives several units of packed red blood cells. Once stabilized, the patient develops a tingling sensation in his toes and fingers. His serum calcium level is noted to be 7.2 mg/dL. Which of the following is the most likely cause of this patient's current symptoms?

A. Increased renal tubular secretion of calcium
B. Calcium chelation by a substance in the transtused blood
C. Electrolyte leakage from red blood cells during pre-transfusion storage
D. Antibody-mediated red blood cell membrane damage
E. Parathyroid gland suppression due to fluid overload

Correct answer is
84% answered correctly

Explanation:

This patient is experiencing paresthesias due to **hypocalcemia**. He has had significant blood loss as a result of his injuries and has received **packed red blood cells** as part of the resuscitation efforts. Prior to storage, whole blood (for transfusions) is generally mixed with solutions containing **citrate anticoagulant**. Packed cells derived from these whole blood collections also contain citrate. Infused citrate can **chelate serum calcium**, causing hypocalcemia. This is most likely after **massive transfusions** of the equivalent of more than one blood volume over 24 hours.

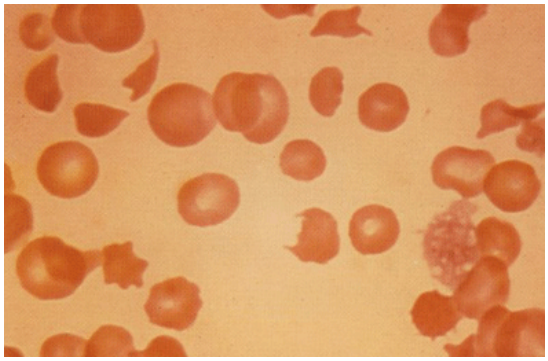
(Choice C) Stored red blood cells gradually lose intracellular potassium to the surrounding solution. This mechanism has the potential to cause hyperkalemia, but not hypocalcemia.

Educational objective:
Patients who have received the equivalent of more than one blood volume of blood transfusions or packed red blood cells over 24 hours may develop elevated plasma levels of citrate, a substance added to stored blood. Citrate chelates calcium and magnesium and may reduce their plasma levels, causing paresthesias.

Time spent:0 Seconds
Subject:
Medicine

QID:4402
System:
Hematology & Oncology (Transfusion medicine)

A 56-year-old man is being evaluated for increased fatigability. His past medical history is significant for severe aortic stenosis that required aortic valve replacement, diabetes mellitus, and osteoarthritis. Peripheral blood smear findings are shown on the slide below.



Which of the following laboratory findings is most likely to be seen in this patient?

A. Increased total serum iron level
B. Decreased serum haptoglobin level
C. Decreased mean corpuscular volume
D. Decreased reticulocyte count
E. Decreased serum albumin level

Correct answer is
81% answered correctly

Explanation:

The fragmented erythrocytes shown on the slide are called **schistocytes** or helmet cells. They are formed during mechanical destruction of erythrocytes in the vasculature. In this patient, destruction of erythrocytes is most likely to be caused by his **aortic valve prosthesis**. Artificial (mechanical) valves are more traumatic for red blood cells (RBCs) than porcine prostheses and frequently cause hemolysis. Schistocytes also appear if erythrocyte destruction occurs due to narrowing of vascular spaces or disseminated thrombosis.

Hemolytic anemia due to intravascular erythrocyte trauma results in laboratory findings similar to other types of hemolytic anemias such as an increase in serum indirect bilirubin and urinary urobilinogen. **Intravascular** erythrocyte destruction results in free hemoglobin in the serum (hemoglobinemia) and in the urine (hemoglobinuria) as well as

increased serum lactate dehydrogenase. Haptoglobin is a serum protein that binds free hemoglobin and promotes its excretion by the reticuloendothelial system. In intravascular hemolysis, the amount of free hemoglobin in the serum exceeds the binding capacity of haptoglobin, thereby decreasing the level of haptoglobin **(Choice B)**.

(Choice A) Increased serum iron occurs in hemochromatosis most classically, but increased serum iron can also be iatrogenic. Hemochromatosis does not cause anemia, but it is associated with cirrhosis, and increased incidence of hepatocellular cancer, skin darkening and insulin resistance.

(Choice C) Most cases of hemolytic anemia are accompanied by an increased mean corpuscular volume (MCV) as intensive erythropoiesis causes the appearance in peripheral blood of premature erythroid forms larger than normal erythrocytes. Less commonly, the MCV can be normal or decreased (eg, due to the presence of smaller spherocytes or due to chronic anemia causing iron deficiency). Decreased haptoglobin is more specific for hemolysis and more likely to be seen in this patient.

(Choice D) A decreased reticulocyte count in the presence of anemia is characteristic of aplastic anemia. In hemolytic anemias, the reticulocyte count is increased in order to compensate for the increased destruction of RBCs.

(Choice E) A decreased serum albumin level is associated with cirrhosis (decreased production), nephrotic syndrome and protein-wasting enteropathy (increased losses).

Educational objective:
Schistocytes (helmet cells) are fragmented erythrocytes. They occur in microangiopathic hemolytic anemias (eg, disseminated intravascular coagulation, hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura) and due to erythrocyte destruction by prosthetic cardiac valves. Hemolytic anemias are characterized by a decreased serum haptoglobin level as well as an increased lactate dehydrogenase and bilirubin.

Time spent:1 Seconds

QID:4406

Subject:
Medicine

System:
Hematology & Oncology (Red blood cell disorders)

A 32-year-old woman comes to the emergency department due to chest pain and shortness of breath that woke her up this morning. The chest pain is sharp and worsens with inspiration. The patient has had no fever or cough but has had worsening right leg swelling over the past several days. Review of systems is positive for myalgias, joint pains, and facial rash brought on by sun exposure. Medical history includes 2 miscarriages at 12 and 16 weeks gestation. She takes no medications and does not use tobacco, alcohol, or illicit drugs. Temperature is 37.2 C (99 F), blood pressure is 152/86 mm Hg, pulse is 98/min, and oxygen saturation is 95% on room air. Physical examination shows clear lungs, normal heart sounds, and no abdominal organomegaly. The right lower extremity is swollen and tender to touch. CT angiography of the chest reveals pulmonary emboli. Which of the following additional laboratory findings is most likely to be present in this patient?

A. Absent von Willebrand factor
B. Decreased D-dimer level
C. Positive factor V Leiden mutation
D. Presence of *JAK2* mutation
E. Prolonged PTT

Correct answer is
54% answered correctly

Explanation:

Diagnostic criteria for antiphospholipid-antibody syndrome (1 clinical & 1 laboratory criterion must be met)	
Clinical	**Vascular thrombosis** • Arterial or venous **Pregnancy morbidity** • ≥3 consecutive, unexplained fetal losses before 10th week • ≥1 unexplained fetal losses after 10th week • ≥1 premature births of normal neonates before 34th week due to preeclampsia, eclampsia, or placental insufficiency
Laboratory	• Lupus anticoagulant • Anticardiolipin antibody • Anti–β2-glycoprotein I antibody

This patient has pulmonary emboli due to a right lower extremity **deep venous thrombosis** (DVT). Although risk of DVT is increased in several inherited and acquired conditions, this patient's history of fetal loss and signs of **systemic lupus**

erythematosus (eg, myalgias, arthralgias, photosensitivity) suggest **antiphospholipid-antibody syndrome** (APS).

APS is characterized by the following:

- Venous, arterial, or small vessel **thromboembolic disease** and/or pregnancy complications such as **fetal loss**
- Laboratory evidence of an antiphospholipid antibody in the serum: lupus anticoagulant (LA), anticardiolipin antibody, and/or beta2-glycoprotein-I antibody

Patients with antiphospholipid antibodies (particularly LA) generally have **prolonged PTT** because antiphospholipid antibodies bind the phospholipids used in most testing assays and prevent them from inducing coagulation. This laboratory artifact will not be fixed by a 1:1 mixing with normal plasma (unlike coagulation factor deficiency). However, adding phospholipids to the testing assay will eventually overcome the presence of the inhibitor and normalize the PTT. This is an indirect way of identifying LA antibodies; it is usually combined with other tests, such as the diluted Russell viper venom test or the kaolin clotting time test for diagnosis.

(Choice A) Patients with rheumatologic disease can develop autoantibodies to von Willebrand factor, leading to acquired von Willebrand disease (vWD). Acquired vWD is generally marked by easy bruising and mucosal bleeding (eg, epistaxis, gum bleeding, heavy menses), but fetal loss and thrombosis would be atypical.

(Choice B) D-dimer is a product of cross-linked fibrin degradation. Therefore, almost all patients (>95%) with ongoing thrombosis have elevated D-dimer levels. Low D-dimer would be highly unusual in the setting of pulmonary emboli and deep vein thrombosis.

(Choice C) Factor V Leiden mutation is an altered form of coagulation factor V that renders it resistant to the anticoagulant effects of activated protein C. Risk of thromboembolism and fetal loss is significantly increased, but factor V Leiden mutation is not linked with systemic lupus erythematosus and would not explain this patient's arthralgias, myalgias, and photosensitivity.

(Choice D) *JAK2* mutation is present in most cases of polycythemia vera, which is associated with increased risk of thromboembolism. However, most cases occur in older individuals; in addition, it would not explain photosensitivity, myalgias, or arthralgias.

Educational objective:
Antiphospholipid-antibody syndrome is common in patients with systemic lupus erythematosus. It generally presents with thromboembolism and/or recurrent fetal loss. Positive testing for lupus anticoagulant (LA), anticardiolipin antibody, and/or beta2-glycoprotein-I antibody is diagnostic. Those with LA have prolonged PTT that does not improve with 1:1 dilution with normal serum (mixing test).

A 25-year-old African American woman comes to the office after experiencing increasingly heavy menstrual cycles for 3 months. The patient has also noticed that her gums frequently bleed when she brushes her teeth. Review of systems is positive for ongoing pain and stiffness in her hands and wrists that is partially responsive to ibuprofen. She is not taking any medications and has no known medical conditions. The patient is afebrile, blood pressure is 149/79 mm Hg, and pulse is 87/min. A nonpainful oral ulcer is present. Multiple petechiae are present on the upper arms and shins. The wrists and hands are tender to palpation and demonstrate reduced range of motion. Laboratory results are as follows:

Hemoglobin	10.8 g/dL
Platelets	40,000/mm^3
Leukocytes	2,500/mm^3
Serum creatinine	1.7 mg/dL

Which of the following is the most likely cause of thrombocytopenia in this patient?

A. Aberrant splenic sequestration
B. Bone marrow invasion by malignancy
C. Dilutional cytopenia
D. Ineffective hematopoiesis
E. Peripheral destruction

44% answered correctly

Explanation:

Hematologic manifestations of SLE		
	Common mechanisms	**Uncommon mechanisms**
Anemia	• Anemia of chronic disease • SLE nephritis • Iron deficiency anemia (gastrointestinal loss) • Immune hemolytic anemia	• Medications • MAHA • Aplastic anemia
Leukopenia	• Immune-mediated destruction	• Medications • Bone marrow dysfunction
Thrombocytopenia	• Immune-mediated destruction	• Medications • TTP (↑ consumption)
MAHA = microangiopathic autoimmune hemolytic anemia; **SLE** = systemic lupus erythematosus; **TTP** = thrombotic thrombocytopenic purpura.		

This patient's presentation (joint pains, oral ulcer, hypertension, pancytopenia, impaired renal function) suggests possible systemic lupus erythematosus (SLE), a systemic autoimmune disorder. Her severe thrombocytopenia (platelet count <50,000/mm^3), manifesting with common associated features of bleeding gums and heavy menstrual periods, is likely due to SLE. In the United States, SLE occurs most commonly in African American, Hispanic, and Asian women. **Hematologic abnormalities** occur in over half of SLE patients and include:

- Anemia, resulting from immune destruction, but also from coexisting renal disease or chronic inflammation
- Leukopenia (eg, neutropenia), often immune-mediated and correlating with disease activity
- Thrombocytopenia, most commonly due to immune thrombocytopenic purpura (ITP)

The presence of **autoantibodies** is the primary mechanism underlying the most common cytopenias in SLE. **Thrombocytopenia** is most often caused by **antiplatelet antibodies**, which trigger **increased destruction** of platelets via immunoglobulin binding in peripheral blood vessels and subsequent macrophage phagocytosis. Less commonly, thrombocytopenia can occur in SLE-associated hypercoagulable states in which platelets are consumed within thrombi (eg, thrombotic thrombocytopenic purpura, associated with schistocytes; disseminated intravascular coagulation, which can occur in antiphospholipid antibody syndrome).

(Choice A) Although splenic sequestration of immunoglobulin-bound platelets may occur downstream, the primary initiating mechanism for platelet destruction in SLE occurs in peripheral blood vessels via the abnormal formation of immune complexes. In contrast, aberrant splenic sequestration occurs in conditions that increase portal pressure and splenic congestion, such as liver disease, hepatic vein thrombosis, or sickle cell anemia. Typically, the thrombocytopenia associated with these conditions is mild (60,000-150,000/mm^3).

(Choices B and D) Malignant invasion of bone marrow, seen in leukemias and lymphomas, may cause pancytopenia. Similarly, pancytopenia can be caused by ineffective hematopoiesis resulting from primary bone marrow disorders (eg, myelodysplastic syndrome, aplastic anemia). However, these conditions are unlikely to explain this patient's new kidney disease, hypertension, nonpainful oral ulcer, and arthralgias.

(Choice C) Dilutional thrombocytopenia can occur following massive transfusion of packed red blood cells or large-volume intravenous fluid resuscitation, in which plasma volume is increased disproportionately to platelet count. This patient has no history of either procedure.

Educational objective:
Pancytopenia (decreased red blood cells, white blood cells, and platelets) is common in patients with systemic lupus erythematosus. It usually indicates concurrent peripheral, immune-mediated destruction of all 3 cell lines.

Time spent:1 Seconds
Subject:
Medicine

QID:4416
System:
Hematology & Oncology (Platelet disorders)

A 58-year-old woman undergoing systemic chemotherapy for advanced breast cancer with metastases to bone comes to the office for routine follow-up. She has mild, vague bone pain that is relieved by over-the-counter analgesics. Physical examination shows a well-healed mastectomy scar on the right. Mucous membranes are moist. Laboratory results are as follows:

Serum chemistry	
Sodium	144 mEq/L
Potassium	3.8 mEq/L
Chloride	102 mEq/L
Bicarbonate	24 mEq/L
Blood urea nitrogen	14 mg/dL
Creatinine	0.8 mg/dL
Calcium	11.4 mg/dL
Glucose	146 mg/dL
Liver function studies	
Albumin	3.4 g/dL

Which of the following is the best next step in management of this patient?

A. Bisphosphonate therapy
B. Corticosteroid therapy
C. Loop diuretic therapy
D. Opioid therapy
E. Radiation therapy

Correct answer is
72% answered correctly

Explanation:

Hypercalcemia of malignancy	
Causes	• PTHrP secretion • Bone metastasis • 1,25-Dihydroxyvitamin D overproduction
Clinical features	• Mild: nausea, fatigue, constipation, ileus (often asymptomatic) • Moderate/severe (>12 mg/dL): confusion, weakness, delirium, coma
Diagnosis	• Elevated corrected serum calcium with suppressed PTH • May have elevated PTHrP • Localization & identification of primary tumor
Management	• Bisphosphonates

	• Denosumab

PTH = parathyroid hormone; **PTHrP** = PTH-related protein.

This patient has **hypercalcemia** in the setting of **metastatic breast cancer to bone**. In osteolytic bone metastases (eg, breast cancer), hypercalcemia of malignancy is common due to the release of osteoclast activating factors and other cytokines. Hypercalcemia of malignancy can also be due to the secretion of parathyroid hormone–related protein (ie, humoral hypercalcemia of malignancy), increased production of calcitriol by malignant cells (eg, certain lymphomas), or, rarely, by ectopic secretion of parathyroid hormone.

Patients with mild hypercalcemia (serum calcium <12 mg/dL) are often asymptomatic or have only nonspecific symptoms (eg, fatigue, lethargy, constipation). Asymptomatic or mild hypercalcemia by itself does not require urgent therapy. However, hypercalcemia of malignancy requires treatment because it may worsen over time. Initial therapy includes intravenous **bisphosphonates** (eg, zoledronic acid, pamidronate), which inhibit the osteoclastic activity, stabilizing destructive bony tumors and reducing the risk for **pathologic fracture** and **malignant hypercalcemia**. An alternate option is denosumab.

(Choice B) Corticosteroids reduce calcitriol release from activated mononuclear cells and are useful for hypercalcemia related to certain lymphomas and granulomatous disease (eg, sarcoidosis). However, they are not effective in hypercalcemia of bone metastasis, which is not due to calcitriol.

(Choice C) Patients with severe hypercalcemia (serum calcium >14 mg/dL) require urgent management, including intravenous hydration (normal saline) and subcutaneous calcitonin, in addition to bisphosphonates. Patients with chronic kidney disease or heart failure may also require loop diuretics (eg, furosemide) to minimize fluid overload, but these drugs are not recommended for asymptomatic mild hypercalcemia.

(Choice D) Opioids are the first-line treatment for metastatic bone pain inadequately controlled by acetaminophen or nonsteroidal anti-inflammatory drugs. This patient has achieved adequate pain relief with nonopioid analgesics; therefore, additional pain control is unnecessary.

(Choice E) Radiation therapy can treat moderate to severe pain caused by bone metastases. However, it would not be indicated at this time because this patient has only mild pain.

Educational objective:
Bisphosphonates (eg, zoledronic acid, pamidronate) are the drugs of choice for stabilizing bony metastatic lesions to prevent hypercalcemia of malignancy and pathologic fractures.

A 19-year-old woman comes to the office due to 2 days of worsened fatigue and exertional dyspnea. Four days ago, she was diagnosed with otitis media and was prescribed amoxicillin. The patient has no other significant medical history. Physical examination shows a soft and nontender abdomen with mild splenomegaly. Scleral icterus is present. The remainder of the physical examination is unremarkable. Laboratory results are as follows:

Complete blood count	
Hemoglobin	7.8 g/dL
Mean corpuscular volume	90 μm^3
Mean corpuscular hemoglobin concentration	32 g/dL
Reticulocytes	10%
Platelets	176,000/mm^3
Leukocytes	7,800/mm^3

Which of the following is the best next step in management of this patient?

A. Amoxicillin discontinuation
B. Antinuclear antibody assay
C. Bone marrow biopsy
D. Hemoglobin electrophoresis
E. Liver function studies
F. Splenectomy

Correct answer is
75% answered correctly

Explanation:

Drug-induced, immune-mediated hemolytic anemia	
Pathogenesis	• Drug coats erythrocytes → IgG binding → splenic destruction of RBCs (extravascular hemolysis) • Drug triggers immune complexes → complement-mediated destruction of RBCs (intravascular hemolysis)
Manifestations	• Sudden onset (within hours of exposure) • Anemia: fatigue, pallor, dyspnea • Hemolysis: jaundice, dark urine, abdominal or back pain ◦ ↑ Reticulocytes, indirect bilirubin & LDH ◦ ↓ Haptoglobin ◦ Spherocytes on peripheral blood smear ◦ + Direct Coombs test (anti-IgG, anti-C3)
Treatment	• Discontinue offending drug • Transfusion (if severe) • ± Glucocorticoids, IVIG
IVIG = intravenous immunoglobulin; **LDH** = lactate dehydrogenase; **RBCs** = red blood cells.	

This patient received amoxicillin and subsequently developed symptomatic anemia (eg, fatigue, exertional dyspnea), splenomegaly, and jaundice, raising strong suspicion for **drug-induced hemolytic anemia**. Penicillins (eg, **amoxicillin**) and cephalosporins are common triggers of drug-induced hemolytic anemia because these medications bind to the surface of erythrocytes, creating a **hapten** for IgG attachment. IgG-coated erythrocytes are then partially or wholly phagocytized by **splenic macrophages**, leading to **extravascular hemolysis**. Complement-mediated intravascular hemolysis may also occur.

Patients generally show signs of anemia (eg, fatigue, pallor, dyspnea) and hemolysis (eg, jaundice, dark urine) within 2-4 days of medication exposure. Laboratory assessment typically reveals indirect hyperbilirubinemia, elevated lactate dehydrogenase, decreased haptoglobin, and **reticulocytosis** (due to the generation of new erythrocytes in response to anemia). Most patients have **normocytic anemia** with a normal or slightly elevated mean corpuscular volume due to the presence of reticulocytes. **Splenomegaly** can also occur due to increased red blood cell sequestration in the spleen.

The diagnosis is made with **direct antiglobulin (Coombs) testing**, which identifies IgG or C3 (a complement fragment) attached to the erythrocyte surface. Because penicillin- and cephalosporin-induced hemolysis is primarily triggered by drug binding to the erythrocyte surface, withdrawal of the medication generally leads to resolution. Therefore, **amoxicillin should be discontinued** in this patient; a different class of antibiotics could be started if needed.

(Choices B, C, and E) Investigation for other causes of hemolytic anemia is not generally necessary when there is a clear inciting factor such as recent administration of a medication known to trigger hemolysis (eg, amoxicillin). However, in patients who do not have resolution of hemolysis after medication cessation, additional workup may be required; this often includes antinuclear antibody testing for systemic lupus erythematosus, bone marrow biopsy for leukemia, and/or liver function testing for viral hepatitis.

(Choice D) Hemoglobin electrophoresis can diagnose sickle cell disease, which causes hemolytic anemia and splenomegaly. However, most cases present in early childhood with vasoocclusive pain crises. This patient with no chronic medical history who developed hemolysis after taking amoxicillin is much more likely to have drug-induced hemolysis.

(Choice F) Splenectomy can improve platelet count in recalcitrant idiopathic thrombocytopenia. Splenectomy is not advised for drug-induced hemolysis because the hemolysis typically resolves rapidly with drug cessation.

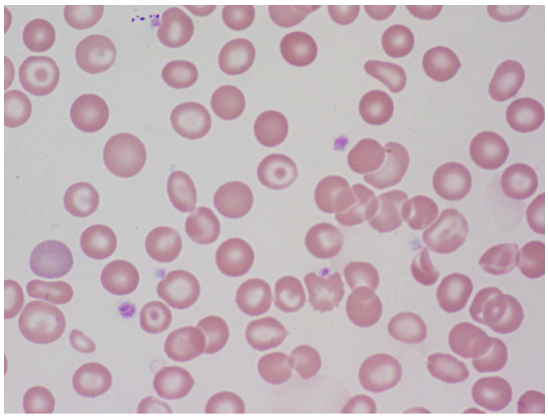
Educational objective:
Drug-induced hemolytic anemia is often triggered by penicillin and cephalosporin medications. It is marked by evidence of extravascular hemolytic anemia such as fatigue, weakness, splenomegaly, dark urine, and jaundice. Discontinuation of the offending drug usually results in complete resolution of symptoms within days. No additional workup is generally required.

Time spent:0 Seconds
QID:4437
Subject:
Medicine
System:
Hematology & Oncology (Red blood cell disorders)

A 32-year-old Italian-American man comes to the office for a routine checkup. The patient is a business executive and has been under significant stress recently. He drinks alcohol occasionally and has a 10-pack-year smoking history. Laboratory results are as follows:

Hemoglobin	10.8 g/dL
Red blood cell count	5.7 million cells/mm^3
Mean corpuscular volume	61 μm^3
Leukocytes	5,500/mm^3
Platelets	170,000/mm^3

Serial fecal occult blood tests are negative. Peripheral blood smear is shown in the image below.



Which of the following is the best treatment for this patient?

A. Cobalamin
B. Deferoxamine
C. Erythropoietin
D. Folic acid
E. Hydroxyurea
F. Iron
G. Prednisone
H. Reassurance with no specific therapy required
I. Splenectomy

Correct answer is
42% answered correctly

Explanation:

Iron deficiency anemia & thalassemias			
Parameter	**Iron deficiency anemia**	**α-Thalassemia minor**	**β-Thalassemia minor**
MCV	↓	↓	↓
RDW	↑	Normal	Normal
RBCs	↓	Normal/↑	Normal/↑
Peripheral smear	Microcytosis, hypochromia	Target cells	Target cells

Serum iron studies	↓ Iron & ferritin ↑ TIBC	Normal/↑ iron & ferritin (RBC turnover)	Normal/↑ iron & ferritin (RBC turnover)
Response to iron supplementation	↑ Hemoglobin	No improvement	No improvement
Hemoglobin electrophoresis	Normal	Normal	↑ Hemoglobin A_2
MCV = mean corpuscular volume; **RBCs** = red blood cells; **RDW** = red blood cell distribution width; **TIBC** = total iron-binding capacity.			

Microcytic anemia (eg, mean corpuscular volume [MCV] <80 μm^3) is most often due to iron deficiency or thalassemia minor. Although both can cause hypochromia and target cells, **significant microcytosis** in the setting of mild anemia and a normal (rather than low) erythrocyte count suggests **thalassemia** (abnormal alpha- or beta-globin synthesis).

Thalassemia is classified based on the number and type of globin chains affected. Mutations to 3 or 4 globin genes are usually incompatible with life or require lifelong blood transfusions. In contrast, patients with defects in 1 or 2 of the alpha-globin chains (alpha-thalassemia minima or minor) or 1 beta-globin chain (**beta-thalassemia minor**) are usually asymptomatic. Patients of **Mediterranean descent** (as in this case) are most likely to have beta-thalassemia, whereas patients from Southeast Asia are more likely to have alpha-thalassemia; electrophoresis can confirm the diagnosis.

Laboratory findings in thalassemia minor typically demonstrate mild hematocrit reduction (>28%), significantly low MCV (55-75 μm^3), and disproportionally elevated red blood cell (RBC) counts. The **disproportionately elevated RBC count** (eg, normal or high rather than low) and decreased MCV help distinguish thalassemia minor from iron deficiency anemia, which does not typically cause microcytosis until hemoglobin is <10 g/dL **(Choice F)**. Patients with thalassemia minor show no improvement in hemoglobin with iron supplementation and **do not require specific treatment**.

(Choices A and D) Cobalamin (vitamin B_{12}) and folic acid deficiency cause macrocytosis rather than microcytosis.

(Choices B and E) Deferoxamine is used to treat iron overload in those with transfusion-dependent thalassemia major or sickle cell disease (eg, sickle cells on smear). Hydroxyurea decreases the frequency and severity of pain crises in patients with sickle cell anemia by increasing hemoglobin F levels.

(Choice C) Erythropoietin (EPO) can be used to treat anemia associated with chronic kidney disease or transient bone marrow failure after chemotherapy. EPO level elevations may occur in thalassemia (in response to anemia) but cannot compensate for the hemoglobin defect.

(Choices G and I) Prednisone is the treatment of choice for autoimmune hemolytic anemia (eg, spherocytes on smear). Splenectomy can reduce erythrocyte or platelet sequestration in certain hematologic conditions (eg, hereditary spherocytosis, immune thrombocytopenia).

Educational objective:
Thalassemia minor is usually asymptomatic and no treatment is required. Patients typically have mild anemia, low mean corpuscular volume (55-75 μm^3), target cells on peripheral smear, and disproportionately high red blood cell (RBC) count. Iron deficiency anemia is associated with low RBC count and no microcytosis until hemoglobin is <10 g/dL.

A 47-year-old man comes to the office due to occasional daytime headaches, dizziness, and nausea. He has not had any chest pain, shortness of breath, or cough. He gets restful sleep and does not snore. The patient has no significant past medical history and takes no medication. He works as a traffic controller in an underground parking garage. He has smoked 2 packs of cigarettes daily for 25 years. Blood pressure is 140/90 mm Hg and pulse is 84/min. Oxygen saturation is 97% on room air. BMI is 24 kg/m^2. There is no jugular venous distension or lymphadenopathy. Pulmonary examination is unremarkable. A grade 2/6 apical holosystolic murmur is present. The abdomen is soft and nontender. The liver span is 8 cm, and the spleen is not palpable. The extremities have no cyanosis, clubbing, or edema. Neurologic examination reveals no abnormalities. Laboratory results are as follows:

Complete blood count	
Hematocrit	60%
Platelets	190,000/mm^3
Leukocytes	7,100/mm^3
Serum chemistry	
Sodium	140 mEq/L
Potassium	4.4 mEq/L
Urea nitrogen	12 mg/dL
Creatinine	0.8 mg/dL
Calcium	8.4 mg/dL
Glucose	80 mg/dL

Which of the following is most likely responsible for this patient's current condition?

A. Carboxyhemoglobinemia
B. Lung cancer
C. Nocturnal hypoventilation
D. Polycythemia vera
E. Right-to-left cardiac shunt

Correct answer is
wered correctly

Explanation:

Carbon monoxide poisoning	
Epidemiology	• Smoke inhalation • Defective heating systems • Gas motors operating in poorly ventilated areas
Manifestations	Mild-moderate • Headache, confusion • Malaise, dizziness, nausea Severe • Seizure, syncope, coma • Myocardial ischemia, arrhythmias
Diagnosis	• ABG: carboxyhemoglobin level • ECG ± cardiac enzymes
Treatment	• High-flow 100% oxygen

	• Intubation/hyperbaric oxygen (severe)
ABG = arterial blood gas.	

This patient, who is exposed to **automobile exhaust** in an enclosed space, has **intermittent headaches, dizziness, nausea**, and **polycythemia** (elevated hematocrit), most likely due to **chronic carbon monoxide** (CO) **poisoning**.

CO is a byproduct of combusting organic matter (eg, oil, gas, wood). Exposure to toxic levels is more likely in enclosed or poorly ventilated areas. CO tightly binds hemoglobin - forming **carboxyhemoglobin** - with an affinity much greater than that of oxygen. Nonsmokers have low levels (<3%) of carboxyhemoglobin (due to normal enzymatic reactions). Cigarette smokers may have carboxyhemoglobin levels as high as 10%. Even though patients at this level are generally asymptomatic, small additional amounts of CO exposure may cause toxicity manifesting as headache, malaise, and nausea.

Carboxyhemoglobin shifts the oxygen dissociation curve to the left, impairing the ability of heme to unload oxygen at the tissue level. This results in **tissue hypoxia**. The kidney responds to tissue hypoxia by producing **more erythropoietin** (EPO). EPO stimulates the bone marrow to differentiate more red blood cells. Chronic CO toxicity is a cause of **secondary polycythemia**.

Pulse oximetry does not differentiate between carboxyhemoglobin and oxyhemoglobin; it cannot be used in the diagnosis of CO poisoning. Diagnosis is made by **arterial blood gas** with cooximetry.

(Choice B) Lung cancer often presents with chest pain, cough, dyspnea, or hemoptysis. Erythrocytosis (increased red blood cell mass)/polycythemia may develop due to EPO-producing tumors (eg, renal cell carcinoma) or as part of a paraneoplastic syndrome, but this patient's intermittent symptoms and employment history make CO poisoning much more likely.

(Choice C) Nocturnal hypoventilation may cause erythrocytosis from tissue hypoxia. However, this patient with a normal BMI has restful sleep and does not snore, making many causes of nocturnal hypoventilation (eg, obstructive sleep apnea, obesity hypoventilation) unlikely.

(Choice D) Polycythemia vera is a clonal myeloproliferative disorder that causes erythrocytosis. Patients are often asymptomatic, but signs of increased blood viscosity (eg, transient neurologic symptoms, thrombosis), aquagenic pruritus, gout, and increases in all 3 cell lines are common.

(Choice E) If severe, right-to-left shunting can cause chronic systemic hypoxemia that may result in an EPO-mediated erythrocytosis. This patient's normal pulse oximetry reading makes a right-to-left shunt unlikely. His cardiac auscultation findings suggest mitral valve regurgitation; most patients with this condition are asymptomatic.

Educational objective:
Carbon monoxide poisoning should be considered in patients with environmental risk factors who present with headache, nausea, and dizziness.

Time spent:1 Seconds
Subject:
Medicine

QID:4446
System:
Hematology & Oncology (Red blood cell disorders)

A 27-year-old man comes to the emergency department (ED) with unremitting nose bleeding. He had a similar bleeding episode one year ago that was stopped in the ED. He works as a computer programmer and has a sedentary lifestyle. He drinks alcohol on social occasions but does not smoke or use illicit substances. On physical examination, there are several ruby-colored papules on his lips that blanch partially with pressure. Digital clubbing is also present. His abdomen is soft and non-tender. The liver span is 8 cm and the spleen is not palpable. Laboratory results are as follows:

Complete blood count

Hematocrit	60%
Platelets	180,000/mm^3
Leukocytes	8,000/mm^3

Which of the following is most likely responsible for this patient's increased hematocrit?

A. Polycythemia vera
B. Plasma volume loss
C. Pulmonary hypertension
D. Arteriovenous shunting
E. Carboxyhemoglobinemia
F. Hypercarbia
G. Nutritional deficiency

. Correct answer is
35% answered correctly

Explanation:

This patient most likely has **hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)**, an autosomal dominant disorder characterized by diffuse telangiectasias (eg, ruby-colored papules that blanch with pressure), recurrent **epistaxis**, and widespread **arteriovenous malformations** (AVMs).

In hereditary hemorrhagic telangiectasia, AVMs tend to occur in the mucous membranes, skin, and gastrointestinal tract, but may also be present in the liver, brain, and lung. AVMs in the lungs can shunt blood

from the right to the left side of the heart, causing chronic hypoxemia, digital clubbing, and a **reactive polycythemia**. **Pulmonary AVMs** can also present as massive, sometimes fatal, hemoptysis.

(Choice A) Polycythemia vera is a myeloproliferative disorder that typically causes increased production of all 3 blood cell lines and splenomegaly. Telangiectasias and digital clubbing are not present. In addition, the median age for patients with polycythemia vera is 60.

(Choice B) Plasma volume loss can cause spurious polycythemia by concentrating red blood cells within the vasculature. The most common causes of decreased plasma volume are diarrhea, vomiting, and poor oral intake.

(Choice C) Pulmonary hypertension and polycythemia commonly co-exist. First, polycythemia can cause pulmonary hypertension by increasing blood viscosity within the pulmonary vasculature. Additionally, in patients with chronic hypoxemia, both pulmonary hypertension and polycythemia can result. However, AVMs and pulmonary hypertension are generally not related.

(Choice E) Carbon monoxide poisoning decreases the amount of oxygen that can be carried in the blood, and the body compensates by developing a secondary polycythemia. Based on this particular patient's history and presentation, hereditary telangiectasia is a more likely diagnosis.

(Choice F) Pulmonary conditions that cause hypercarbia often also cause polycythemia, but it is not the hypercarbia itself that causes the increased red blood cell production.

(Choice G) Certain vitamin deficiencies (eg, vitamin C, vitamin K) can cause bleeding but are typically not associated with polycythemia or telangiectasias.

Educational objective:
Patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) can develop pulmonary arteriovenous malformations associated with hemoptysis and right-to-left shunt physiology. This diagnosis must be entertained in a patient with recurrent nose bleeds and oral lesions.

Time spent:1 Seconds
Subject:
Medicine

QID:4447
System:
Hematology & Oncology (Red blood cell

A 55-year-old man comes to the office for an annual visit. Medical history includes hypertension and hypercholesterolemia, for which he takes amlodipine and atorvastatin. He is adherent to his medication regimen. The patient feels well in general, but over the past few months, he has had difficulty achieving and maintaining an erection, despite having a normal libido. He drinks 2 or 3 glasses of wine daily and does not smoke. He works for a lawn care company, frequently driving the grass cutter. Blood pressure is 160/100 mm Hg and pulse is 80/min. BMI is 45 kg/m^2. Cardiopulmonary examination is normal. The abdomen is soft and nontender. The liver and spleen are not palpable. Laboratory results are as follows:

Complete blood count	
Hemoglobin	19 g/dL
Hematocrit	57%
Platelets	240,000/mm^3
Leukocytes	5,100/mm^3
Serum chemistry	
Blood urea nitrogen	14 mg/dL
Creatinine	0.9 mg/dL

Which of the following is most likely responsible for this patient's increased hematocrit?

A. Carboxyhemoglobinemia
B. Clonal proliferation of myeloid cells
C. Increased erythropoietin production
D. Plasma volume contraction
E. Testosterone deficiency

Correct answer is
56% answered correctly

Explanation:

Obstructive sleep apnea	
Pathophysiology	• Relaxation of pharyngeal muscles, leading to closure of airway • Loud snoring with periods of apnea
Symptoms	• Daytime somnolence • Nonrestorative sleep with frequent awakenings • Morning headaches • Affective & cognitive symptoms
Sequelae	• Systemic hypertension • Pulmonary hypertension & right heart failure

This patient's presentation is most consistent with **obstructive sleep apnea (OSA)**. **Obesity** (particularly BMI >35 kg/m^2) is the strongest risk factor for OSA. Not all patients have obvious respiratory symptoms (eg, snoring, gasping for air); the sequelae of OSA (eg, **erectile dysfunction**, arterial **hypertension**) may be what prompts the initial evaluation.

In patients with OSA, recurrent collapse of the pharynx during sleep results in transient airway obstruction. This causes short periods (20-40 seconds) of apnea or hypopnea, which

reduce blood oxygen levels. The kidneys respond to the hypoxemia by **increasing erythropoietin**, which stimulates the bone marrow to differentiate more red blood cells (RBCs). Therefore, it is quite common for patients with OSA to have **elevated hematocrit** levels (polycythemia).

The terms polycythemia and erythrocytosis are often used interchangeably. Polycythemia is a laboratory finding of elevated RBC count and hematocrit. Relative polycythemia is generally due to reduced plasma volume, whereas absolute polycythemia (ie, erythrocytosis) is due to increased RBC mass and can be primary (eg, polycythemia vera) or secondary (eg, due to chronic hypoxia or erythropoietin-producing tumors).

(Choice A) Carbon monoxide (CO) poisoning increases carboxyhemoglobin levels, shifting the oxygen dissociation curve to the left and resulting in tissue hypoxia. The kidneys respond by increasing erythropoietin, which may cause erythrocytosis. However, patients with CO poisoning typically have dizziness, headaches, nausea, and confusion. This patient has obesity, hypertension, and erectile dysfunction, making OSA far more likely.

(Choice B) The clonal proliferation of myeloid cells can cause erythrocytosis in polycythemia vera. Patients are often asymptomatic, but signs of increased blood viscosity (eg, transient neurologic symptoms, thrombosis), aquagenic pruritus, and gout are common.

(Choice D) Significant plasma volume contraction causes relative polycythemia because RBCs are concentrated due to lower intravascular volume. This patient's normal blood urea nitrogen and creatinine levels make significant volume contraction very unlikely.

(Choice E) Testosterone deficiency can result in erectile dysfunction. However, erythrocytosis can be caused by testosterone excess (eg, androgen use) rather than testosterone deficiency. OSA is an independent risk factor for erectile dysfunction, and treatment with continuous positive airway pressure may improve sexual function. Notably, testosterone supplementation (even to normal levels) can worsen OSA.

Educational objective:
Obstructive sleep apnea (OSA) can present without symptoms of snoring or witnessed apneic events. OSA causes transient periods of hypoxemia. The kidneys respond by increasing erythropoietin, which can result in erythrocytosis.

Time spent:1 Seconds	**QID**:4448
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 66-year-old woman comes to the office due to 2 days of increasing productive cough and low-grade fever. She was treated for community-acquired pneumonia 4 months ago and sinusitis 2 months ago. Her review of systems is positive for fatigue, generalized weakness, and right-sided chest pain. The patient is otherwise healthy and takes no medications. She has never smoked cigarettes and drinks alcohol only on rare social occasions. Temperature is 38.4 C (101.2 F), blood pressure is 126/72 mm Hg, pulse is 98/min, and respirations are 16/min. Pulse oximetry is 96%. She is well-appearing. There is mucosal pallor. There is no lymphadenopathy in her cervical or supraclavicular chains. Bronchial breath sounds and crackles are present in the left lower lung field. There is point tenderness over the right seventh and eighth ribs at the midclavicular line. The abdomen is soft with no hepatosplenomegaly. Laboratory results are as follows:

Complete blood count

Hemoglobin	9.4 g/dL
Mean corpuscular volume	88 μm^3
Platelets	235,000/mm^3
Leukocytes	13,500/mm^3

Chest x-rays shows consolidation in the left lower lung and right-sided osteolytic lesions with fractures at the seventh and eighth ribs. This patient is at increased risk for recurrent infections due to which of the following abnormalities?

A. Complement deficiency
B. Defective membrane attack complex
C. Destruction of CD4+ T lymphocytes
D. Impaired chemotaxis
E. Impaired effective antibody production
F. Impaired phagocytic oxidative metabolism

61% answered correctly

Explanation:

Multiple myeloma	
Pathophysiology	• Plasma cell neoplasm produces **monoclonal** paraprotein (immunoglobulin)
Manifestations	• Bone pain, fractures • Constitutional symptoms (weight loss, fatigue) • Recurrent infections
Laboratory	• Normocytic anemia • Renal insufficiency • Hypercalcemia (constipation, muscle weakness)

	• Monoclonal paraproteinemia **(M-spike)**
Radiology	• **Osteolytic lesions**/osteopenia (osteoclast activation)

Multiple myeloma (MM) is a monoclonal plasma cell neoplasm. **Bone marrow infiltration** by neoplastic cells causes **osteolytic lesions, fractures**, hypercalcemia (from bone destruction), and anemia. In addition, the excessive production of monoclonal protein can clog the renal tubules, resulting in renal insufficiency.

Patients with MM are prone to **infection**. Neoplastic infiltration of the bone marrow alters and impairs the normal lymphocyte population, resulting in ineffective antibody production and **hypogammaglobulinemia**. Respiratory (eg, streptococcal pneumonia) and urinary tract infections are the most common infections seen in MM.

(Choices A and B) The complement system helps form the terminal membrane attack complex. Deficiencies in this system cause problems with the innate immune system, making patients particularly vulnerable to encapsulated bacteria (eg, *Neisseria meningitides*). These are relatively rare disorders and would not account for this patient's osteolytic lesions and fractures.

(Choice C) CD4+ T lymphocytes are destroyed by HIV. HIV increases infection risk but would not account for this patient's osteolytic lesions and pathologic fractures.

(Choice D) Defective chemotaxis may contribute to recurrent infections in patients with rare genetic conditions, HIV, and bone marrow transplants. It does not contribute significantly to the predisposition to infection in patients with MM.

(Choice F) Defects in phagocytic oxidative metabolism impair the ability of phagocytes to produce reactive oxygen intermediaries that aid in the destruction of pathogens and cancerous cells. This may be seen in chronic granulomatous disease. These defects would not explain this patient's osteolytic lesions and laboratory abnormalities.

Educational objective:
Patients with multiple myeloma are at increased risk for infection due to bone marrow infiltration by neoplastic cells, which alters the normal leukocyte population and causes hypogammaglobulinemia.

Time spent:1 Seconds
Subject:
Medicine

QID:4466
System:
Hematology & Oncology (Plasma cell disorders)

A 35-year-old woman with no past medical history is hospitalized with severe shortness of breath. She also has swelling and tenderness of her right calf. CT angiogram of the chest shows pulmonary embolism. Compression ultrasonography is consistent with right femoral vein thrombosis. The patient is started on anticoagulation therapy. On the sixth day of hospitalization, she develops right arm pain. Physical examination shows a cold right upper extremity with no palpable peripheral pulse. Laboratory results are as follows:

Hematocrit	42%
Leukocytes	8,500/μL
Platelets	76,000/μL (246,000/μL at presentation)
Prothrombin time	13 sec
Activated partial thromboplastin time (aPTT)	63 sec

Which of the following drugs was most likely used to treat this patient's deep venous thrombosis?

A. Enoxaparin
B. Fondaparinux
C. Rivaroxaban
D. Unfractionated heparin
E. Warfarin

80% answered correctly

Explanation:

This patient's markedly elevated aPTT is suggestive of unfractionated heparin use. The presentation of new-onset thrombocytopenia and arterial thrombosis in the setting of heparin use is due to heparin-induced thrombocytopenia (HIT). The 2 forms of HIT differ in onset, clinical course, and severity of disease.

Type 1 HIT occurs due to a nonimmune direct effect of heparin on platelet activation and usually presents within the first 2 days of heparin exposure. The platelet count then normalizes with continued heparin therapy and there are no clinical consequences.

Type 2 HIT is a more serious immune-mediated disorder due to **antibodies to platelet factor 4 (PF4)** complexed with heparin. This leads to platelet aggregation, thrombocytopenia, and thrombosis (both arterial and venous). Platelet counts usually drop ≥50% from baseline, with a nadir of 30,000-60,000/μL. Type 2 HIT usually presents **5-10 days** after the initiation of heparin therapy and may lead to life-threatening consequences (eg, limb ischemia, stroke).

(Choice A) Enoxaparin typically does not prolong the activated partial thromboplastin time (it may in rare cases cause mild prolongation). However, the risk of HIT is lower with enoxaparin than with unfractionated heparin therapy.

(Choices B and C) The risk of developing HIT is negligible with factor X-a inhibitors such as fondaparinux and rivaroxaban.

(Choice E) Oral warfarin is typically co-administered with intravenous unfractionated heparin (or low-molecular-weight heparin) in the initial treatment of venous thromboembolism. It is not used alone due to initial hypercoagulable state from transient protein C depletion and risk of thrombosis and skin necrosis. Warfarin typically causes prothrombin time prolongation (normal in this patient) and does not affect platelet count.

Educational objective:
Heparin-induced thrombocytopenia should be suspected in patients receiving heparin anticoagulation who have thrombocytopenia, thrombosis (arterial or venous), or a >50% drop in the platelet count from baseline 5-10 days after the initiation of treatment.

Time spent:1 Seconds

QID:4616

Subject:
Medicine

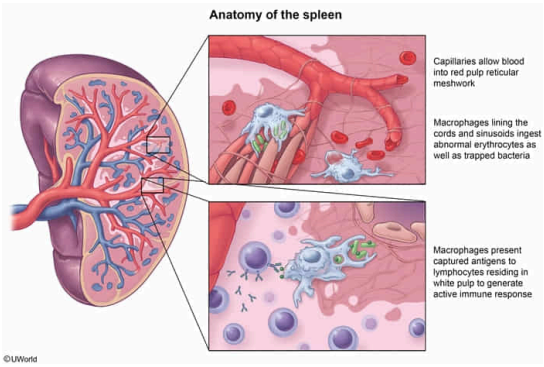
System:
Hematology & Oncology (Hemostasis and thrombosis)

A 34-year-old man is brought to the emergency department due to several hours of confusion. His wife reports that he has had fever, malaise, and cough for the past 2 days. A year ago, the patient required prolonged hospitalization and extensive surgery for multiple gunshot wounds to the abdomen. He takes no medications regularly and has no other medical problems. The patient does not use tobacco, alcohol, or illicit drugs. He has no history of recent travel. Temperature is 40.5 C (104.9 F), blood pressure is 80/50 mm Hg, pulse is 110/min, and respirations are 32/min. Mucous membranes are moist and no cervical lymphadenopathy is present. Dullness to percussion and crackles over the left lower chest are present. Cardiovascular examination reveals normal first and second heart sounds and bounding peripheral pulses. The abdomen has several well-healed surgical scars. Intravenous fluids and broad-spectrum antibiotics are initiated. The next day, blood cultures show gram-positive cocci. Which of the following is the most likely underlying mechanism leading to this patient's clinical presentation?

A. Complement deficiency
B. Destruction of CD4+ cells
C. Immunoglobulin A deficiency
D. Impaired antibody-facilitated phagocytosis
E. Impaired B cell isotype switching
F. Impaired chemotaxis
G. Impaired oxidative burst

Correct answer is
47% answered correctly

Explanation:



This patient likely had a **splenectomy** during his operation for multiple gunshot wounds to the abdomen. He now has high fever, hypotension, tachypnea, and tachycardia in the setting of bacteremia with **gram-positive cocci**, suggesting an overwhelming ***Streptococcus pneumoniae*** infection.

Encapsulated organisms such as *S pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* have a polysaccharide exterior that conceals antigenic epitopes and resists innate phagocytosis. Therefore, these pathogens are largely

eliminated via the humoral immune response with **antibody-mediated phagocytosis** (opsonization) and antibody-mediated complement activation. Much of this is dependent on **splenic** macrophages and the generation of splenic opsonizing antibodies. As such, patients with asplenia are at high risk for fulminant infection with encapsulated organisms. These patients should be immunized with pneumococcal, meningococcal, and *H influenzae* type B vaccines and take oral antibiotics early in the course of any febrile illness.

(Choice A) Deficiencies of the complement system can be inherited or acquired (eg, systemic lupus erythematosus, antiphospholipid antibody syndrome) and can increase risk of infection with encapsulated bacteria (classic complement pathway). However, such deficiencies are rare, and splenectomy is far more likely to be the cause of this patient's bloodstream infection given his history of multiple abdominal gunshot wounds.

(Choice B) CD4+ lymphocyte cells are destroyed by HIV, and patients are at increased risk of infection with a wide range of pathogenic organisms (including encapsulated bacteria). However, this patient is more likely to have asplenia with defects in antibody production and antibody-mediated phagocytosis.

(Choices C and E) Impaired B cell isotype switching is seen in some patients with common variable immunodeficiency. They have normal B cell numbers but significantly reduced Ig subtypes. Patients with common variable immunodeficiency are at risk for recurrent infections (eg, sinopulmonary, gastrointestinal) and autoimmune disease. Patients with IgA deficiency are often asymptomatic and rapid, fulminant infection is uncommon. This patient is far more likely to have had a splenectomy.

(Choice F) Chemotaxis is impaired in patients with leukocyte adhesion deficiency. Patients with this condition have recurrent bacterial infections, primarily of the skin and mucosa.

(Choice G) Patients with chronic granulomatous disease have impaired oxidative burst and often present with recurrent bacterial or fungal infections due to catalase-producing organisms (eg, *Aspergillus nidulans*, *Staphylococcus aureus*). Host response against pneumococci (catalase-negative) is not affected by oxidative burst deficiency.

Educational objective:
Patients with asplenia are at risk for fulminant infection with encapsulated bacteria (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*) due to deficits in antibody response and antibody-mediated phagocytosis/complement activation.

Time spent:2 Seconds	**QID**:4633
Subject:	**System:**
Medicine	Hematology & Oncology (White blood cell disorders)

A 32-year-old man comes to the emergency department due to a day of worsening pain and swelling in his right leg. He has no fever, chest pain, or shortness of breath. The patient was hospitalized 2 weeks ago for right lower extremity deep vein thrombosis after a minor sports injury; he was discharged on warfarin. When he left the hospital, his INR was 2.2 (goal: 2-3). The patient has been taking warfarin daily; however, due to a busy work schedule, his dietary intake has been variable and last week he missed his clinic appointment for anticoagulation monitoring. He has no other medical problems. Blood pressure is 120/70 mm Hg, pulse is 70/min, and respirations are 14/min. Examination shows moderate pretibial edema in the right leg. Today, his INR is 1.3. Platelet count, creatinine, and liver function tests are within normal limits. Venous Doppler ultrasound shows a right popliteal vein thrombus that extends into the femoral vein and is worse than on previous ultrasound. What is the best next step in management of this patient?

A. Increase warfarin dose and follow up in 3 days
B. Initiate thrombolytic therapy
C. Place inferior vena cava filter
D. Replace warfarin with rivaroxaban
E. Start low-dose aspirin

Correct answer is
40% answered correctly

Explanation:

Treatment of acute deep vein thrombosis/pulmonary embolism		
	Oral factor Xa inhibitors	**Warfarin**
Mechanism of action	Direct factor Xa inhibition	Vitamin K antagonism
Therapeutic onset	2-4 hr	5-7 days
Overlap needed?	No	Yes, overlap with UFH or LMWH for ~5 days
Laboratory monitoring	No	PT/INR
LMWH = low molecular weight heparin; **UFH** = unfractionated heparin.		

This patient was recently diagnosed with **deep vein thrombosis (DVT)**. He has been compliant with taking his warfarin, but his schedule has prevented proper anticoagulation monitoring; his DVT has now progressed in the setting of a subtherapeutic INR. The risk of pulmonary embolism (PE) is higher with proximal (eg, femoral vein, iliac vein) than distal (eg, below the knee) DVT; therefore, he needs immediate anticoagulation.

Oral direct factor Xa inhibitors (eg, **rivaroxaban**, apixaban) are as effective as warfarin in the treatment of **acute DVT or PE** and do not increase the risk of

bleeding complications. These drugs have the advantage of rapid onset of action, **no requirement for laboratory (eg, INR) monitoring**, and **no requirement for overlap therapy** with heparin. Therefore, these agents are becoming preferred for the treatment of acute DVT and PE. These drugs are an especially good option in patients who have difficulty with the dietary restrictions or frequent INR monitoring required with warfarin.

(Choice A) In this patient with a worsening DVT and an INR of <2.0, it is not appropriate to increase the warfarin dose without overlapping with heparin anticoagulation. In addition, if this patient remains on warfarin, it is likely that his diet and schedule will continue to cause issues with maintaining a therapeutic INR.

(Choice B) Thrombolytic therapy is typically reserved for hemodynamically unstable patients with PE. Less commonly, it is used for massive proximal DVT associated with significant symptomatic swelling and/or limb ischemia. It is not indicated in this patient with moderate pretibial edema and absence of hypotension and tachycardia.

(Choice C) Anticoagulation failure (eg, recurrent or extending thromboembolism while fully anticoagulated) or anticoagulation contraindication (eg, active bleeding) are indications for inferior vena cava filter placement. This patient is not considered to have anticoagulation failure as his INR is grossly subtherapeutic (he is not fully anticoagulated).

(Choice E) Aspirin is inadequate for the treatment of acute DVT.

Educational objective:
Oral direct factor Xa inhibitors (eg, rivaroxaban, apixaban) have similar efficacy to warfarin in the treatment of acute venous thromboembolism and do not increase the risk of bleeding complications. These drugs do not require laboratory monitoring or overlap therapy with heparin and are becoming preferred agents for the treatment of acute venous thromboembolism.

Time spent:1 Seconds	**QID**:4647
Subject:	**System:**
Medicine	Hematology & Oncology (Hemostasis and thrombosis)

A 29-year-old man comes to the emergency department following a motor vehicle collision. The patient is alert and oriented; trauma evaluation shows an unstable pelvis with a pelvic fracture confirmed on imaging. He receives multiple boluses of intravenous fluids and is started on a packed red blood cell transfusion. A few minutes after the transfusion starts, the patient develops shortness of breath and has an episode of nonbloody emesis. He has no chest or back pain. Temperature is 37 C (98.6 F), blood pressure is 88/40 mm Hg, pulse is 140/min, and respirations are 30/min. Pulse oximetry is 86% on 100% oxygen provided via a nonrebreather mask. The patient answers questions in short phrases. Lung examination shows decreased breath sounds bilaterally. Pulses are weak. Urinalysis is normal. Which of the following is the most likely cause of this patient's respiratory distress?

A. Anaphylactic reaction
B. Aspiration pneumonitis
C. Fat embolism
D. Hemolytic reaction from ABO incompatibility
E. Reaction from cytokines in transfused blood
F. Volume overload

Correct answer is
50% answered correctly

Explanation:

Transfusion reactions associated with hypotension			
Reaction	**Onset***	**Cause**	**Clinical features**
Anaphylaxis	Seconds to minutes	Recipient anti-IgA antibodies	• Shock, angioedema/urticaria & respiratory distress
Transfusion-related acute lung injury	Minutes to hours	Donor antileukocyte antibodies	• Respiratory distress & noncardiogenic pulmonary edema • Bilateral pulmonary infiltrates
Acute hemolysis	Minutes to hours	ABO incompatibility	• Fever, flank pain, hemoglobinuria & DIC
Bacterial sepsis	Minutes to hours	Bacterial contamination of donor product	• Fever, chills, septic shock & DIC
*Time after transfusion initiation. **DIC** = disseminated intravascular coagulation.			

This patient's rapid deterioration immediately after blood transfusion initiation is consistent with an **anaphylactic reaction**. Anaphylaxis occurs **seconds to minutes** after initiation of transfusion due to massive histamine release. Symptoms include **respiratory distress** (eg, dyspnea, hypoxia), angioedema, and **hypotension**. Wheezing is often appreciated, although decreased breath sounds can occur with severe bronchospasm preventing air entry.

Vomiting and urticaria may also be present. Without treatment, symptoms can rapidly progress to respiratory failure and **shock**.

The first step in management is to immediately **stop the transfusion** and administer **intramuscular epinephrine**. Bronchodilators and antihistamines are typically also administered. In some cases, hemodynamic and respiratory support (eg, vasopressors, mechanical ventilation) may be required.

Patients with **IgA deficiency** are at **higher risk** of anaphylactic transfusion reaction because they may have **anti-IgA antibodies** that react with donor blood IgA and contribute to histamine release. Although IgA deficiency can present with recurrent sinopulmonary infections, it is often asymptomatic and may be diagnosed only after an anaphylactic transfusion reaction. Future transfusions should include IgA-deficient plasma and washed red blood cell products.

(Choice B) Aspiration pneumonitis is caused by gastric acid aspiration, most commonly in the setting of altered mental status or dysphagia. It can lead to hypoxia but typically causes crackles and would be unexpected in a patient with no history of aspiration.

(Choice C) Fat embolism can be a complication of femoral or pelvic fracture and typically presents with respiratory distress and hypoxia. However, patients typically develop symptoms >24 hours after injury and often also have altered consciousness and petechial rash.

(Choice D) Acute hemolytic transfusion reaction from ABO incompatibility is rare but can occur due to clerical errors (eg, misidentification of patient). Patients are hypotensive but also have fever, flank pain, and hemoglobinuria.

(Choice E) Febrile nonhemolytic transfusion reaction, the most common adverse reaction to transfusion, occurs within 1-6 hours of transfusion. During blood storage, leukocytes release cytokines that, when transfused, cause transient fevers, chills, and malaise. Febrile nonhemolytic transfusion reaction is unlikely given this patient's respiratory distress, shock, and lack of fever.

(Choice F) Transfusion-associated circulatory overload is characterized by pulmonary edema due to volume overload. Patients have respiratory distress and hypoxia, but hypotension would not be expected (many patients are hypertensive).

Educational objective:
Anaphylactic transfusion reaction is characterized by a rapid onset (seconds to minutes) of respiratory distress and hypotension, which quickly progresses to respiratory failure and shock. Acute management includes immediate transfusion cessation and administration of epinephrine. IgA-deficient patients are at increased risk.

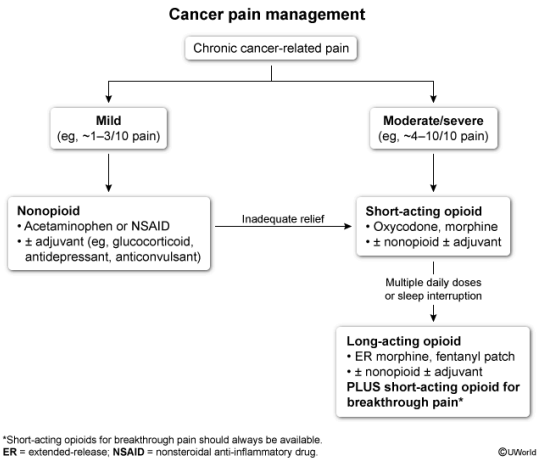
Time spent:0 Seconds
QID:4672
Subject:
Medicine
System:
Hematology & Oncology (Transfusion medicine)

A 71-year-old man with metastatic prostate cancer comes to the office due to progressively worsening back pain. The patient reports pain of 5 on a 10-point scale. The pain is notably worse with movement and limits his activity. He reports no lower extremity weakness or numbness and no bladder or bowel dysfunction. He is taking ibuprofen 3 or 4 times a day, and his pain is not controlled. The patient takes androgen deprivation therapy and has also received palliative radiotherapy for multiple lumbar spine metastases recently. Temperature is 37 C (98.6 F), blood pressure is 140/86 mm Hg, and pulse is 88/min. Lower extremity motor strength, deep tendon reflexes, and sensation are normal. Which of the following is the most appropriate initial therapy for this patient's pain?

A. Short-acting opioid
B. Substitution of ibuprofen with naproxen
C. Systemic glucocorticoid
D. Topical capsaicin
E. Transdermal fentanyl patch

Correct answer is
48% answered correctly

Explanation:



This patient has **bone metastases with progressive pain** despite specific cancer-directed treatment (ie, androgen deprivation therapy, radiotherapy).

Mild cancer-related pain can usually be managed with nonopioid analgesics (eg, acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs]). However, if nonopioid interventions are ineffective, as in this patient with **moderate to severe** (eg, >4/10) pain limiting activity despite NSAIDs, **short-acting opioids** (eg, oxycodone, morphine) should be offered. Short-acting opioids are safe and well tolerated when taken as directed, and the dose and schedule can be easily adjusted to the patient's pain pattern.

Once short-acting opioids have been started, if the patient's pain requires frequent dosing or if bedtime doses do not provide adequate relief through the night,

conversion to long-acting opioids can improve convenience (eg, less frequent dosing) and help stabilize pain control (eg, steady drug levels). Options include extended-release morphine and transdermal fentanyl. However, due to the risk of respiratory depression, patients not receiving opioids should generally **not** be started on **long-acting opioids initially (Choice E)**.

Rather, they should have a trial of short-acting opioids that can be readily titrated and then converted to a long-acting opioid dose that can be safely tolerated. This approach provides adequate analgesia while avoiding the risk of "overshoot" from the accumulation of long-acting opioids prior to reaching their steady state. Even after transition to a long-acting formulation, short-acting opioids should still be available for rescue treatment of breakthrough pain.

(Choice B) Naproxen has a longer duration of action than ibuprofen and can be used in patients who require frequent dosing. Switching from one NSAID to another can be considered for patients with mild pain, but this patient's activity-limiting pain warrants a trial of opioids.

(Choice C) Systemic glucocorticoids (eg, dexamethasone) are used urgently for the treatment of malignant neurologic compromise (eg, spinal cord compression). They are also sometimes used as adjunctive therapy in patients who have bone pain without neurologic deficits if there is incomplete improvement on opioid therapy alone.

(Choice D) Topical capsaicin is useful for mild to moderate joint and neuropathic pain (eg, postherpetic neuralgia); it is unlikely to relieve metastatic bone pain.

Educational objective:
Mild cancer-related pain can usually be managed with nonopioid analgesics. However, if initial interventions are not effective, intermittent doses of short-acting opioids should be offered. If the pain requires frequent dosing or if bedtime dosing does not provide relief through the night, then conversion to a long-acting opioid is helpful.

Time spent:1 Seconds	**QID**:2621
Subject:	**System:**
Medicine	Hematology & Oncology (Miscellaneous)

A 55-year-old woman comes to the office due to right leg swelling and tenderness. She has a history of ovarian cancer and is currently undergoing chemotherapy. A duplex venous ultrasound of the right lower extremity shows thrombosis of the right popliteal vein. The patient is sent home with subcutaneous enoxaparin. A week later, the patient returns to the office for a follow-up appointment. Laboratory results are as follows:

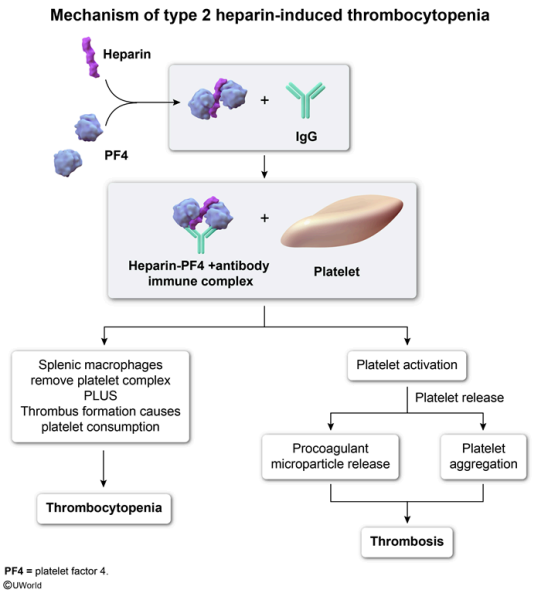
	At Discharge	**Now**
Hematocrit	44%	43%
Leukocytes	6,500/mm^3	6,100/mm^3
Platelets	210,000/mm^3	70,000/mm^3
INR	0.9	1.0

This patient's current condition predisposes her to which of the following?

A. Acute interstitial nephritis
B. Arterial thrombosis
C. Coronary vasospasm
D. Hemarthrosis
E. Mycotic aneurysm

53% answered correctly

Explanation:



This patient was initiated on low molecular weight **heparin** (enoxaparin) due to an acute deep venous thrombosis. A week later, laboratory studies show a significant reduction in platelet count, suggesting type 2 **heparin-induced thrombocytopenia** (HIT). A drop in platelets by **>50%** or a new thrombus within **5-10 days** of heparin initiation should raise suspicion for HIT (HIT may manifest sooner in patients previously exposed to heparin).

Heparin induces a conformational change to a platelet surface protein (platelet factor 4 [PF4]), which creates a neoantigen. In patients with HIT, the immune system responds by forming an IgG autoantibody (HIT antibody). HIT antibodies then coat the surface of platelets, causing:

- **Thrombocytopenia** - the reticuloendothelial system (largely the spleen) removes HIT antibody-coated platelets, causing mild to moderate thrombocytopenia (mean nadirs of 60,000/mm^3). Severe thrombocytopenia (<20,000/mm^3) is uncommon.
- **Thrombus** - HIT antibodies activate platelets, resulting in platelet aggregation and the release of procoagulant factors. This puts patients at very high risk (as high as 50%) for **arterial and venous thrombus**. Venous thrombosis in the leg veins, cardiac vessels, and skin (at the site of heparin injection) is common. Arterial thrombosis may occur in the heart, limbs, or central nervous system.

If HIT is suspected, all heparin products should be **discontinued immediately** and **anticoagulation** should be initiated with a non-heparin medication (eg, argatroban, fondaparinux). Diagnosis is confirmed by functional assay (eg, serotonin-release assay [gold standard]) or high-titer immunoassay of the blood.

(Choice A) Acute interstitial nephritis (AIN) presents with renal dysfunction and is typically caused by medications, autoimmune disorders (eg, systemic lupus erythematosus), or infections. Heparin is not commonly associated with AIN.

(Choice C) Coronary vasospasm is caused by hyperreactivity of the coronary vessels and may result in anginal symptoms. Patients with HIT are at risk for venous and arterial thrombus in the coronary vessels (not vasospasm).

(Choice D) Hemarthrosis is usually due to trauma (most common), vascular damage, or coagulopathy (eg, hemophilia). It is uncommon for HIT to cause bleeding issues.

(Choice E) Mycotic aneurysms are bacterial infections of the vascular wall that tend to occur after trauma or with preexisting aneurysm. Deep venous thrombosis typically does not put patients at increased risk for a mycotic aneurysm.

Educational objective:
Heparin-induced thrombocytopenia (HIT) is an immune-mediated process that causes thrombocytopenia several days after initiation of heparin therapy. HIT is highly thrombogenic and patients must be placed on alternate forms of anticoagulation due to the risk for arterial and venous clots.

Time spent:1 Seconds	**QID**:4859
Subject:	**System:**
Medicine	Hematology & Oncology (Hemostasis and thrombosis)

A 5-year-old boy is brought to the emergency department by his mother's boyfriend for evaluation of thigh pain. This morning, the patient bumped into the edge of a table in the living room and now has swelling and pain in the right thigh. Family history is significant for a maternal uncle who died after developing intracranial hemorrhages from a minor head injury last year. Examination shows an uncomfortable-appearing boy with marked ecchymoses and swelling over the right quadriceps. Which of the following will most likely be found on further history and examination of this patient?

A. Episodes of joint pain with swelling
B. Old, healed rib fractures
C. Pinpoint red spots on extremities
D. Red papules on the trunk and lips
E. Sister with heavy menstrual bleeding

. Correct answer is
57% answered correctly

Explanation:

Hemophilia A & B	
Inheritance	• X-linked recessive

Clinical features	• Delayed/prolonged bleeding after mild trauma
	  ◦ Hemarthrosis, intramuscular hematomas
	  ◦ Gastrointestinal or genitourinary tract bleeding
	  ◦ Intracranial hemorrhage
	• Complications: hemophilic arthropathy

Laboratory findings	• ↑ Activated PTT • Normal platelet count & PT • Absent or ↓ factor VIII (hemophilia A) or factor IX (hemophilia B) activity
Treatment	• Factor replacement • Desmopressin for mild hemophilia A

This patient's thigh **hematoma** after minor trauma and family history of a bleeding disorder in a maternal uncle are concerning for **hemophilia**. Hemophilia is an **X-linked recessive** bleeding disorder due to deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B). The most common sites of bleeding are the joints (80%), especially the knee. **Hemarthrosis** presents with **joint pain and swelling** after minimal or no trauma, and episodes typically begin during toddlerhood when the child is ambulatory. Hemorrhage into the skeletal muscle (ie, hematoma) after minor trauma is also common.

Characteristic laboratory findings include a **prolonged PTT** and **decreased or absent factor VIII or IX activity**. Treatment involves replacing the missing factor with a recombinant or purified product.

(Choice B) Posterior rib fractures are a red flag for child abuse. However, bruising on an extremity, as seen in this child, is often unintentional. Suspicious bruises include those that are patterned (eg, belt buckle, hand) or located on the neck, ear, torso, and buttocks.

(Choice C) Petechiae (pinpoint red spots) are a result of broken capillaries and are associated with platelet disorders. Platelet disorders can present with mucosal bleeding but do not typically cause bleeding into muscle.

(Choice D) Red papules on the trunk and lips represent cutaneous arteriovenous malformations. They can be seen in hereditary telangiectasia, an autosomal dominant disorder characterized by recurrent epistaxis and telangiectasias. Patients with hereditary telangiectasia are not predisposed to skeletal muscle hematomas.

(Choice E) Heavy menstrual bleeding is common in women with von Willebrand disease. Abnormalities in platelet plug formation lead to prolonged mucosal bleeding (eg, oropharyngeal, gastrointestinal, uterine), but bleeding into deep tissue is not seen.

Educational objective:
Hemophilia is an X-linked recessive bleeding disorder that can present with recurrent hemarthrosis and skeletal muscle hematoma after minor trauma.

Time spent:0 Seconds

QID:4861

Subject:
Medicine

System:
Hematology & Oncology (Hemostasis and thrombosis)

A 27-year-old woman, gravida 1 para 0, at 9 weeks gestation comes to the clinic for an initial prenatal visit. The patient has mild nausea but is otherwise feeling well. She recently completed law school and is studying for the bar examination. The patient has no known medical conditions and has had no surgeries. Her mother and sister have anemia. The patient eats fish but otherwise usually follows a vegetarian diet. Prior to this pregnancy, menses occurred monthly with 5-6 days of bleeding that was heaviest the first 2 days. The patient does not use tobacco, alcohol, or recreational drugs. Temperature is 36.7 C (98.1 F), blood pressure is 110/80 mm Hg, pulse is 76/min, and respirations are 16/min. Examination shows no abnormalities. Laboratory results are as follows:

Hemoglobin	9 g/dL
Mean corpuscular volume	75 μm^3
Leukocytes	7,000/mm^3
Platelets	300,000/mm^3
Ferritin	110 ng/mL (normal: 12-150)
Iron	90 µg/dL
Total iron binding capacity	310 µg/dL

Transvaginal ultrasound shows a 9-week intrauterine gestation with normal cardiac activity. Which of the following is the best next step in management of this patient?

A. Folate level
B. Hemoglobin electrophoresis
C. Lead level
D. TSH level
E. Vitamin B_{12} level

Correct answer is
61% answered correctly

Explanation:

During **pregnancy**, a mild **physiologic anemia** occurs due to hemodilution (increased plasma volume), but mean corpuscular volume (MCV) does not typically change. Therefore, pregnant patients with **normocytic**, mild anemia do not require additional evaluation. In contrast, microcytic and macrocytic anemias indicate pathology.

This patient at 9 weeks gestation has **microcytic anemia** (eg, **MCV <80 μm^3**). Serum iron studies (eg, iron, ferritin, total iron binding capacity [TIBC]) can help determine the underlying etiology:

- Iron deficiency is most common cause of microcytic anemia in pregnancy due to increased demand for red blood cell production. This patient's normal serum iron level and normal TIBC make iron deficiency unlikely.

- Anemia of chronic disease is associated with high ferritin (an inflammatory marker) and low iron.
- Lead toxicity inhibits heme synthesis and causes sideroblastic anemia. Lead toxicity is associated with high serum iron and ferritin because lead inhibits ferrochelatase, causing iron to accumulate; in contrast, this patient's serum iron and ferritin are normal **(Choice C)**.
- Hemoglobinopathy causes anemia due to either abnormal globin production (eg, alpha- or beta-thalassemia) or hemoglobin structure (eg, Hgb S, C, E).

In patients with microcytic anemia but **normal serum iron studies**, as seen in this patient, **hemoglobinopathy** is most likely. The best next step is **hemoglobin electrophoresis**, which would confirm the diagnosis and potentially change management. Hemoglobinopathy traits are inherited in an autosomal recessive manner. Therefore, if the mother is identified as a carrier, the father is also tested; and if both parents are carriers, genetic counseling (regarding implications for the offspring) and fetal testing (eg, chorionic villus sampling) are offered.

(Choices A and E) Folate and vitamin B_{12} requirements increase in pregnancy, and deficiency of either causes anemia. Folate deficiency is common with malnutrition or antiepileptic drug use; vitamin B_{12} deficiency may be seen with poor gastrointestinal absorption (eg, gastric bypass) or inadequate dietary intake of vitamin B_{12}–rich animal products (eg, vegetarianism). However, folate and vitamin B_{12} deficiencies cause macrocytic (MCV ≥100 μm^3) anemia.

(Choice D) Hypothyroidism typically causes anemia via decreased red blood cell mass with a normocytic MCV (80-100 μm^3) or in association with pernicious anemia (ie, macrocytic). In addition, TSH screening is not recommended for asymptomatic pregnant patients.

Educational objective:
Pregnant patients with microcytic anemia and normal iron studies require evaluation for hemoglobinopathy with hemoglobin electrophoresis.

Time spent:1 Seconds	**QID**:8894
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 53-year-old woman recently diagnosed with systemic sclerosis comes to the emergency department with headaches, increasing dyspnea, malaise, and nausea. Her medications include lansoprazole for heartburn and nifedipine for finger discoloration and pain. Physical examination reveals a distressed and anxious woman. Her blood pressure is 235/117 mm Hg and pulse is 120/min. She has visible skin tightening over the face, forearms, chest, and legs. She has difficulty opening her mouth due to tightening of the skin around the mouth. Lung examination shows bibasilar inspiratory crackles. Laboratory studies are as follows:

Hemoglobin	6.9 g/dL
Platelets	57,000/μL
Leukocytes	5,700/μL
Total bilirubin	2.2 mg/dL
Creatinine	3.8 mg/dL

Which of the following red blood cell abnormalities is most likely to be present in the peripheral blood smear?

A. Burr cells
B. Howell-Jolly bodies
C. Schistocytes
D. Spur cells
E. Target cells

68% answered correctly

Explanation:

This patient's marked hypertension and acute kidney injury in the setting of systemic sclerosis (scleroderma) suggests scleroderma renal crisis (SRC), which can occur in up to 20% of patients with diffuse cutaneous systemic sclerosis (SSc). SRC usually occurs within the first 5 years of SSc diagnosis. The likely mechanism involves increased vascular permeability, activation of the coagulation cascade, and increased renin secretion. Patients typically develop sudden onset of renal failure (without previous kidney disease), and malignant hypertension (eg, headache, blurry vision, nausea). Urinalysis can be normal or show mild proteinuria. Peripheral blood smear can show microangiopathic

hemolytic anemia (similar to hemolytic uremic syndrome/thrombotic thrombocytopenic purpura) or disseminated intravascular coagulation with fragmented red blood cells (eg, schistocytes) and thrombocytopenia.

(Choice A) Burr cells (also known as echinocytes) are spiculated appearing red blood cells (RBCs) with serrated edges that can be seen in liver disease and end-stage renal disease (ESRD). However, burr cells are less common in the acute kidney injury seen in SRC.

(Choice B) Howell-Jolly (HJ) bodies are basophilic remnants of the nucleus that appear as small, black pellets in RBCs. They are seen in patients with a history of splenectomy or functional asplenia. HJ bodies are not seen in healthy individuals as a normal spleen efficiently removes them.

(Choice D) Spur cells (acanthocytes) are RBCs with irregularly sized and spaced projections that are most commonly seen in liver disease.

(Choice E) Target cells are red blood cells with a central density surrounded by pallor (bull's eye appearance). They are usually seen in patients with hemoglobinopathies (eg, thalassemia) or chronic liver disease (especially obstructive liver disease).

Educational objective:
Scleroderma renal crisis typically presents with acute renal failure (without previous kidney disease) and malignant hypertension (eg, headache, blurry vision, nausea). Urinalysis may show mild proteinuria. Peripheral blood smear can show microangiopathic hemolytic anemia with fragmented red blood cells (eg, schistocytes) and thrombocytopenia.

Time spent:1 Seconds

Subject:
Medicine

QID:10767
System:
Hematology & Oncology (Red blood cell disorders)

A 44-year-old-man comes to the emergency department due to a day of fever, chills, and productive cough. Over the past several weeks, the patient has also had progressive fatigue and dyspnea to the point that he was unable to mow the lawn last weekend. The patient has no prior medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Temperature is 38.8 C (102 F), blood pressure is 100/60 mm Hg, pulse is 110/min, and respirations are 24/min. Examination shows mucosal pallor and scattered ecchymoses. Lung auscultation reveals left-sided crackles and bronchial breath sounds. There is no lymphadenopathy or splenomegaly. Laboratory results are as follows:

Complete blood count	
Hemoglobin	6 g/dL
Mean corpuscular volume	98 μm^3
Reticulocytes	0.3%
Platelets	17,000/mm^3
Leukocytes	2,000/mm^3
Serum chemistry	
Creatinine	0.8 mg/dL
Calcium	8.8 mg/dL
Coagulation studies	
INR	1.0 (normal: 0.8-1.2)
Activated PTT	23 sec
Lactate dehydrogenase, serum	85 U/L

Left lower lobe consolidation is seen on chest x-ray. Peripheral blood smear reveals decreased leukocytes, erythrocytes, and platelets but is otherwise unremarkable. Which of the following is the most likely cause of this patient's hematologic abnormalities?

A. Aplastic anemia
B. Bone marrow myelofibrosis
C. Deficiency in vitamin B_{12} level
D. Hairy cell leukemia
E. Multiple myeloma

Correct answer is
53% answered correctly

Explanation:

Causes of pancytopenia	
Bone marrow aplasia	• Aplastic anemia • Infection (eg, parvovirus, HIV, viral hepatitis) • Nutritional deficiency (eg, vitamin B_{12}/folate) • Medications (eg, hydroxyurea)
Bone marrow infiltration	• Cancer (eg, hematologic, metastatic) • Myelofibrosis • Infection (eg, tuberculosis, fungal infection)
Mature blood cell destruction	• Intravascular (eg, DIC, TTP) • Extravascular (eg, hypersplenism)
DIC = disseminated intravascular coagulation; **TTP** = thrombotic thrombocytopenic purpura.	

This patient with pneumonia (fever, cough, consolidation) has low leukocytes, low hematocrit (with fatigue and mucosal pallor), and low platelets (with ecchymoses). **Pancytopenia**, a decrease in all 3 blood cell lines, is usually caused by damage to hematopoietic stem cells, infiltration of the bone marrow with atypical cells, or peripheral destruction of mature blood cells. Although identifying the underlying cause

usually requires additional testing (eg, bone marrow biopsy), a presumptive diagnosis can often be made based upon laboratory and clinical findings.

In this case, the **absence of splenomegaly** and the presence of **diminished, morphologically normal** cells on peripheral smear suggest the pancytopenia is due to **aplastic anemia** (AA), a form of bone marrow failure caused by **damage to multipotent hematopoietic stem cells** (ie, which can give rise to multiple cell lines). Most cases are triggered by an alteration to stem cell surface antigens, which leads to subsequent cytotoxic T-cell destruction. Although exposures (eg, drugs, toxins, radiation), viral infections (eg, parvovirus B19), and autoimmune conditions (eg, lupus, eosinophilic fasciitis) can cause AA, most cases are idiopathic.

Patients usually present with complications of pancytopenia, including the following (seen in this patient):

- Fatigue, dyspnea, and pallor (anemia)
- Infections such as pneumonia (leukopenia)
- Bruising or bleeding (thrombocytopenia)

Laboratory evaluation will show inadequate erythropoiesis (eg, **low reticulocyte count**) and a diminished quantity of morphologically normal cells on peripheral smear. Bone marrow biopsy will demonstrate a hypocellular marrow with a few normal hematopoietic cells, no myeloid infiltration or fibrosis, and increased stroma/adipocytes.

(Choice B) Myelofibrosis is marked by collagen or reticulin deposition in the bone marrow, which can lead to diminished (or increased) peripheral blood counts. However, patients have significant hepatosplenomegaly due to extramedullary hematopoiesis, and peripheral blood smear reveals immature leukocytes and fragmented megakaryocytes.

(Choice C) Nutrient deficiencies (eg, vitamin B_{12}, folate) or antimetabolite drugs (eg, azathioprine, methotrexate) can cause impaired DNA synthesis in precursor cells. However, these are associated with megaloblastic anemia and typically lead to macrocytic (MCV >100 μm^3) erythrocytes, mild thrombocytopenia, and multilobed neutrophils on peripheral smear.

(Choice D) Malignant proliferation of mature lymphocytes is seen in chronic lymphocytic leukemia (CLL) and hairy cell leukemia (HCL). Both present with bleeding, anemia, fevers, and splenomegaly. On peripheral smear, HCL has lymphocytes with hairy projections whereas CLL has smudge cells and numerous mature lymphocytes.

(Choice E) Replacement of bone marrow by plasma cells is seen in multiple myeloma, which usually manifests with hypercalcemia, anemia, renal disease, and lytic bone lesions.

Educational objective:
Aplastic anemia is an acquired deficiency of multipotent hematologic stem cells that can result from certain exposures, viral infections, or autoimmune conditions. Patients have manifestations of pancytopenia. Cellular morphology is normal and splenomegaly is absent.

Time spent:2 Seconds
Subject:
Medicine

QID:12394
System:
Hematology & Oncology (White blood cell disorders)

A 66-year-old man comes to the office due to several months of progressive lower back pain. The pain is constant and dull and often bothers him during sleep. Initially, acetaminophen provided temporary relief but has not adequately controlled the pain lately. He has had no leg weakness, sensory loss, or bowel dysfunction. The patient is anuric due to end-stage renal disease from hypertensive nephrosclerosis, and he receives intermittent hemodialysis. He does not use tobacco, alcohol, or illicit drugs. Temperature is 37.1 C (98.8 F), blood pressure is 130/86 mm Hg, and pulse is 88/min. Back examination shows midline tenderness over the lumbar area. Lower extremity deep tendon reflexes are normal, and flexor plantar response is present bilaterally. Spine radiography reveals irregular and hyperdense areas of bony sclerosis in the L1 and L2 vertebrae. There are no other bony lesions, fractures, or dislocations. Laboratory results are as follows:

Complete blood count	
Hemoglobin	10.4 g/dL
Leukocytes	9100/mm^3
Serum chemistry	
Calcium	8.4 mg/dL
Phosphorus	5.2 mg/dL
Liver function studies	
Alkaline phosphatase	300 U/L

Which of the following is the most likely cause of this patient's lower back pain?

A. Colon adenocarcinoma
B. Metastatic prostate cancer
C. Multiple myeloma
D. Paget disease of bone
E. Renal osteodystrophy
F. Vertebral osteomyelitis

Correct answer is
29% answered correctly

Explanation:

This elderly man with several months of progressive back pain has focal lumbar tenderness, increased alkaline phosphatase, and L1/L2 sclerotic lesions suggesting osteoblastic bone disease due to **metastatic prostate cancer**.

Prostate adenocarcinoma is the most common cancer in men and often presents with manifestations of metastatic disease. Symptoms usually arise after spread to the **axial skeleton** (vertebral bodies, ribs) with resultant **progressive lower back**

pain or acute functional issues (eg, motor weakness, incontinence) from pathologic fracture or spinal cord impingement.

Unlike many other forms of metastatic cancer to the spine, prostate cancer usually causes pure **osteoblastic** lesions. This leads to normal or low serum calcium (unlike osteolytic disease), elevations in alkaline phosphatase, and imaging evidence of **focal, sclerotic bone lesions**. Further evaluation with a radionuclide bone scan and prostate-specific antigen test is required. A prostate biopsy is likely needed.

(Choice A) Colorectal cancer often causes abdominal symptoms (eg, pain, change in bowel habits, bleeding) and usually spreads to the liver and lungs. Osteoblastic bone lesions would be atypical.

(Choice C) Multiple myeloma is a plasma cell neoplasm that often presents with bone pain due to lytic lesions (not blastic lesions), hypercalcemia (not normal calcium), anemia, and renal disease.

(Choice D) Paget disease is a common disorder of bone remodeling that is often asymptomatic and diagnosed after incidentally discovering an elevated alkaline phosphatase. Radiographs typically reveal osteolytic lesions or mixed osteolytic/osteoblastic lesions (not osteoblastic alone).

(Choice E) Chronic kidney disease often causes hyperphosphatemia (as in this patient), hypocalcemia, and secondary hyperparathyroidism and is frequently associated with renal osteodystrophy. Manifestations include increased bone turnover, with radiographic evidence of widespread osteopenia and subperiosteal bone reabsorption (not focal, sclerotic lesions).

(Choice F) Vertebral osteomyelitis often causes slowly progressive back pain; however, imaging typically reveals vertebral body destruction and collapse of the disc space (not sclerotic lesions).

Educational objective:
Prostate cancer may initially present with symptoms related to metastatic disease. Spread to the axial skeleton is common, and manifestations typically include slowly progressive lower back pain or functional impairment (eg, motor weakness, incontinence). Prostate cancer usually causes osteoblastic bone lesions with normal or low calcium, elevated alkaline phosphatase, and radiographic evidence of focal, sclerotic lesions.

Time spent:1 Seconds
Subject:
Medicine

QID:12403
System:
Hematology & Oncology (Principles of oncology)

A 32-year-old man comes to the emergency department due to a persistent nosebleed lasting an hour. Over the past week, he has had several episodes of epistaxis that stopped after prolonged nose pinching. The patient has also noticed more fatigue and skin bruising than usual over the past month. He has not had any recent nasal trauma or upper respiratory tract infections and does not use any intranasal medications. The patient does not use tobacco or alcohol and maintains a vegan diet. Temperature is 37.2 C (99 F), blood pressure is 130/80 mm Hg, pulse is 96/min, and respirations are 18/min. Physical examination shows dried blood in the right nostril with no intranasal lesions. No enlarged lymph nodes are present. Lung fields are clear to auscultation and heart sounds are normal. The abdomen is soft and nontender with no hepatosplenomegaly. Scattered ecchymoses are present on the extremities. Laboratory results are as follows:

Complete blood count	
Hemoglobin	7.1 g/dL
Platelets	22,000/mm^3
Leukocytes	2,800/mm^3
Coagulation studies	
PT	20 sec (INR 1.8)
Activated PTT	44 sec
Plasma fibrinogen	140 mg/dL (normal: 200-400 mg/dL)
Lactate dehydrogenase, serum	400 U/L (normal: 60-100 U/L)

Which of the following is most likely associated with this patient's current condition?

A. Atypical promyelocytes in the bone marrow
B. Decreased plasma von Willebrand factor activity
C. Decreased serum vitamin B_{12} levels
D. Diffuse blastic lesions on bone scan
E. Mediastinal mass on chest imaging
F. Monoclonal protein on serum electrophoresis

Correct answer is
62% answered correctly

Explanation:

Acute myeloid leukemia	
Background	• Most common adult acute leukemia • Median age 65

Manifestations	• **Fatigue** is common (other B symptoms unusual)
	• Often presents with **symptoms from cytopenias**:
	  ◦ Fatigue, weakness (anemia)
	  ◦ Bleeding, bruising (thrombocytopenia)
	  ◦ Infection (granulocytopenia)
	• Hepatosplenomegaly/lymphadenopathy rare
	• Disseminated intravascular coagulation (if APML)

Laboratory	• Cytopenias (leukocytes may be ↑, normal or ↓) • Elevated lactate dehydrogenase • Peripheral smear - usually **myeloblasts** with **Auer rods**
Diagnosis	• **Bone marrow biopsy** - usually hypercellular with myeloid blasts
APML = acute promyelocytic leukemia.	

This patient with fatigue, prolonged bleeding, and easy bruising has pancytopenia, coagulopathy, and elevated lactate dehydrogenase, suggesting **acute promyelocytic leukemia** (APL), a form of acute myeloid leukemia (AML).

AML is a clonal myeloproliferative disorder characterized by the accumulation of blastic or immature myeloid cells in the bone marrow and peripheral blood. Patients often develop **fatigue** and symptoms related to ≥1 **cytopenias**, including fatigue/weakness (anemia), bleeding/bruising (thrombocytopenia), and/or infection (granulocytopenia). Examination may show pallor and ecchymosis, but lymphadenopathy and hepatosplenomegaly are rare. Leukocyte count may be elevated (sometimes >100,000/mm^3), normal, or low.

One unique type of AML is APL, which is characterized by life-threatening coagulopathy due to **disseminated intravascular coagulation** (prolonged PT/activated PTT, hypofibrinogenemia). In APL, bone marrow biopsy would reveal **atypical promyelocytes**.

(Choice B) Von Willebrand disease, an inherited bleeding disorder associated with factor VIII deficiency, is often asymptomatic but may present with mucocutaneous bleeding and easy bruising. Platelets are usually normal or mildly (not severely) low, pancytopenia is uncommon, and coagulation studies other than activated PTT should be normal.

(Choice C) Vitamin B_{12} is derived from meat ingestion; therefore, patients on a vegan diet are at increased risk of deficiency. Deficiency can cause pancytopenia, but coagulation studies should be normal.

(Choice D) Malignancies that cause diffuse blastic bone lesions may infiltrate the bone marrow, resulting in pancytopenia. Most patients with diffuse blastic lesions have bone pain from metastasis from a primary tumor in another location. In addition, coagulopathy is atypical.

(Choice E) Hodgkin lymphoma may cause a mediastinal mass, pancytopenia, and an elevated lactate dehydrogenase level. However, B symptoms (eg, fever, night sweats) and painless lymphadenopathy are usually prominent (unlike in this patient).

(Choice F) Multiple myeloma is associated with monoclonal protein on electrophoresis and may sometimes cause pancytopenia (isolated anemia is most common). However, disseminated intravascular coagulation would be unusual, and patients typically have bone pain.

Educational objective:
Acute myeloid leukemia (AML) is the most common acute leukemia in adults and is typically associated with fatigue and symptoms related to ≥1 cytopenias. Acute promyelocytic leukemia is a unique form of AML that often presents with life-threatening coagulopathy due to disseminated intravascular coagulation.

A 22-year-old woman comes to the emergency department due to continuous gum bleeding after a mouth injury a few hours ago. She was playing doubles tennis and was accidentally struck on her bottom lip by her partner's racquet. The patient has a history of bruising with minor trauma and of heavy menstruation with crampy pain. She has no other medical conditions and takes no medications other than occasional ibuprofen. The patient does not use tobacco, alcohol, or illicit drugs; she eats a balanced diet. Her mother also had a history of "bleeding issues." Blood pressure is 120/70 mm Hg and pulse is 80/min. Oropharyngeal examination shows blood oozing from a gum abrasion. A fading ecchymosis is present on the right calf, but there are no other skin abnormalities. The remainder of the physical examination is normal. Laboratory results are as follows:

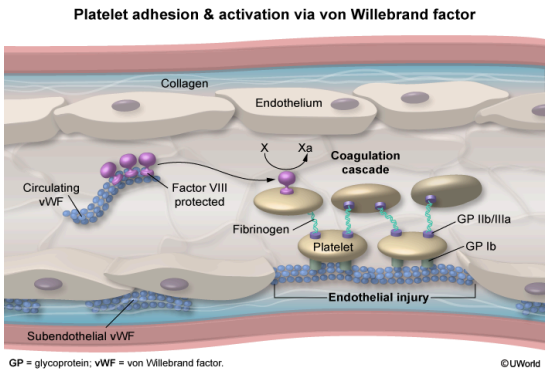
Complete blood count	
Hemoglobin	10.2 g/dL
Mean corpuscular volume	76 μm^3
Platelets	150,000/mm^3
Coagulation studies	
PT	12 sec
INR	1
Activated PTT	44 sec

Which of the following is the most likely cause of this patient's bleeding problem?

A. Abnormal activation of coagulation and fibrinolysis
B. Decreased factor VIII production
C. Factor VIII inhibitor production
D. Immune-mediated platelet destruction
E. Impaired platelet-endothelial binding
F. Reduced gamma-carboxylation of vitamin K–dependent clotting factors

. Correct answer is
57% answered correctly

Explanation:



Von Willebrand disease (vWD) is the most common inherited bleeding disorder and is typically transmitted in an autosomal dominant fashion. Therefore, a family history of prolonged bleeding is an important diagnostic clue. Most patients are asymptomatic, but a minority (~1%) have easy bruising, skin bleeding, and mucosal bleeding (eg, menstruation), which can occasionally result in iron deficiency (microcytic anemia) due to chronic blood loss.

VWD is associated with impaired quantity/activity of **von Willebrand factor** (vWF), a glycoprotein produced by endothelial cells and platelets. VWF contributes to hemostasis by:

1. Binding platelets to subendothelial components at the site of vascular injury and aggregating platelets to each other, leading to the formation of a platelet plug. Therefore, patients with vWD have impaired **platelet-endothelial binding** and platelet aggregation, which prolongs bleeding times.

2. Acting as a carrier protein for factor VIII, which is part of the intrinsic (contact activation) coagulation cascade and contributes to fibrin clot formation. Because factor VIII degrades rapidly when not bound to vWF, patients with vWD generally have low factor VIII levels, which may **prolong activated PTT**. In contrast, **PT is normal** because the extrinsic coagulation pathway is unaffected.

(Choice A) Disseminated intravascular coagulation is marked by abnormal activation of coagulation and fibrinolysis, leading to thrombocytopenia and prolonged PT/PTT. It is triggered primarily by malignancy, infection, trauma, or obstetric complication.

(Choice B) Hemophilia A, an X-linked recessive disorder that dramatically reduces factor VIII production, usually causes severe bleeding episodes (eg, soft tissue bleeding, hemarthrosis). VWD does not reduce factor VIII production (it increases factor VIII destruction).

(Choice C) Factor VIII inhibitors are antibodies that prevent factor VIII function; they usually form due to medications, autoimmune disease, malignancy, or pregnancy (postpartum period). Factor VIII inhibitors are much less common than vWD and are not generally associated with a family history of bleeding.

(Choice D) Immune thrombocytopenia is associated with the autoimmune-mediated platelet destruction, leading to easy bleeding, petechiae, purpura, or epistaxis; laboratory examination reveals thrombocytopenia and normal PT/PTT.

(Choice F) Vitamin K is a coenzyme necessary for the carboxylation of factors II, VII, IX, and X. Vitamin K deficiency/antagonists (eg, warfarin) prolong INR/PT, leading to increased bleeding risk. This patient's INR and PT are normal.

Educational objective:
Von Willebrand disease is a genetic disorder associated with impaired activity/quantity of von Willebrand factor, leading to poor platelet-endothelial binding and reduced factor VIII levels. Patients are usually asymptomatic but may have prolonged mucocutaneous bleeding, easy bruising, and prolonged PTT.

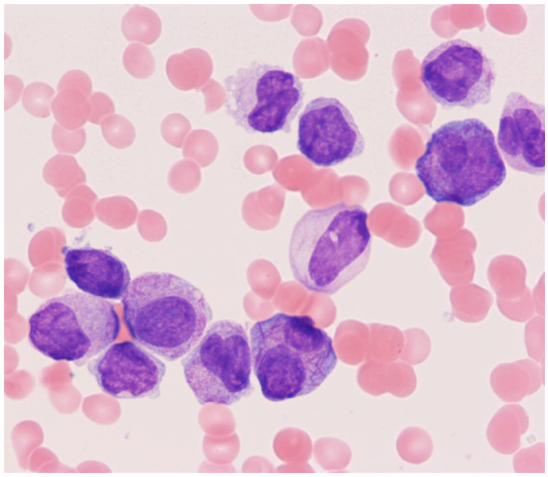
Time spent:1 Seconds
Subject:
Medicine

QID:12461
System:
Hematology & Oncology (Hemostasis and thrombosis)

A 41-year-old man comes to the office due to worsening fatigue and dyspnea on exertion. Over the past week, he has been feeling short of breath while riding his bike to work, which is unusual for him. He has had no chest pain, palpitations, syncope, or pedal edema. The patient has no prior medical conditions and takes no medications. He occasionally drinks alcohol but does not use tobacco or illicit drugs. Temperature is 37.2 C (99 F), blood pressure is 130/80 mm Hg, pulse is 96/min, and respirations are 18/min. Physical examination shows moist mucous membranes, normal thyroid, clear lungs, and normal heart sounds. The abdomen is soft and nontender with normal bowel sounds. Laboratory results are as follows.

Hemoglobin	8.8 g/dL
Platelets	78,000/mm^3
Leukocytes	2,600/mm^3

Peripheral blood smear shows numerous atypical leukocytes, some of which contain cytoplasmic inclusions, as shown below.

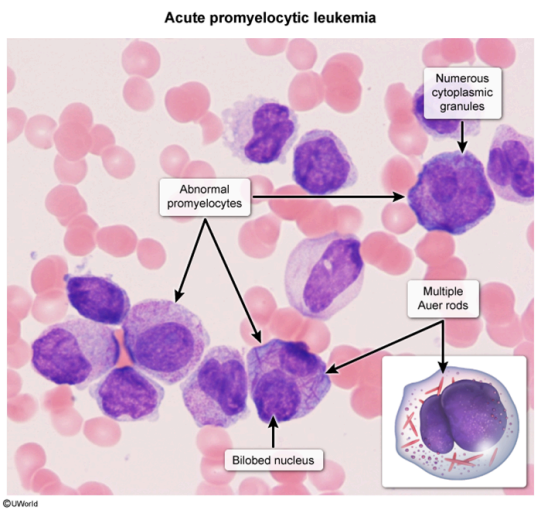


This patient is at greatest risk of which of the following due to his current condition?

A. Consumption coagulopathy
B. Hyperviscosity syndrome
C. Inflammatory myopathy
D. Spontaneous spleen rupture
E. Subacute spinal cord degeneration

Correct answer is
59% answered correctly

Explanation:



This patient's pancytopenia and atypical myeloid cells with Auer rods on peripheral blood smear raises suspicion for **acute promyelocytic leukemia (APL)**, a clinically unique form of acute myelogenous leukemia (AML) that primarily affects young and middle-aged adults.

In APL, clonal promyelocytes fill the bone marrow and interfere with normal hematopoiesis, leading to **pancytopenia** with anemia (eg, dyspnea on exertion, fatigue), thrombocytopenia (eg, bleeding complications), and neutropenia (eg, infections). The diagnosis is often suspected when a peripheral blood smear shows numerous atypical **promyelocytes** (large myeloid cells with intracytoplasmic violet granules) that contain **Auer rods** (seen with other forms of AML). However, confirmation of the diagnosis of APL requires cytogenic analysis for the characteristic mutation, the fusion of the promyelocytic leukemia gene and the retinoic acid receptor alpha gene (t[15;17]).

APL is considered a **medical emergency** due to the high risk of pulmonary/cerebrovascular **hemorrhage** from tumor-induced **consumptive coagulopathy**. Although the exact mechanism is unclear, APL appears to promote a bleeding diathesis via the activation of tissue factor (disseminated intravascular coagulation) and the increased generation of plasmin (primary hyperfibrinolysis). Urgent treatment with **all-trans retinoic acid**, which promotes differentiation of the atypical promyelocytes, is required to prevent life-threatening bleeding complications and induce long-term remission.

(Choice B) Plasma cell neoplasms, particularly Waldenstrom macroglobulinemia, can cause hyperviscosity syndrome (eg, blurred vision, diplopia, confusion). However, a peripheral blood smear generally shows rouleaux formation, not abundant atypical myelocytes with Auer rods.

(Choice C) Dermatomyositis, an inflammatory myopathy, can be associated with certain solid tumors (eg, cervical, lung, ovary, gastric, pancreatic). APL is not strongly associated with dermatomyositis.

(Choice D) Hematologic malignancies associated with massive splenomegaly (eg, myelofibrosis, splenic lymphoma) can lead to spontaneous splenic rupture. Although APL impairs hematopoiesis, significant extramedullary hematopoiesis (eg, splenomegaly) does not generally occur. Therefore, splenic rupture is not generally seen.

(Choice E) Vitamin B_{12} deficiency can cause subacute combined degeneration of the dorsal columns (leading to loss of vibratory sensation/proprioception and gait ataxia) and the lateral corticospinal tracts (leading to positive Babinski sign and hyperreflexia). This condition is often associated with megaloblastic changes on peripheral smear (eg, hypersegmented neutrophils, macrocytosis), not Auer rods.

Educational objective:
Acute promyelocytic leukemia (APL), a unique form of acute myelogenous leukemia, generally presents with symptoms related to pancytopenia. Individuals with APL are at an extremely high risk for catastrophic hemorrhage due to tumor-induced consumptive coagulopathy. Therefore, patients require urgent treatment with all-trans retinoic acid, which differentiates the abnormal promyelocytes into mature myelocytes and rapidly reduces bleeding risk.

Time spent:3 Seconds
Subject:
Medicine

QID:12465
System:
Hematology & Oncology (White blood cell disorders)

A 57-year-old woman receiving chemotherapy for stage IV Hodgkin lymphoma has severe nausea, vomiting, and general malaise. Her last bowel movement was yesterday, and she has had crampy abdominal pain on and off since the vomiting began. The patient's second cycle of chemotherapy ended 3 days ago. Her temperature is 36.7 C (98 F), blood pressure is 109/68 mm Hg, pulse is 88/min, and respirations are 18/min. Pulse oximetry reading is 95% on room air. BMI is 18 kg/m^2. Physical examination shows dry mucous membranes and enlarged cervical lymph nodes. The chest is clear to auscultation. Mild epigastric tenderness is present on abdominal palpation, but there is no guarding or rebound. Laboratory studies are as follows:

Complete blood count	
Hemoglobin	9.5 g/dL
Platelets	98,000/mm^3
Leukocytes	5,500/mm^3 (30% neutrophils)
Liver function studies	
Total bilirubin	1.2 mg/dL
Alkaline phosphatase	98 U/L
Aspartate aminotransferase (SGOT)	54 U/L
Alanine aminotransferase (SGPT)	23 U/L
Lipase	90 U/L (normal: 0-160 U/L)

Intravenous fluids are started. Which of the following is the best next step in the management of this patient?

A. Anticholinergic agent
B. Broad-spectrum antibiotics
C. Dopamine antagonist
D. Motilin receptor agonist
E. Opioid antagonist
F. Serotonin receptor antagonist

Correct answer is
49% answered correctly

Explanation:

This patient's laboratory values are relatively unremarkable aside from mild anemia and thrombocytopenia, two common findings in patients with lymphoproliferative disorders on chemotherapy. Her symptoms of **vomiting** and malaise are likely **side effects of chemotherapy**. In the setting of normal lipase

levels, an abdominal examination without rebound or guarding, and a bowel movement yesterday, other diagnoses such as pancreatitis, perforation, or bowel obstruction are less likely. The presence of dry mucous membranes suggests mild volume depletion due to vomiting; therefore, intravenous fluid administration is a good first step in this patient's management. The subsequent step would be to treat her nausea and vomiting.

Serotonin (5HT) receptor antagonists (eg, ondansetron) that target the **5HT3 receptor** are considered first-line treatment for chemotherapy-induced nausea. They have a low side-effect profile and are highly efficacious. These medications can be used to manage acute emesis but are also useful as prophylaxis, sometimes in combination with corticosteroids.

(Choice A) The primary anticholinergic agent used to treat vomiting is scopolamine, but this is usually given in the form of a patch to help reduce motion sickness. This drug is not as effective as 5HT3 antagonists for chemotherapy-induced symptoms.

(Choice B) Patients on chemotherapy, especially in the setting of a lymphoproliferative disorder, are at a higher risk for infection. However, this patient is afebrile and not neutropenic (with absolute neutrophil count >1500 cells/mm^3), making ongoing infection unlikely.

(Choice C) Dopamine antagonists such as metoclopramide and prochlorperazine are useful second- or third-line agents for refractory vomiting. However, in the setting of recent chemotherapy, 5HT3 antagonists have a better side-effect profile and are more efficacious.

(Choice D) Motilin receptors promote gastrointestinal motility. Erythromycin is primarily used as an antibiotic, but it also functions as a motilin receptor agonist and can help treat nausea secondary to gastroparesis.

(Choice E) Gastrointestinal-specific opioid antagonists such as methylnaltrexone can be used in patients to reverse opioid-induced constipation. Although severe constipation can cause nausea and vomiting, it is less likely to be a factor in this patient who had a bowel movement yesterday.

Educational objective:
Serotonin (5HT) antagonists that block 5HT3 receptors are the drugs of choice for treating and preventing chemotherapy-induced nausea and vomiting.

Time spent:4 Seconds	**QID**:2623
Subject:	**System:**
Medicine	Hematology & Oncology (Principles of oncology)

A 64-year-old woman comes to the office due to a bitemporal headache that has slowly worsened over the past week. The patient has also had dizziness, blurry vision, and tingling and numbness of her feet. She has had no fever or jaw pain. The patient has a history of hypertension, for which she takes lisinopril. She does not use tobacco or alcohol. Temperature is 37.2 C (99.0 F), blood pressure is 140/90 mm Hg, pulse is 70/min, and respirations are 16/min. Physical examination shows moist mucous membranes, normal tympanic membranes, and no sinus or temporal area tenderness. Bilateral pupils are equal and reactive. Visual acuity is decreased in both eyes, and funduscopic examination reveals dilated, segmented, and tortuous retinal veins. Facial sensation and strength are normal. Bilateral upper and lower extremity muscle strength is normal. There is decreased pinprick sensation and loss of ankle reflex bilaterally in the feet. Laboratory results are as follows:

Complete blood count	
Hemoglobin	11.2 g/dL
Platelets	180,000/mm^3
Leukocytes	8,000/mm^3
Serum chemistry	
Creatinine	0.8 mg/dL
Calcium	9.6 mg/dL
Total protein	10.5 g/dL
Albumin	3.7 g/dL
Erythrocyte sedimentation rate	80 mm/hr

Which of the following is the best next diagnostic study for this patient?

A. Antineutrophil cytoplasmic antibodies
B. Hemoglobin A1c level
C. MRI of the brain
D. Serum protein electrophoresis
E. Temporal artery biopsy

. Correct answer is
36% answered correctly

Explanation:

Waldenström macroglobulinemia vs multiple myeloma		
	Waldenström macroglobulinemia	**Multiple myeloma**
Major manifestations	• Hyperviscosity syndrome • Neuropathy • Bleeding • Hepatosplenomegaly • Lymphadenopathy	• Osteolytic lesions/fractures • Anemia • Hypercalcemia • Renal insufficiency
Monoclonal antibody	• IgM	• IgG, IgA, light chains
Peripheral smear	• Rouleaux	• Rouleaux
Bone marrow biopsy	• >10% clonal B cells	• >10% clonal plasma cells

This patient with a week of headaches, dizziness, and blurry vision has a large gamma gap (difference between total protein and albumin) and "sausage-link" retinal changes, suggesting hyperviscosity syndrome due to **Waldenström macroglobulinemia (WM)**.

WM is a B-cell malignancy characterized by the excessive production of **monoclonal IgM antibody**. IgM is a large immunoglobulin, and high levels can clog the microvasculature, resulting in **hyperviscosity syndrome**. Symptoms typically include vision changes, headaches, vertigo, dizziness, and/or ataxia; rarely, stroke or coma may occur. Other IgM-mediated conditions commonly seen in patients with WM include **peripheral neuropathy**, cryoglobulinemia, and renal insufficiency. Physical examination typically shows **"sausage-link"** (dilated, segmented, tortuous) retinal veins, and laboratory studies usually reveal anemia, a **gamma gap**, and elevated erythrocyte sedimentation rate (ESR).

The screening test for WM is **serum protein electrophoresis (SPEP)**, which can identify a monoclonal IgM spike. If positive, bone marrow biopsy is performed (lymphocytic infiltration with certain immunophenotype markers). This patient would also require serum viscosity testing as urgent plasmapheresis may be required.

(Choice A) Antineutrophil cytoplasmic antibody is associated with microscopic polyangiitis and granulomatosis with polyangiitis. Patients often have ear, nose, throat, upper airway, and renal manifestations. These conditions are usually associated with a marked elevation in ESR, but a sizable gamma gap and "sausage-link" retinal veins would be uncommon.

(Choice B) Diabetes mellitus is associated with elevated hemoglobin A1c levels and commonly causes peripheral neuropathy and retinopathy. Funduscopic examination in patients with diabetic retinopathy typically reveals hemorrhages and cotton wool spots (not "sausage-link" changes). In addition, a large gamma gap would be atypical.

(Choice C) MRI of the brain may be useful for multiple sclerosis, which can cause vision changes, sensory symptoms, and elevated ESR. However, this patient with "sausage-link" retinal changes and elevated gamma gap has neurologic symptoms likely due to hyperviscosity syndrome. She requires a SPEP and serum viscosity measurement; MRI of the brain is likely to be normal.

(Choice E) Temporal artery biopsy helps diagnose giant cell arteritis, which usually manifests in older individuals with headaches, visual changes, jaw claudication, fever, anemia, and elevated ESR. This patient has peripheral neuropathy, a gamma gap, and no jaw symptoms, making WM more likely.

Educational objective:
Waldenström macroglobulinemia is a B-cell neoplasm associated with elevated monoclonal IgM. High levels of IgM may cause hyperviscosity syndrome (vision changes, headaches, vertigo, dizziness, ataxia), peripheral neuropathy, cryoglobulinemia, and/or renal insufficiency. Diagnosis requires serum protein electrophoresis and bone marrow biopsy.

Time spent:1 Seconds
QID:12473
Subject:
Medicine
System:
Hematology & Oncology (Miscellaneous)

A 17-year-old girl is brought to the emergency department due to acute abdominal pain, nausea, and vomiting. She has no chronic medical conditions and has had no surgery. The patient has had irregular menstruation and is not sexually active. Family history is significant for deep venous thrombosis following knee replacement in her mother, who takes apixaban. Temperature is 38.3 C (101 F). BMI is 18 kg/m^2. Physical examination shows right lower quadrant abdominal tenderness. CT scan of the abdomen reveals acute appendicitis, and laparoscopic appendectomy is planned. Preoperative laboratory studies demonstrate a platelet count of 400,000/mm^3. Coagulation study results are as follows:

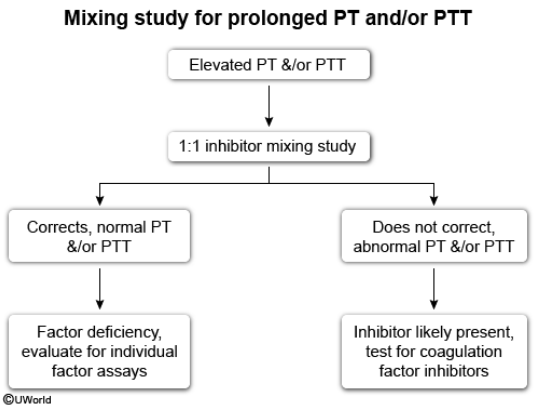
Prothrombin time	12 sec
International Normalized Ratio (INR)	1.2 (normal: 0.8-1.2)
Activated partial thromboplastin time	52 sec
Thrombin time	15 sec (normal: 14-19 sec)

Mixing the patient's plasma sample with normal plasma fails to correct the coagulation abnormalities. Which of the following best explains this patient's coagulation study results?

A. Autoantibodies against phospholipids
B. Decreased von Willebrand factor level
C. Inherited deficiency of factor IX
D. Nutritional deficiency of vitamin K
E. Uncontrolled consumption of clotting factors

Correct answer is
59% answered correctly

Explanation:



This patient's prolonged activated PTT does not correct when mixed with normal plasma. Normal plasma provides coagulation factors; therefore, it corrects prolonged PTT in the setting of coagulation factor deficiency but fails to correct prolonged PTT in the setting of a **coagulation inhibitor**.

One of the most common coagulation inhibitors is **lupus anticoagulant** (LA), a type of an **antiphospholipid antibody**. LA binds to the phospholipids used in most PTT tests and prevents them from inducing coagulation (thereby prolonging PTT). This laboratory artifact is not improved with the addition of plasma **(mixing test)** but is resolved with the addition of phospholipids (which eventually overwhelm all the antibody binding sites).

Patients with antiphospholipid antibodies may remain asymptomatic but are at increased risk for antiphospholipid-antibody syndrome, which is associated with thromboembolism and fetal loss. Most cases occur sporadically; this patient's mother's deep venous thrombus likely was related to her orthopedic surgery rather than a clotting disorder. Furthermore, the patient's thrombophilia is likely a byproduct of her infection rather than of a platelet disorder.

(Choice B) Most patients with von Willebrand deficiency are asymptomatic, but a minority develop easy bruising or mucocutaneous bleeding. PTT is sometimes prolonged because von Willebrand factor acts as a carrier for clotting factor VIII (degradation is increased in the setting of reduced von Willebrand factor). However, a mixing study would correct PTT.

(Choice C) Hemophilia B is an inherited deficiency of clotting factor IX. Although it causes prolonged PTT, it corrects with mixing studies. Furthermore, almost all cases present in early childhood and occur in male children (because it is X-linked recessive).

(Choice D) Vitamin K is found in green, leafy vegetables and is required to generate clotting factors VII, IX, X, and prothrombin. Although deficiency is rare in healthy individuals, it usually manifests with prolonged PT because of clotting factor VII deficiency. In severe cases, PTT can be prolonged, but both PT and PTT would correct with mixing studies.

(Choice E) Infections can sometimes cause disseminated intravascular coagulation, which is marked by the excessive consumption of clotting factors. However, most patients have thrombocytopenia (due to the formation of intravascular microthrombi) and prolonged PT and PTT. Furthermore, signs of bleeding (eg, oozing at venipuncture sites) and thrombosis are often present.

Educational objective:
Patients with antiphospholipid antibodies (eg, lupus anticoagulant) have prolonged PTT that fail to correct with a mixing test (combination with normal plasma). Most patients with antiphospholipid antibodies are asymptomatic, but a minority develop antiphospholipid-antibody syndrome (thromboembolism, fetal loss).

Time spent:1 Seconds	**QID**:15112
Subject:	**System:**
Medicine	Hematology & Oncology (Hemostasis and thrombosis)

A 33-year-old man comes to the office due to 6 weeks of nonproductive cough and fatigue. The patient has also had subjective fevers and a 2.26-kg (5-lb) unintended weight loss over the same period. He has no prior medical conditions and takes no medications. The patient drinks alcohol socially and has a 6-pack-year history of smoking but quit 2 years ago. Vital signs are within normal limits. Lungs are clear on auscultation, and heart sounds are normal. Chest x-ray reveals clear lung fields but an enlarged mediastinum; subsequent CT scan of the chest shows hilar and mediastinal adenopathy. A positron emission tomography scan using 18-fluorodeoxyglucose demonstrates avid tracer uptake in the brain, kidneys, urinary bladder, and supraclavicular and mediastinal lymph nodes. Which of the following is the most likely diagnosis in this patient?

A. Glioblastoma multiforme
B. Hodgkin lymphoma
C. Renal cell carcinoma
D. Small cell lung cancer
E. Transitional cell carcinoma

Correct answer is
69% answered correctly

Explanation:

This young patient with hilar and mediastinal lymphadenopathy and B symptoms (eg, fevers, weight loss) likely has **Hodgkin lymphoma**, a lymphoid neoplasm with peak incidence in **early adulthood** and in those age >60. Most cases come to clinical attention due to **painless lymphadenopathy** in the cervical and/or supraclavicular chains or after chest radiograph shows a **mediastinal mass**. B symptoms are present in approximately 40% of cases.

The diagnosis is generally made by excisional lymph node biopsy; those with no clear evidence of peripheral lymphadenopathy on physical examination usually undergo imaging to identify a potential biopsy site. **Positron emission tomography (PET) scan with 18-fluorodeoxyglucose** (FDG), an analog of glucose, is often the imaging test of choice. Neoplastic cells (eg, supraclavicular and mediastinal lymph nodes in this patient) have a high metabolic rate and readily take up radiotracer on PET scan. However, **radiotracer also pools** in healthy

organs with high glucose requirements such as the brain, kidneys, and liver; excretion of radiotracer also leads to enhancement throughout the urinary collecting system.

(Choice A) Glioblastoma multiforme would cause focal FDG uptake in the brain lesion and does not generally lead to cough or spread to the hilar or mediastinal lymph nodes.

(Choice C) Renal cell carcinoma usually metastasizes to the pulmonary parenchyma, which would be seen on PET scan.

(Choice D) Small cell lung cancer frequently spreads to the ipsilateral hilar and mediastinal lymph nodes; however, cases are rare in young adults, and a pulmonary mass is generally seen on imaging.

(Choice E) Transitional cell carcinoma would cause increased uptake of tracer in the urinary bladder, but abdominal lymphadenopathy would be seen rather than hilar or mediastinal lymphadenopathy.

Educational objective:
A positron emission tomography scan using a radiolabeled glucose analog can identify areas of enhanced metabolic activity (eg, cancer, infection). However, the tracer will also pool in healthy organs with high glucose requirements such as the brain, liver, and kidneys; uptake will also be seen in the urinary collecting system due to radiotracer excretion.

Time spent:1 Seconds	**QID**:15628
Subject:	**System:**
Medicine	Hematology & Oncology (Principles of oncology)

A 60-year-old man comes to the clinic due to 2 months of fatigue. He has also had an intermittent cough and fever, for which he takes ibuprofen. The patient is otherwise healthy and takes no other medications. He does not smoke cigarettes or drink alcohol. Weight is 72.5 kg (160 lb), decreased from 79.4 kg (175 lb) 6 months ago. Temperature is 38 C (100.4 F), and pulse is 110/min. Cervical and axillary lymphadenopathy is present. Cardiopulmonary examination is unremarkable. The liver is palpable 4 cm below the costal margin. Skin examination shows pallor but is otherwise unremarkable. Complete blood count results are as follows:

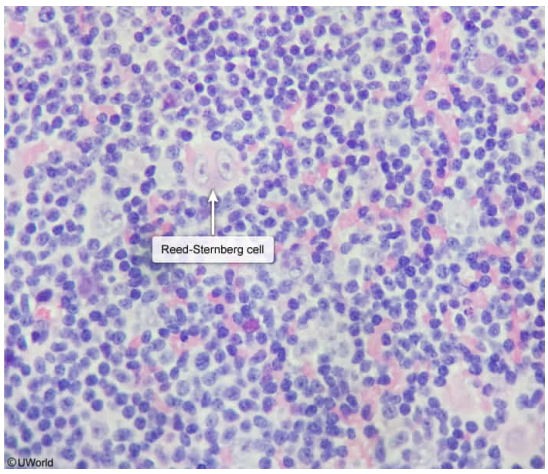
Hemoglobin	9.5 g/dL
Platelets	160,000/mm^3
Leukocytes	13,800/mm^3
Neutrophils	60%
Eosinophils	4%
Lymphocytes	32%
Monocytes	4%

Biopsy of a lymph node is shown in the exhibit. Which of the following is the best next step in evaluation of this patient?

A. Blood *BCR-ABL* PCR testing
B. Bronchoalveolar lavage
C. Liver biopsy
D. Lymph node mycobacterial culture
E. PET scan

Correct answer is
62% answered correctly

Explanation:



This patient's lymph node biopsy reveals a mixed inflammatory infiltrate with a **Reed-Sternberg (RS) cell**—a large cell with **2 nucleoli in separate nuclear lobes**, creating an "**owl's eye**" appearance. RS cells are pathognomonic for **Hodgkin lymphoma** (HL), a germinal B-cell malignancy that has peak prevalence during adolescence (age 15-19) and in those **age >50**.

Adults with HL most often have:

- **Painless lymphadenopathy** (LAD) that is typically **nontender**, rubbery, and firm; it most often occurs in the **cervical and axillary areas**.

- A **mediastinal mass** that is often asymptomatic at diagnosis but may cause chest pain, **cough**, or shortness of breath.

- **B-symptoms** that may include fever, night sweats, and **weight loss**.

Hepatomegaly and/or splenomegaly (reflecting HL involvement of these organs) can also be seen. Other, less common symptoms in adults include generalized pruritus and severe, generalized pain following alcohol ingestion.

Complete blood count can be normal (or near normal) in early disease, but many patients with HL have leukocytosis, eosinophilia, and/or ≥1 cytopenia (eg, anemia). Lactate dehydrogenase and inflammatory markers (eg, ESR) are often quite elevated due to increased cancer cell turnover or tissue destruction. Diagnosis is confirmed when excisional lymph node biopsy reveals RS cells (usually 0.1%-10% of total cells) admixed with an inflammatory cell infiltrate. A **PET scan**, which uses a radiolabeled glucose analogue to identify areas of increased metabolic activity (eg, tumors), is required for staging.

(Choice A) Chronic myelogenous leukemia is associated with a *BCR-ABL1* fusion gene, which results in a constitutively active tyrosine kinase. Patients often have nonspecific manifestations (eg, fatigue, weight loss) and splenomegaly at diagnosis. Significant leukocytosis (eg, >100,000/mm^3) is frequently present, but mildly elevated leukocytes can occasionally be seen. However, LAD is uncommon, RS cells would not be present, and immature neutrophil precursors (eg, myelocytes) and basophilia would classically be seen.

(Choice B) Bronchoalveolar lavage can identify pulmonary infections (particularly in immunosuppressed individuals) and acute eosinophilic pneumonia. Although this patient has cough, fever, and leukocytosis, the presence of LAD, hepatomegaly, and RS cells on biopsy make HL likely.

(Choice C) Although this patient has evidence of hepatomegaly on examination, excisional lymph node biopsy shows an RS cell, indicating HL. Hepatosplenomegaly can reflect HL involvement, and a PET scan should be obtained. A liver biopsy would be invasive and unlikely to provide additional information at this time.

(Choice D) Although disseminated mycobacterial infection could cause pulmonary symptoms, nonspecific manifestations, hepatomegaly, and nontender LAD, biopsy would show caseating granulomas, not RS cells.

Educational objective:
Hodgkin lymphoma often presents with painless lymphadenopathy and nonspecific symptoms. Excisional lymph node biopsy will reveal Reed-Sternberg cells—giant cells with at least 2 nucleoli in separate nuclear lobes, creating an "owl's eye" appearance. PET scan is required for staging.

Time spent:1 Seconds
Subject:
Medicine

QID:16134
System:
Hematology & Oncology (White blood cell disorders)

A 24-year-old Indian man comes to the emergency department due to 3 days of left upper quadrant abdominal pain. The pain began after he flew back from India, where he was visiting family. He has had no fever, palpitations, nausea, vomiting, or diarrhea. He does not use tobacco or alcohol regularly, but on the flight back to the United States, he had some alcohol to help him sleep. He has no chronic medical conditions and takes no medications. Temperature is 37.3 C (99.1 F), blood pressure is 120/80 mm Hg, pulse is 96/min, and respirations are 16/min. Pulse oximetry is 97% on room air. Mucous membranes are moist, and there is no jugular venous distension or palpable lymphadenopathy. Cardiopulmonary auscultation is normal. Abdominal examination reveals left upper quadrant tenderness with no rigidity or rebound guarding. Bowel sounds are present, and there is no hepatosplenomegaly. There is no lower extremity edema or skin rashes. Laboratory results are as follows:

Complete blood count

Hemoglobin	14.1 g/dL
Reticulocytes	2.5%
Platelets	220,000/mm^3
Leukocytes	10,400/mm^3

Liver function studies

Indirect bilirubin	1.7 mg/dL

Abdominal ultrasound shows normal liver size, but the spleen is slightly enlarged with a hypoechoic wedge consistent with an infarction. Which of the following would be most helpful in determining the underlying cause of his current condition?

A. 24-hour ECG monitoring
B. Bacterial blood cultures
C. Bone marrow biopsy
D. Factor V Leiden mutation testing
E. Hemoglobin electrophoresis

Correct answer is
59% answered correctly

Explanation:

This patient underwent a long plane flight and developed a **splenic infarction**, an uncommon condition that usually arises in the setting of acute splenic artery (or subbranch) occlusion; possible underlying etiologies include a hypercoagulable state, embolic disease, or hemoglobinopathy. In this patient, a mild hemoglobinopathy such as **sickle cell trait** is most likely given the mild intravascular hemolysis (eg, elevated reticulocyte count, indirect

hyperbilirubinemia), normal hemoglobin level, and negative past medical history for pain crises (making sickle cell disease unlikely).

Sickle hemoglobin mutations are often linked to Sub-Saharan Africa but are also common in other regions that have a high burden of malaria, including Central/South America, the Caribbean, the Middle East, the Mediterranean, and **India**. Most patients with sickle cell trait (eg, one altered beta-hemoglobin chain) are asymptomatic and considered benign carriers; however, certain stressors, such as **flying at high altitude** or dehydration due to **alcohol consumption**, can sometimes lead to intravascular hemolysis, tissue ischemia (eg, splenic infarction), and/or vasoocclusive pain. **Hemoglobin electrophoresis** is diagnostic.

(Choice A) 24-hour ECG monitoring can diagnose atrial fibrillation, which can cause splenic infarction due to atrial thromboembolism. However, atrial fibrillation would be unusual in a 24-year-old and does not typically cause reticulocytosis or bilirubinemia.

(Choice B) Blood cultures can diagnose infective endocarditis, which can cause splenic infarction due to septic thromboembolism. However, most patients are ill (eg, fever, chills, anorexia, weight loss) and cardiac murmur is usually present on examination.

(Choice C) Bone marrow biopsy can diagnose hematopoietic malignancies such as myelofibrosis, which may cause splenic infarction due to venous occlusion from congestive splenomegaly. However, myelofibrosis typically presents in older adults and causes splenomegaly (a hallmark feature not seen in this patient).

(Choice D) Factor V Leiden mutation is a common cause of thrombosis in middle-aged adults and typically causes venous thromboembolism, which can occasionally lead to splenic infarction. However, signs of intravascular hemolysis are not typically present.

Educational objective:
Splenic infarction usually occurs in the setting of splenic artery (or subbranch) occlusion due to hypercoagulable states, embolic disease, or hemoglobinopathy (eg, sickle cell disease or trait). Although patients with sickle cell trait are generally asymptomatic, they occasionally develop splenic infarction and intravascular hemolysis in the setting of certain stressors such as air travel or dehydration. Diagnosis of most hemoglobinopathies is made by hemoglobin electrophoresis.

Time spent:5 Seconds	**QID**:16278
Subject:	**System:**
Medicine	Hematology & Oncology (Red blood cell disorders)

A 17-year-old boy comes to the office due to fatigue. For the past 6 weeks, the patient has had difficulty attending evening soccer practice due to excessive tiredness and feverishness. He has also had generalized itching but no rash. The patient has no nasal congestion, sore throat, cough, dyspnea, abdominal pain, or diarrhea. He has no significant medical history and takes no medications. Temperature is 38 C (100.4 F), blood pressure is 118/66 mm Hg, and pulse is 86/min. Physical examination shows no scleral icterus or conjunctival pallor. There are several enlarged, nontender, and firm cervical and supraclavicular lymph nodes. Oropharyngeal mucosa and tonsils are normal. The lungs are clear on auscultation, and heart sounds are normal. The abdomen is soft and nontender with no organomegaly. There is no extremity edema or skin rash. Which of the following is most appropriate to establish a diagnosis for this patient?

A. Antinuclear antibody assay
B. Excisional lymph node biopsy
C. Heterophile antibody testing
D. Rapid plasma reagin
E. Serum erythropoietin level testing

Correct answer is
64% answered correctly

Explanation:

Hodgkin lymphoma	
Epidemiology	• Bimodal peak incidence: age 15-35 & >60 • Association with EBV in immunosuppression
Manifestations	• Painless lymphadenopathy • Mediastinal mass • B symptoms (ie, fever, sweats, weight loss) • Pruritus
Diagnosis	• Lymph node biopsy • Reed-Sternberg cells on histology
EBV = Epstein-Barr virus.	

This young patient's subacute fever, pruritus, fatigue, and painless cervical and supraclavicular lymphadenopathy (LAD) raise strong suspicion for **Hodgkin lymphoma** (HL). Cases generally arise in a bimodal distribution, with peak incidence in patients **age 15-35** and >60.

HL usually arises in a single lymph node and disseminates to contiguous nodes via the lymphatic and thoracic ducts. Patients generally present with **painless peripheral LAD**, particularly in the **cervical and supraclavicular** chains. Significant

mediastinal LAD also occurs in ~50% of cases and may lead to cough, shortness of breath, or chest pain. Most patients have long-standing B symptoms (eg, **fever**, night sweats, weight loss) and **pruritus** (a paraneoplastic process classically associated with HL and likely due to cytokine and interleukin release).

Individuals with unexplained LAD and findings concerning for malignancy (eg, supraclavicular LAD) require **excisional lymph node biopsy**. Malignant Reed-Sternberg cells admixed with nonneoplastic inflammatory cells are diagnostic of HL.

(Choice A) Antinuclear antibodies are elevated in systemic lupus erythematosus (SLE), which can cause fatigue, fever, and painless peripheral LAD in the cervical, axillary, or inguinal chains. However, supraclavicular LAD is quite uncommon and strongly suggests malignancy. In addition, this patient has no diagnostic features of SLE (eg, malar rash, arthralgia, serositis).

(Choice C) Heterophile antibody testing can diagnose infectious mononucleosis, which often causes fatigue, fever, and peripheral LAD (primarily in the cervical chain). However, most patients have sore throat and evidence of pharyngitis on examination, and almost all cases resolve within a month. In addition, LAD tends to be tender (not nontender), and splenomegaly is common. Therefore, heterophile antibody testing is unlikely to establish a diagnosis in this patient.

(Choice D) Rapid plasma reagin testing can assist in the diagnosis of syphilis. Secondary syphilis often causes painless peripheral LAD (characteristically in the epitrochlear nodes). However, supraclavicular LAD is uncommon, and most patients have a diffuse, symmetric maculopapular rash that includes the palms and soles.

(Choice E) Erythropoietin level testing is part of the diagnostic workup for polycythemia vera, which is a chronic myeloproliferative disorder associated with elevated red blood cell mass. Although this disease is often associated with aquagenic pruritus (itching with warm water exposure), LAD does not generally occur. In addition, most cases occur in patients age >60.

Educational objective:
Hodgkin lymphoma often presents with painless peripheral lymphadenopathy (LAD) in the cervical and/or supraclavicular chains. Patients may also have mediastinal LAD, B symptoms, and pruritus. Diagnosis is usually made with excisional lymph node biopsy (Reed-Sternberg cells).

Time spent:1 Seconds
Subject:
Medicine

QID:16585
System:
Hematology & Oncology (White blood cell disorders)

A 65-year-old man is brought to the emergency department due to chest pain. The patient has had fatigue, retrosternal heaviness, and a nonproductive cough for several weeks. Today, he developed severe chest pain after drinking a beer at a retirement party. The patient has no chronic medical conditions but has been taking diphenhydramine for the last month due to generalized pruritus. He does not smoke but drinks alcohol socially. Temperature is 36.5 C (97.7 F), blood pressure is 132/84 mm Hg, and pulse is 86/min. Physical examination shows clear lungs and normal heart sounds. ECG reveals sinus rhythm with no ST-segment or T-wave changes. Chest x-ray reveals a large, anterior mediastinal mass displacing the trachea. Laboratory results are as follows:

Complete blood count	
Hemoglobin	10.8 g/dL
Mean corpuscular volume	92 μm^3
Platelets	240,000/mm^3
Leukocytes	11,000/mm^3
Neutrophils	70%
Eosinophils	10%
Lymphocytes	18%
Monocytes	2%
Serum lactate dehydrogenase	820 U/L
Serum troponin I	normal

Which of the following is the most likely diagnosis for this patient?

A. Germ cell tumor
B. Histoplasmosis
C. Hodgkin lymphoma
D. Sarcoidosis
E. Thymoma

. Correct answer is
48% answered correctly

Explanation:

Hodgkin lymphoma	
Epidemiology	• Bimodal peak incidence: age 15-35 & >60 • Association with EBV in immunosuppression
Manifestations	• Painless lymphadenopathy • Mediastinal mass • B symptoms (ie, fever, sweats, weight loss) • Pruritus
Diagnosis	• Lymph node biopsy • Reed-Sternberg cells on histology
EBV = Epstein-Barr virus.	

This patient with a large **anterior mediastinal mass**, pruritus, alcohol-associated pain, elevated lactate dehydrogenase (LDH), and eosinophilia likely has **Hodgkin lymphoma** (HL).

HL is a lymphoid neoplasm that most often affects those age 15-35 or **>60**. It generally develops in a single lymph node and spreads to contiguous nodes via the lymphatic and thoracic ducts. Although most patients have painless peripheral lymphadenopathy in the cervical/supraclavicular chains, approximately 50% have significant **mediastinal lymphadenopathy**. This can compress adjacent structures and cause a nonproductive **cough**, shortness of breath, and/or **retrosternal pain**.

Patients with HL occasionally have severe pain in areas of lymphadenopathy (eg, chest) following exposure to small quantities of **alcohol** (eg, drinking a beer). The etiology is unclear, but the pain may be due to alcohol-induced vasodilation within the lymph nodes, causing capsular distension. Patients also frequently have long-standing fatigue, B symptoms, and pruritus. Laboratory evaluation often reveals normocytic anemia, **eosinophilia** (tumor cells secrete cytokines that generate eosinophils), lymphopenia, and **elevated LDH** (associated with high tumor burden). Lymph node biopsy showing Reed-Sternberg cells is diagnostic.

(Choice A) Germ cell tumors can also cause an anterior mediastinal mass, compressive symptoms (eg, nonproductive cough), and elevated LDH levels. However, the tumors most often arise in individuals age 20-40 (vs 65), and eosinophilia is uncommon. In addition, pain does not typically worsen with exposure to alcohol, and pruritus is unexpected.

(Choice B) Histoplasmosis occasionally causes a mediastinal mass (eg, due to granuloma formation). However, most patients have pulmonary infiltrates, fever, and other systemic symptoms (eg, headache, myalgia). In addition, eosinophilia is uncommon, and there is often an antecedent history of exposure to bird (eg, chicken coop) or bat (eg, cave) droppings.

(Choice D) Sarcoidosis can present with chest pain, cough, anemia, and eosinophilia. However, it is usually characterized by hilar (vs mediastinal) lymphadenopathy, and most cases arise in young adults. ACE (vs LDH) is usually elevated.

(Choice E) Thymomas often cause an anterior mediastinal mass, and their growth can cause compressive symptoms (eg, nonproductive cough). However, eosinophilia is uncommon, and alcohol-associated pain and pruritus suggest HL. In addition, patients with thymoma often develop paraneoplastic myasthenia gravis.

Educational objective:
Hodgkin lymphoma is a common cause of a mediastinal mass that often presents with compressive symptoms (eg, cough, shortness of breath, retrosternal pain). Peripheral lymphadenopathy, B symptoms, pruritus, and alcohol-associated pain may also be present. Laboratory evaluation often reveals elevated serum lactate dehydrogenase and eosinophilia.

Time spent:1 Seconds
Subject:
Medicine

QID:16586
System:
Hematology & Oncology (White blood cell disorders)

A 28-year-old man comes to the office for follow-up. Two years ago, he was diagnosed with early-stage nodular sclerosis Hodgkin lymphoma after a chest x-ray revealed a mediastinal mass. The patient underwent combination chemotherapy and radiation treatment. Follow-up imaging has revealed no evidence of disease, and he currently feels well. The patient has no other medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Vital signs and physical examination are normal. Compared to the general population, this patient is at greatest risk for which of the following?

A. Diabetes mellitus
B. Osteoporosis
C. Primary sclerosing cholangitis
D. Rheumatoid arthritis
E. Solid organ malignancy

Correct answer is
79% answered correctly

Explanation:

Patients with **Hodgkin lymphoma** (HL) are generally treated with combination **chemotherapy and radiation therapy**, which cures >75% of cases. However, these treatments are associated with serious **long-term complications**, including:

- **Secondary malignancy**: Radiation exposure increases the risk of **solid organ** (eg, breast, lung) malignancy, and chemotherapy increases the risk of hematologic malignancy. Most cases arise >5 years after treatment. Secondary malignancies are the **leading cause of death** in those who have been cured of HL.
- **Cardiovascular disease**: Risk of coronary artery disease, valve damage, peripheral vascular disease, and cardiomyopathy are increased in those who have been treated for HL.

Cardiovascular disease is the leading nonmalignant cause of death in long-term HL survivors.

Other common treatment-related complications include pulmonary disease (eg, fibrosis, bronchiectasis) and hypothyroidism from chest radiation and neuropathy from chemotherapy.

(Choice A) Survivors of HL do not have an increased risk of diabetes mellitus (DM). However, patients who have concomitant DM are at increased risk for cardiovascular complications of treatment.

(Choice B) Early osteoporosis is often seen in those who take glucocorticoids, anticonvulsants, and antidepressants; risk is also increased in those who have disorders of calcium metabolism due to inflammatory bowel disease, celiac disease, hyperthyroidism, and hyperparathyroidism. It is not linked to treatment for HL.

(Choice C) Primary sclerosing cholangitis often occurs in patients with ulcerative colitis (and to a lesser extent, Crohn disease). It is not linked to treatment for HL.

(Choice D) Rheumatoid arthritis can increase the risk of developing lymphoma due to chronic immune activation and treatment with alkylating agents (eg, azathioprine, methotrexate). However, lymphoma does not increase the risk of developing rheumatoid arthritis.

Educational objective:
Hodgkin lymphoma is generally treated with combination chemotherapy and radiation therapy. Although >75% of patients are cured, treatment can lead to long-term complications, most notably secondary malignancy (eg, solid organ, hematologic) and cardiovascular disease.

Time spent:1 Seconds

QID:16590

Subject:
Medicine

System:
Hematology & Oncology (White blood cell disorders)

A 35-year-old man comes to the office due to concern that his HIV medication is no longer working. Over the last 6 weeks, the patient has had intermittent fevers and awakened several times drenched in sweat. He has not used injection drugs since he was diagnosed with HIV a year ago, and he lives in a house with other individuals recovering from substance use disorder. The patient takes antiretroviral therapy and trimethoprim-sulfamethoxazole. Temperature is 37.9 C (100.2 F), blood pressure is 126/72 mm Hg, and pulse is 102/min. Physical examination reveals several enlarged cervical, supraclavicular, and epitrochlear lymph nodes that are rubbery and mobile. Cardiopulmonary examination is normal, and no organomegaly is present on abdominal examination. There is no rash. Chest x-ray reveals an enlarged cardiac silhouette. Current CD4 count is 208/mm^3 and the viral load is undetectable. Which of the following underlying pathogens is most likely responsible for this patient's symptoms?

A. *Bartonella henselae*
B. Cytomegalovirus
C. Epstein-Barr virus
D. Hepatitis C virus
E. Human papillomavirus
F. *Toxoplasma gondii*

Correct
57% answered correctly

Explanation:

This patient with HIV has diffuse lymphadenopathy (LAD), intermittent fevers, and night sweats. Although this constellation of findings can be seen in untreated HIV, the presence of an undetectable viral load indicates compliance with antiretroviral therapy. Therefore, the differential diagnosis primarily includes hematologic malignancy, rheumatic disease, and other systemic infections. Given the presence of supraclavicular, epitrochlear, and mediastinal LAD, a lymphoid neoplasm such as **non-Hodgkin lymphoma** (NHL) is most likely.

Patients with HIV are at a dramatically elevated risk of **malignancy** due to immune dysregulation and impaired cytokine signaling. This limits the ability of patrolling cytotoxic T-cells to induce apoptosis in cells that have accumulated genomic mutations. It also promotes reactivation of **latent oncogenic viruses**, which can cause AIDS-defining malignancies such as invasive cervical carcinoma (human papillomavirus), Kaposi sarcoma (human herpesvirus 8), CNS system lymphoma (Epstein-Barr virus [EBV]), and NHL.

Approximately 10% of patients with AIDS develop NHL; nearly all cases in this population are linked to the **reactivation of EBV** and the subsequent production of oncogenic viral proteins. Major manifestations include **diffuse LAD**, which may involve the epitrochlear, supraclavicular, and mediastinal (enlarged cardiac

silhouette) lymph nodes. **B symptoms** (eg, night sweats, fevers, weight loss) are generally present. Diagnosis is usually made by excisional lymph node biopsy.

EBV is also associated with development of Hodgkin lymphoma, which can develop in patients with HIV, although NHL is more common in this population (possibly reflecting the immune interaction between Reed-Sternberg cells and nonmalignant inflammatory cells needed for the development of Hodgkin lymphoma).

(Choice A) *Bartonella henselae*, the causative pathogen of catscratch disease, can cause regional LAD in the epitrochlear, supraclavicular, and cervical chains. However, the LAD is usually tender and erythematous, and mediastinal LAD is atypical.

(Choice B) Cytomegalovirus is a common pathogen in patients with advanced AIDS; it frequently attacks the gastrointestinal tract and retina. Although this virus can cause an infectious mononucleosis–like illness with significant peripheral LAD (eg, cervical, axillary, inguinal), the presence of supraclavicular, mediastinal, and epitrochlear LAD is more consistent with a lymphoid malignancy (CMV is not oncogenic).

(Choice D) Although hepatitis C virus causes chronic immune stimulation, which increases the risk for lymphoma, patients with AIDS develop NHL almost exclusively due to EBV reactivation.

(Choice E) Human papillomavirus is oncogenic and contributes to invasive cervical and esophageal cancers. It has tropism for epithelial cells, not B-lymphocytes, so it does not increase risk of lymphoma.

(Choice F) *Toxoplasma gondii* is a common cause of encephalitis in patients with advanced AIDS. Although disseminated toxoplasmosis can be associated with diffuse LAD, this patient is on prophylaxis (trimethoprim-sulfamethoxazole) for this infection.

Educational objective:
Patients with HIV are at significantly increased risk of malignancy due to immune dysregulation and reactivation of oncogenic viruses. One of the most common malignancies is non-Hodgkin lymphoma, which is due to the reactivation of the Epstein-Barr virus in B-lymphocytes. Patients generally present with diffuse lymphadenopathy and B symptoms.

Time spent:2 Seconds	**QID**:16776
Subject:	**System:**
Medicine	Hematology & Oncology (White blood cell disorders)

A 47-year-old woman with a long-standing history of systemic lupus erythematosus (SLE) comes to the office due to a month of worsening fatigue and low-grade fevers. She has lost 4.6 kg (10 lb) during this time but has no joint pain, cough, dyspnea, or chest pain. Other medical conditions include hypertension, hypothyroidism, and anemia of chronic disease. The patient takes hydroxychloroquine for SLE and uses glucocorticoids intermittently for acute symptom flares. Temperature is 37.5 C (99.5 F), blood pressure is 132/84 mm Hg, pulse is 78/min, and respirations are 14/min. Physical examination shows no scleral icterus, oral ulcers, or skin rashes. The cervical and axillary lymph nodes are enlarged. The lungs are clear on auscultation, and heart sounds are normal. The abdomen is soft and nontender with no organomegaly. There is no extremity edema or joint tenderness. Laboratory results are as follows:

Complete blood count	
Hemoglobin	11 g/dL
Mean corpuscular volume	82 μm^3
Platelets	225,000/mm^3
Leukocytes	6,200/mm^3
Serum chemistry	
Blood urea nitrogen	14 mg/dL
Creatinine	1.1 mg/dL
Lactate dehydrogenase, serum	828 U/L
TSH	2.2 µU/mL

Which of the following is the most likely cause of this patient's current condition?

A. Acute lymphoblastic leukemia
B. Infectious mononucleosis
C. Medication adverse effect
D. Non-Hodgkin lymphoma
E. Tuberculosis infection

Correct answer is
59% answered correctly

Explanation:

This patient with long-standing systemic lupus erythematosus (SLE) has fatigue, low-grade fevers, and lymphadenopathy. Although these symptoms can be seen in the setting of an acute SLE flare, additional manifestations of the disease (eg, joint symptoms, rash, oral ulcers, serositis) are usually present. Furthermore, patients with well-controlled SLE rarely have significant weight loss and elevated lactate dehydrogenase (LDH) levels. Given this constellation of findings, the most likely diagnosis is **non-Hodgkin lymphoma** (NHL).

Patients with **chronic autoimmune diseases** (eg, SLE, Sjögren syndrome) are at increased risk for NHL due to persistent B-cell stimulation, immune dysregulation, and exposure to immunosuppressive agents (eg, hydroxychloroquine). NHL often presents with progressive, **painless lymphadenopathy** and **B symptoms** (eg, weight loss, fever, night sweats). Laboratory evaluation often reveals **elevated LDH**, likely due to tumor burden, liver involvement, or occasional hemolysis. Confirmation is usually made by excisional lymph node biopsy.

(Choice A) Although the risk of most lymphoproliferative disorders is elevated in patients with autoimmune disease, acute lymphoblastic leukemia generally manifests in children, not adults. Bone pain is often a prominent complaint. In addition, complete blood count usually shows significant neutropenia and thrombocytopenia, with a white blood cell count that can be decreased or markedly elevated.

(Choice B) Infectious mononucleosis often causes peripheral lymphadenopathy, fatigue, and low-grade fever, but most patients have a sore throat/pharyngitis. Furthermore, significant weight loss and LDH elevation would be atypical.

(Choice C) Certain medications (eg, phenytoin) can cause painless peripheral lymphadenopathy with or without signs of serum sickness (eg, fever, rash, arthralgia). However, hydroxychloroquine does not typically cause these manifestations.

(Choice E) Tuberculosis is a leading cause of peripheral lymphadenopathy in the developing world. Although it is more likely to arise in those taking immunosuppressive agents, patients with tuberculosis lymphadenopathy rarely have systemic manifestations such as fevers or weight loss. Those with disseminated tuberculosis usually have pulmonary symptoms.

Educational objective:
Patients with chronic autoimmune diseases are at increased risk for lymphoproliferative disorders such as non-Hodgkin lymphoma (NHL) due to chronic B-cell stimulation, immune dysregulation, and use of immunosuppressive agents. NHL often presents with painless lymphadenopathy and B symptoms.

Time spent:3 Seconds
Subject:
Medicine

QID:16777
System:
Hematology & Oncology (White blood cell disorders)

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A 74-year-old man comes to the office for follow-up. He was diagnosed with chronic lymphocytic leukemia 2 years ago during evaluation for diffuse lymphadenopathy. The patient has had no other symptoms and has received no treatment for the disease. However, he now has significant fatigue, and laboratory evaluation reveals worsening lymphocytosis and anemia. Treatment with combination chemotherapy is planned. Which of the following therapies is most likely to reduce this patient's risk of developing acute kidney injury during treatment initiation?

A. Calcitonin
B. Leucovorin
C. N-acetylcysteine
D. Normal saline
E. Sodium bicarbonate

Correct answer is
75% answered correctly

Explanation:

Tumor lysis syndrome	
Risk	• Tumors with high cell burden or rapid turnover • Combination chemotherapy/immunotherapy
Manifestations	• Severe electrolyte abnormalities ◦ ↑ Phosphorus, potassium, uric acid ◦ ↓ Calcium • Acute kidney injury • Cardiac arrhythmias • Seizures
Prophylaxis	• Intravenous fluids • Xanthine oxidase inhibitor* or rasburicase
Treatment	• Intravenous fluids + rasburicase • Continuous telemetry • Aggressive electrolyte monitoring & treatment
*Allopurinol or febuxostat.	

Patients who have a malignancy with a high tumor burden (eg, chronic lymphocytic leukemia) or a rapid cell turnover rate are at risk for **tumor lysis syndrome** (TLS) with the initiation of **cytotoxic chemotherapy** or immunotherapy. TLS is caused by the massive release of intracellular contents into the circulation due to widespread tumor cell death. It is generally marked by significant

electrolyte abnormalities (eg, hyperkalemia) and **acute kidney injury**, which is due to the following:

- **Hyperuricemia:** Lysed tumor cells release purine nucleic acids into the circulation, which are subsequently metabolized by xanthine oxidase into **uric acid**. Because uric acid is poorly soluble in the renal tubules and collecting system, it precipitates into obstructing urate crystals.
- **Hyperphosphatemia:** Phosphate levels in tumor cells are up to 3 times higher than in normal cells. Therefore, widespread tumor cell lysis is usually associated with hyperphosphatemia. Phosphate is subsequently excreted into the renal tubules and collecting system, where it binds to calcium and causes obstructing calcium-phosphate stones.

TLS prophylaxis generally includes a **normal saline infusion** to flush the renal system and prevent crystal deposition and an agent (eg, allopurinol, rasburicase) to reduce systemic uric acid levels.

(Choice A) Calcitonin increases renal excretion of calcium and decreases bone resorption by inhibiting osteoclasts. It is used primarily for severe hypercalcemia (eg, due to hypercalcemia of malignancy).

(Choice B) Leucovorin is administered in patients receiving methotrexate (eg, some leukemias) or other folic acid antagonists to prevent adverse events from damage to rapidly dividing cells in the gastrointestinal system and liver.

(Choice C) N-acetylcysteine, an antioxidant precursor to glutathione, is used primarily for acetaminophen poisoning and acute liver failure.

(Choice E) Sodium bicarbonate alkalinizes the urine. Although uric acid is more likely to precipitate in acidic urinary environments, studies have shown that urinary alkalization does not reduce the risk of kidney injury in TLS. It is generally reserved for patients with TLS who have severe metabolic acidosis.

Educational objective:
Patients who undergo initial cytotoxic chemotherapy or immunotherapy for hematologic malignancies with high tumor burden or rapid division rate are at risk for tumor lysis syndrome due to the massive release of intracellular tumor products into the circulation. Major manifestations include electrolyte abnormalities and renal insufficiency due to the precipitation of uric acid and calcium-phosphate. Renal injury can often be prevented with intravenous fluids to flush the kidneys and uric acid inhibitors to reduce serum uric acid levels.

Time spent:0 Seconds
QID:18770
Subject:
Medicine
System:
Hematology & Oncology (Principles of oncology)

A 68-year-old man comes to the office due to 2 weeks of worsening fatigue and exertional dyspnea. The patient was diagnosed with early-stage chronic lymphocytic leukemia a year ago but has not required treatment because he has not had significant symptoms. Vital signs are within normal limits. Physical examination shows generalized lymphadenopathy and hepatosplenomegaly. Laboratory results are as follows:

Complete blood count

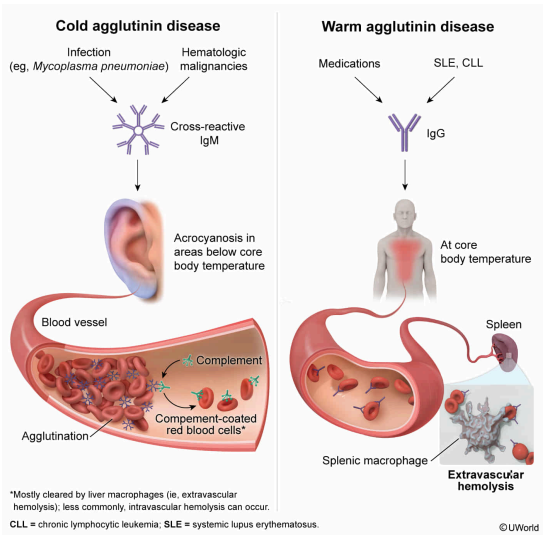
Hemoglobin	7.1 g/dL
Reticulocytes	10%
Platelets	210,000/mm^3
Leukocytes	44,800/mm^3 (80% lymphocytes)

Hemoglobin was within normal limits a month ago. Which of the following is the most likely underlying cause of this patient's anemia?

A. Cytokine-mediated iron dysregulation
B. Folate consumption by leukemic cells
C. Immune-mediated hemolysis
D. Leukemic bone marrow infiltration
E. Selective suppression of erythroid precursors

Correct answer is
43% answered correctly

Explanation:



This patient's fatigue, exertional dyspnea, and low hemoglobin suggest **acute symptomatic anemia**. Although anemia can be triggered by a wide

range of conditions, concurrent clinical data often narrows the differential diagnosis.

In this case, a **high reticulocyte count** suggests that there are adequate levels of iron, folate, and vitamin B_{12}, to generate new erythrocytes, which makes cytokine-mediated iron dysregulation (eg, anemia of chronic disease) and folate deficiency (eg, leukemic folate consumption) unlikely **(Choices A and B)**. It also suggests that the bone marrow is responding appropriately to the anemia by increasing the production of erythrocytes, which (along with the normal platelet count) makes bone marrow infiltration with leukemic cells less likely **(Choice D)**.

Most cases of anemia with a high reticulocyte count are caused by acute bleeding or **hemolysis**. In this case, hemolysis is most likely because patients with **chronic lymphocytic leukemia** often have significant immune dysregulation, which triggers the formation of **IgG autoantibodies** against the erythrocyte membrane (**warm agglutinins**). Red blood cells (RBCs) coated with IgG are subsequently identified by the Fc receptor on splenic macrophages and partially or wholly phagocytized, leading to extravascular, **immune-mediated hemolysis** (ie, autoimmune hemolytic anemia). Patients typically present with signs of acute anemia and RBC lysis (eg, jaundice, dark urine, elevated indirect bilirubin). The diagnosis is confirmed with a direct antiglobulin (Coombs) test, which detects the presence of IgG or C3 (a complement fragment) on erythrocytes.

(Choice E) Autoantibodies against erythroid precursors can lead to pure red cell aplasia, which is marked by anemia with a paucity of reticulocytes (not reticulocytosis).

Educational objective:
Anemia with reticulocytosis suggests that the bone marrow is responding appropriately to the anemia by generating new erythrocytes and that sufficient levels of folate, vitamin B_{12}, and iron are available for erythrocytosis. Anemia with reticulocytosis is commonly seen in acute bleeding conditions and hemolysis. Chronic lymphocytic leukemia is associated with warm autoimmune hemolytic anemia.

Time spent:1 Seconds

QID:19159

Subject:
Medicine

System:
Hematology & Oncology (Red blood cell disorders)

A 27-year-old man with sickle cell anemia comes to the emergency department due to increasing dyspnea that started 3 hours ago. The patient was seen in the emergency department 5 days ago for symptomatic anemia, and his hemoglobin level was 6.2 g/dL. He received a blood transfusion, after which his hemoglobin level improved to 8 g/dL, and he was sent home. Temperature is 38.1 C (100.6 F), blood pressure is 105/66 mm Hg, pulse is 112/min, and respirations are 28/min. Oxygen saturation is 97%. The patient appears pale; scleral icterus is present. Lungs are clear. Abdomen is soft and nontender with no hepatosplenomegaly. Laboratory results are as follows:

Complete blood count
- Hemoglobin 4.5 g/dL
- Reticulocytes 7%
- Platelets 327,000/mm^3

Liver function studies
- Bilirubin, indirect4.5 mg/dL

Which of the following is the most likely cause of his current symptoms?

A. Delayed hemolytic transfusion reaction
B. Iron deficiency anemia
C. Splenic sequestration crisis
D. Transfusion-transmitted parvovirus infection
E. Transfusion-transmitted viral hepatitis

Correct answer is
73% answered correctly

Explanation:

Delayed hemolytic transfusion reaction	
Pathogenesis	• Anamnestic antibody response: antibody production against minor RBC antigen to which patient was previously* exposed
Clinical findings	• Onset >24 hr to a month after transfusion • Often asymptomatic • Fatigue, dyspnea, tachycardia • Jaundice • Low-grade fever

Laboratory findings	• Hemolytic anemia
	  ◦ ↑ Indirect bilirubin, LDH, reticulocyte count
	  ◦ ↓ Hemoglobin, haptoglobin
	• New positive direct antiglobulin (Coombs) test

Management	• Supportive (eg, fluids)
Prevention	• Review transfusion history & prior antibody screens • Transfuse when necessary with extended-antigen cross-matched blood

*Prior transfusion (eg, sickle cell disease), pregnancy, or transplant.

LDH = lactate dehydrogenase; **RBC** = red blood cell.

This patient with sickle cell disease has symptomatic anemia, indirect hyperbilirubinemia, and low-grade fever days after receiving a blood transfusion. These findings are concerning for a **delayed hemolytic transfusion reaction** (DHTR).

DHTRs occur in patients who have been previously exposed to a foreign red blood cell (RBC) antigen (eg, **prior transfusion**, pregnancy). The antigen is minor (non-ABO) and typically causes a low, often undetectable antibody response after initial exposure (ie, alloimmunization, similar to that seen in a Rhesus-negative primigravida with a Rhesus-positive fetus). However, on subsequent exposure via repeat transfusion, an **anamnestic antibody response** occurs in which memory B cells rapidly produce more antibodies; these antibodies bind to donor RBCs, causing extravascular hemolysis.

Sickle cell disease patients are at **high risk** of DHTRs due to **frequent exposure** to minor antigens via repeated transfusions. Onset of DHTR is **>24 hours** up to a month **after transfusion**. Most patients are asymptomatic. However, sickle cell disease patients are more likely to have symptomatic, severe anemia due to sickle cell-related intravascular hemolysis in addition to DHTR-related extravascular hemolysis. Symptomatic DHTR causes fatigue, dyspnea, **jaundice**, and **low-grade fever**, with laboratory evidence of hemolysis, including elevated **indirect bilirubin**, lactate dehydrogenase, and **reticulocyte count** as well as decreased haptoglobin. Because these results may be present at baseline in sickle cell disease patients, a **new positive direct antiglobulin (Coombs) test** is important for diagnosing DHTR.

Management is supportive. Prevention includes thorough review of prior antibody screens and use of extended-antigen cross-matched blood when transfusion is required.

(Choice B) Patients with sickle cell disease often have iron overload, not deficiency, due to frequent transfusions. In addition, iron deficiency anemia is associated with a low reticulocyte count.

(Choice C) Splenic sequestration in young children with sickle cell disease causes splenomegaly and a rapid drop in hemoglobin with compensatory reticulocytosis. This patient's age is inconsistent with this diagnosis.

(Choices D and E) Transfusion-transmitted parvovirus infection in sickle cell disease can cause a transient aplastic crisis with severe, acute anemia. However, reticulocyte count is low due to decreased erythropoiesis. Transfusion-transmitted viral hepatitis causing jaundice and hepatomegaly is rare due to blood donor screening, and it does not cause anemia.

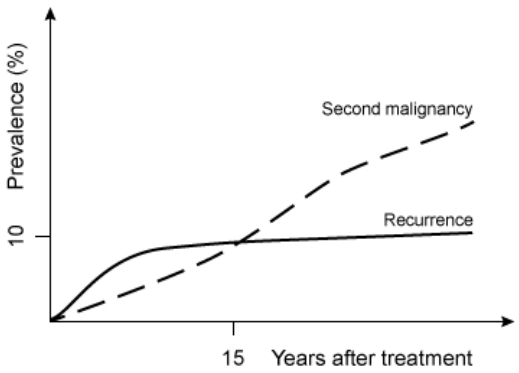
Educational objective:
Sickle cell disease patients are at high risk of delayed hemolytic transfusion reactions due to alloimmunization from frequent transfusions. Reactions develop >24 hours after transfusion and can cause hemolytic anemia. Diagnosis is confirmed with a newly positive Coombs test.

Time spent:1 Seconds
Subject:
Medicine

QID:19721
System:
Hematology & Oncology (Red blood cell disorders)

A 26-year-old woman comes to the office for evaluation of right-sided neck swelling. Enlarged, nontender lymph nodes are palpable in the submandibular and anterior cervical regions. After initial evaluation, the patient is diagnosed with stage 2 Hodgkin lymphoma. She receives combination chemotherapy with doxorubicin, bleomycin, vinblastine, and dacarbazine along with radiation therapy with good response. The patient asks about the long-term prognosis after treatment. Which of the following curves shown below best describes her long-term risk of disease recurrence (solid line) and second malignancy (dashed line)?

A.



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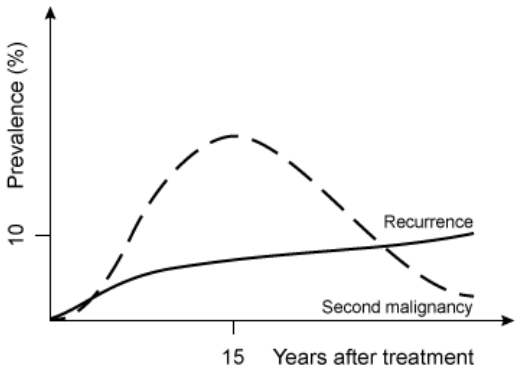

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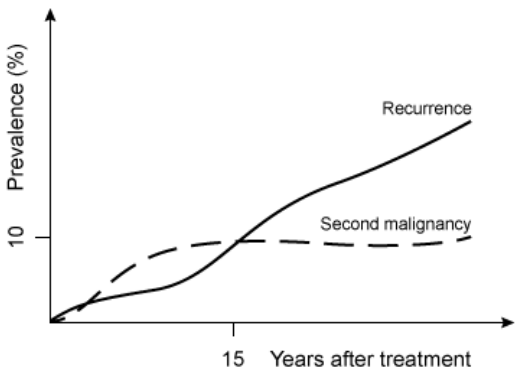

. Correct answer is
59% answered correctly

Explanation:

This patient with **Hodgkin lymphoma** (HL) was treated with **chemotherapy and radiation therapy**, which cures most cases. However, patients who undergo treatment for HL are at increased risk of death compared to an age-matched population due to the following:

- **HL relapse** (or recurrence)**:** The leading cause of death for the first **8-10 years** after treatment is HL relapse. Relapses primarily occur in the first 2 years, but risk remains **mildly elevated** for life.
- **Second malignancy:** The leading cause of death **>8-10 years** after treatment is second malignancy, and this **risk increases with time**. **Breast and lung** malignancies are most common due to their proximity to the mediastinum, which is often irradiated as part of HL treatment. **Hematologic malignancy** (eg, non-Hodgkin lymphoma) can also occur due to damage to hematologic stem cells from alkylating chemotherapy; milder chemotherapy regimens (eg, doxorubicin, bleomycin, vinblastine, and dacarbazine) are associated with less risk of second hematologic malignancy.
- **Cardiovascular disease:** The leading cause of death not due to malignancy is cardiovascular disease. Most cardiovascular complications arise >10 years after treatment and are due to chemotherapy- or radiation-related damage to the heart muscle, valves, and vasculature.

Patients who undergo treatment for HL typically receive intensive screening for HL relapse early after treatment and for malignancy and cardiovascular disease as time progresses (eg, >5 years after treatment). Modifiable risk factors for cancer (eg, quitting smoking) and heart disease (eg, control of hypertension and hyperlipidemia) should be addressed to lessen the risk of early death from these conditions.

Educational objective:
Hodgkin lymphoma (HL) is usually curable with chemotherapy and radiation therapy. However, the risk of death is significantly elevated in those who undergo treatment compared to an age-matched population. For the first 8-10 years, most deaths are due to HL relapse; thereafter, most are due to a second malignancy and cardiovascular disease.

Time spent:1 Seconds
Subject:
Medicine

QID:21981
System:
Hematology & Oncology (Principles of oncology)

A 25-year-old man comes to the emergency department due to a day of fever, sore throat, and malaise. He has no other symptoms. The patient was diagnosed with inflammatory bowel disease–associated spondylarthritis a month ago and started on sulfasalazine at that time. Temperature is 38.8 C (101.8 F), blood pressure is 120/80 mm Hg, pulse is 90/min, and respirations are 15/min. There is mild oropharyngeal erythema with no exudate. Examinations of the ears, nose, sinuses, lungs, abdomen, perineal region, and extremities reveal no abnormalities. Laboratory results are as follows:

Complete blood count	
Hemoglobin	12 g/dL
Platelets	230,000/mm^3
Leukocytes	1,800/mm^3
Neutrophils	20%
Lymphocytes	80%
Urinalysis	
Leukocyte esterase	negative
Nitrites	negative
Bacteria	none
White blood cells	1-2/hpf

Chest x-ray is normal. What is the most appropriate next step in management?

A. Administer corticosteroid
B. Discontinue sulfasalazine
C. Obtain antinuclear antibody level
D. Obtain bone marrow biopsy
E. Obtain Epstein-Barr virus serology testing

Correct answer is
67% answered correctly

Explanation:

Drug-induced neutropenia	
Common triggers	• Methimazole, propylthiouracil • Trimethoprim-sulfamethoxazole • Clozapine • Sulfasalazine
Mechanism	• Immune mediated: drug or metabolite binds to neutrophils & triggers a cell-mediated or humoral response • Bone marrow toxicity: drug or metabolite directly or indirectly damages granulocyte precursors
Manifestations	• Usually within 3 months of drug exposure • Oropharyngeal ulceration ± fever • Other cell lines unaffected

Management	• Discontinue inciting medication • Antibiotics in setting of treatable infection • Consider granulocyte colony-stimulating factor

This patient with fever and pharyngitis has **severe neutropenia** (absolute neutrophil count [ANC] <500/mm^3) with normal platelet and erythrocyte counts. Given the recent initiation of **sulfasalazine**, the most likely underlying etiology is **drug-induced neutropenia**.

Medications trigger neutropenia due to 1 of the following mechanisms:

- **Direct toxicity**: The medication directly destroys granulocyte precursors in the bone marrow. Direct toxicity is usually dose dependent and is seen most often with cytotoxic chemotherapy medications, clozapine, and dapsone.
- **Immune-mediated destruction**: The medication (or a metabolite) adheres to the neutrophil surface and acts as a hapten, which triggers a cytotoxic T-cell or antibody response that destroys the cell. Most cases are idiopathic (not dose dependent); common triggers include **sulfasalazine**, trimethoprim-sulfamethoxazole, propylthiouracil, and flecainide.

Drug-induced neutropenia usually presents with **oropharyngeal mucositis** (eg, sore throat, pharyngeal erythema, ulcers) with or without **fever**. Platelet and leukocyte counts are generally normal. When a patient is taking a medication associated with neutropenia (eg, sulfasalazine), the most important first step is to **immediately stop the offending agent**. Most cases resolve within 1-3 weeks.

Although oropharyngeal erythema, malaise, fever, and neutropenia can occur with viral infections (eg, Epstein-Barr virus), the neutrophil nadir is usually mild (ANC 500-1,500/mm^3) and patients typically have other prominent symptoms (eg, lymphadenopathy, splenomegaly) **(Choice E)**. Neutropenia due to bacterial infection (eg, sepsis) is usually associated with a decrease in the other cell lines (eg, anemia, thrombocytopenia).

(Choice A) Corticosteroid therapy is used to treat some conditions that cause immune-mediated blood cell destruction (eg, thrombotic thrombocytopenic purpura, immune thrombocytopenia). Although immune-mediated destruction of neutrophils may have a role in the pathogenesis of drug-induced neutropenia, steroids have not been shown to improve outcomes.

(Choice C) Rheumatologic conditions (eg, systemic lupus erythematosus) typically cause mild neutropenia. Stopping a common offending medication (eg, sulfasalazine) would take precedence over additional testing (eg, antinuclear antibody) at this time.

(Choice D) Bone marrow sampling is painful and invasive. Therefore, it is usually reserved for cases of neutropenia that do not resolve with discontinuation of a possible inciting medication or when there is a high degree of diagnostic uncertainty.

Educational objective:
Drug-induced neutropenia is typically severe (absolute neutrophil count <500/mm^3), isolated to leukocytes (eg, no anemia or thrombocytopenia), and often manifests with oropharyngeal mucositis and fever. The most important first step is discontinuation of the offending medication. Commonly implicated agents include cytotoxic chemotherapy drugs, clozapine, dapsone, sulfasalazine, trimethoprim-sulfamethoxazole, and propylthiouracil.

A 54-year-old man comes to the emergency department due to a day of fever, chills, and sore throat. He has had no other upper respiratory, urinary, or gastrointestinal symptoms. The patient's medical history includes cirrhosis due to alcohol use disorder. He was hospitalized 3 weeks ago for treatment of spontaneous bacterial peritonitis and hepatic encephalopathy. Since being discharged from the hospital, the patient has been taking lactulose and trimethoprim-sulfamethoxazole for prophylaxis. He has been unable to quit drinking alcohol but is drinking less than before. Temperature is 38.8 C (101.8 F), blood pressure is 116/68 mm Hg, pulse is 98/min, and respirations are 18/min. Physical examination shows pharyngeal erythema and ulceration with no exudate or tonsil enlargement. There is no cervical lymphadenopathy. The lungs are clear to auscultation, and there is no abdominal tenderness. Laboratory results are as follows:

Hemoglobin	11.8 g/dL
Mean corpuscular volume	102 μm^3
Platelets	105,000/mm^3
Leukocytes	1,500/mm^3
Neutrophils	15%
Eosinophils	3%
Lymphocytes	70%
Monocytes	12%

Leukocyte count was normal at the time of hospital discharge. Which of the following best explains this patient's leukopenia?

A. Alcohol-induced bone marrow toxicity
B. Medication adverse effect
C. Sepsis-induced bone marrow suppression
D. Splenic sequestration
E. Vitamin B_{12} deficiency

Correct answer is
68% answered correctly

Explanation:

Drug-induced neutropenia	
Common triggers	• Methimazole, propylthiouracil • Trimethoprim-sulfamethoxazole • Clozapine • Sulfasalazine
Mechanism	• Immune mediated: drug or metabolite binds to neutrophils & triggers a cell-mediated or humoral response • Bone marrow toxicity: drug or metabolite directly or indirectly damages granulocyte precursors
Manifestations	• Usually within 3 months of drug exposure • Oropharyngeal ulceration ± fever • Other cell lines unaffected

Management	• Discontinue inciting medication • Antibiotics in setting of treatable infection • Consider granulocyte colony-stimulating factor

Patients with **alcohol use disorder** and **cirrhosis** may develop **leukopenia** due to a variety of conditions. Two of the most common etiologies are alcohol-induced bone marrow toxicity and vitamin B_{12}/folate deficiency. However, these causes tend to be slow in onset and to cause mild neutropenia (eg, absolute neutrophil count nadir >1000/mm^3) **(Choices A and E)**. Given the recent initiation of **trimethoprim-sulfamethoxazole** for spontaneous bacterial peritonitis prophylaxis, the most likely etiology of this patient's **severe neutropenia** (absolute neutrophil count <500/mm^3) is **drug-induced neutropenia**.

Drug-induced neutropenia is generally triggered by **direct bone marrow toxicity** in a dose-dependent manner (eg, chemotherapy) or an **idiosyncratic reaction** due to the attachment of a drug or drug metabolite to the neutrophil surface, which triggers a cell-mediated or humoral immune response. Most cases present with **oropharyngeal ulcerations** and **fever**. The other cell lines (eg, erythrocytes, platelets) are generally normal unless a different condition is altering rates of production or destruction; in this case, the patient likely has mild **macrocytic anemia** due to alcohol toxicity or vitamin B12/folate deficiency and mild thrombocytopenia due to hypersplenism.

The next best step would be to **stop** trimethoprim-sulfamethoxazole, which should resolve the neutropenia within 1-3 weeks. Administering **granulocyte colony-stimulating factor** may speed resolution.

(Choice C) Although pancytopenia (due to bone marrow suppression) can be caused by sepsis, this patient does not have clinical evidence of sepsis (eg, hypotension, tachycardia). In addition, sepsis does not typically cause severe neutropenia out of proportion to other blood cell counts.

(Choice D) Hypersplenism can cause thrombocytopenia but does not usually cause leukopenia. In addition, severe neutropenia (absolute neutrophil count <500/mm^3) would be very uncommon.

Educational objective:
Trimethoprim-sulfamethoxazole can cause drug-induced neutropenia, which typically presents with sudden, severe neutropenia, oropharyngeal ulcers, and fever. The other cell lines are usually unaffected, but they may be reduced due to other ongoing conditions.

Time spent:1 Seconds
Subject:
Medicine

QID:106468
System:
Hematology & Oncology (White blood cell disorders)

A 52-year-old woman is hospitalized for induction chemotherapy to treat acute myeloid leukemia. The patient has no prior medical concerns. She had been experiencing worsening fatigue, dyspnea, and exercise intolerance. Evaluation revealed anemia, thrombocytopenia, and leukocytosis with circulating myeloblasts. Bone marrow biopsy established the diagnosis of acute myeloid leukemia. Pretreatment medical evaluation showed no abnormalities. The day following chemotherapy, laboratory results reveal the following:

Serum chemistry	
Sodium	136 mEq/L
Potassium	5.7 mEq/L
Blood urea nitrogen	20 mg/dL
Creatinine	0.8 mg/dL
Calcium	7.0 mg/dL
Phosphorus	7.2 mg/dL
Lactate dehydrogenase	984 U/L
Uric acid	11.2 mg/dL

In addition to intravenous hydration, which of the following is the best treatment for this patient?

A. Allopurinol
B. Hemodialysis
C. No additional therapy
D. Rasburicase
E. Urinary alkalinization

Correct answer is
41% answered correctly

Explanation:

Tumor lysis syndrome	
Risk	• Tumors with high cell burden or rapid turnover • Combination chemotherapy/immunotherapy

Manifestations	• Severe electrolyte abnormalities
	  ◦ ↑ Phosphorus, potassium, uric acid
	  ◦ ↓ Calcium
	• Acute kidney injury
	• Cardiac arrhythmias
	• Seizures

Prophylaxis	• Intravenous fluids • Xanthine oxidase inhibitor* or rasburicase
Treatment	• Intravenous fluids + rasburicase • Continuous telemetry • Aggressive electrolyte monitoring & treatment
*Allopurinol or febuxostat.	

This patient has developed significant laboratory abnormalities (eg, hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia) a day following **chemotherapy**, indicating **tumor lysis syndrome** (TLS). TLS typically develops in patients who have tumors with high cell burden or rapid cellular turnover (eg, **acute leukemia**) and is characterized by rapid release of intracellular potassium, phosphate, and **nucleic acids** into the circulation.

Phosphate binds up calcium to cause hypocalcemia, and purine nucleic acids are **metabolized** into **uric acid** (ie, urate) by xanthine oxidase, leading to hyperuricemia and risk of acute kidney injury (AKI) due to renal tubular crystal deposition. This risk can be reduced by pretreatment with intravenous fluids and **urate-lowering therapy** consisting of medications that perform the following:

- **Reduce new urate formation:** xanthine oxidase inhibitors (eg, allopurinol, febuxostat)
- **Directly break down urate:** recombinant urate oxidase analogues (eg, rasburicase)

Xanthine oxidase inhibitors are commonly given in conjunction with intravenous fluids *prior* to chemotherapy to reduce urate formation. However, in this patient with hyperuricemia and evidence of TLS following chemotherapy, xanthine oxidase inhibition (eg, with allopurinol) would not be effective because it does not eliminate urate that has already formed **(Choice A)**. Urate oxidase breaks down urate to reduce hyperuricemia that has already developed, making **rasburicase** the preferred urate-lowering therapy for the treatment of TLS.

(Choice B) Hemodialysis is usually needed only in patients with TLS who have severe AKI and electrolyte derangements that are refractory to medical treatment. This patient with normal renal function should receive medical treatment with intravenous fluids and rasburicase.

(Choice C) In addition to treatment of hyperuricemia, patients with TLS should undergo monitoring of other electrolyte derangements (eg, hyperkalemia, hyperphosphatemia, hypocalcemia) and treatment if necessary.

(Choice E) Urinary alkalinization prior to chemotherapy theoretically reduces renal tubular precipitation of urate by increasing its solubility. However, this is not routinely performed due to a lack of evidence and the potential risk of promoting calcium phosphate deposition in the renal tubules (ie, nephrocalcinosis).

Educational objective:
Tumor lysis syndrome can occur after chemotherapy and results in significant elevations in serum potassium, phosphate (with decreased serum calcium), and uric acid (ie, urate). In patients with preexisting hyperuricemia or in those who develop hyperuricemia following chemotherapy, the administration of rasburicase directly breaks down urate and rapidly lowers its serum concentration.

Time spent:1 Seconds
Subject:
Medicine

QID:107069
System:
Hematology & Oncology (Miscellaneous)