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Item 1 of 34
Question Id: 1629

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A 23-year-old man comes to the office due to a rapidly enlarging left jaw mass that has developed over the past several weeks. The patient is a political refugee from East Africa. He has no known medical problems and takes no medications. Temperature is 37.1 C (98.8 F). Physical examination shows a large left-sided tumor on his jaw with surrounding lymphadenopathy but no erythema or warmth. The rest of the examination is unremarkable. HIV testing is negative. The lesion is biopsied, and numerous mitotic figures and apoptotic bodies are observed on histopathologic examination. Which of the following genetic features is most likely to be present in this tissue?

A. BCL2 overexpression
B. *BCR-ABL* rearrangement
C. c-*Myc* oncogene overexpression
D. n-*Myc* oncogene overexpression
E. Tyrosine kinase activation

Submit

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Settings

Item 1 of 34
Question Id: 1629

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A 23-year-old man comes to the office due to a rapidly enlarging left jaw mass that has developed over the past several weeks. The patient is a political refugee from East Africa. He has no known medical problems and takes no medications. Temperature is 37.1 C (98.8 F). Physical examination shows a large left-sided tumor on his jaw with surrounding lymphadenopathy but no erythema or warmth. The rest of the examination is unremarkable. HIV testing is negative. The lesion is biopsied, and numerous mitotic figures and apoptotic bodies are observed on histopathologic examination. Which of the following genetic features is most likely to be present in this tissue?

- A. BCL2 overexpression [7%]
- B. *BCR-ABL* rearrangement [3%]
- ✔ C. c-*Myc* oncogene overexpression [85%]
- D. n-*Myc* oncogene overexpression [1%]
- E. Tyrosine kinase activation [1%]

Omitted
Correct answer
C

85%
Answered correctly

5 Seconds
Time Spent

11/13/2018
Last Updated

Explanation

This patient has the typical presentation of endemic (African-type) **Burkitt lymphoma**, of which jaw involvement is a characteristic feature. Almost all cases of endemic Burkitt lymphoma are associated with Epstein-Barr virus (EBV) infection. EBV has been implicated in the immortalization of lymphoma cells. Histologically, Burkitt lymphoma has a **"starry sky" appearance** due to the presence of macrophages and apoptotic bodies in a

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Explanation

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Up to 90% of Burkitt lymphoma cases are associated with translocation of the c-*Myc* gene on chromosome 8, usually onto the Ig heavy chain region of chromosome 14 **[t(8;14)].** This translocation leads to overexpression of the **c-*Myc*** oncogene and tumor growth. Burkitt lymphoma is a high-grade lymphoma. Although it is very aggressive, the tumor responds well to short-term, intensive high-dose chemotherapy. Patients with limited disease have an excellent prognosis.

(Choice A) In follicular lymphoma, there is overexpression of the antiapoptotic BCL2 as a result of the t(14;18) translocation. Follicular lymphoma causes generalized lymphadenopathy and tends to affect the elderly. Jaw involvement would be very unusual.

(Choices B and E) The *BCR-ABL* rearrangement is found in chronic myelogenous leukemia and some forms of acute lymphoblastic leukemia. The translocation causes increased tyrosine kinase activity.

(Choice D) Overexpression of the n-*Myc* oncogene is usually seen in neuroblastoma.

Educational objective:
Histologically, Burkitt lymphoma has a "starry sky" appearance due to the presence of macrophages and apoptotic bodies in a sea of medium-sized lymphocytes. The rates of mitosis and apoptosis in the cancerous tissue are high. Almost all cases of Burkitt lymphoma are associated with translocations of the c-*Myc* gene on chromosome 8, usually onto the Ig heavy chain region of chromosome 14 [t(8;14)].

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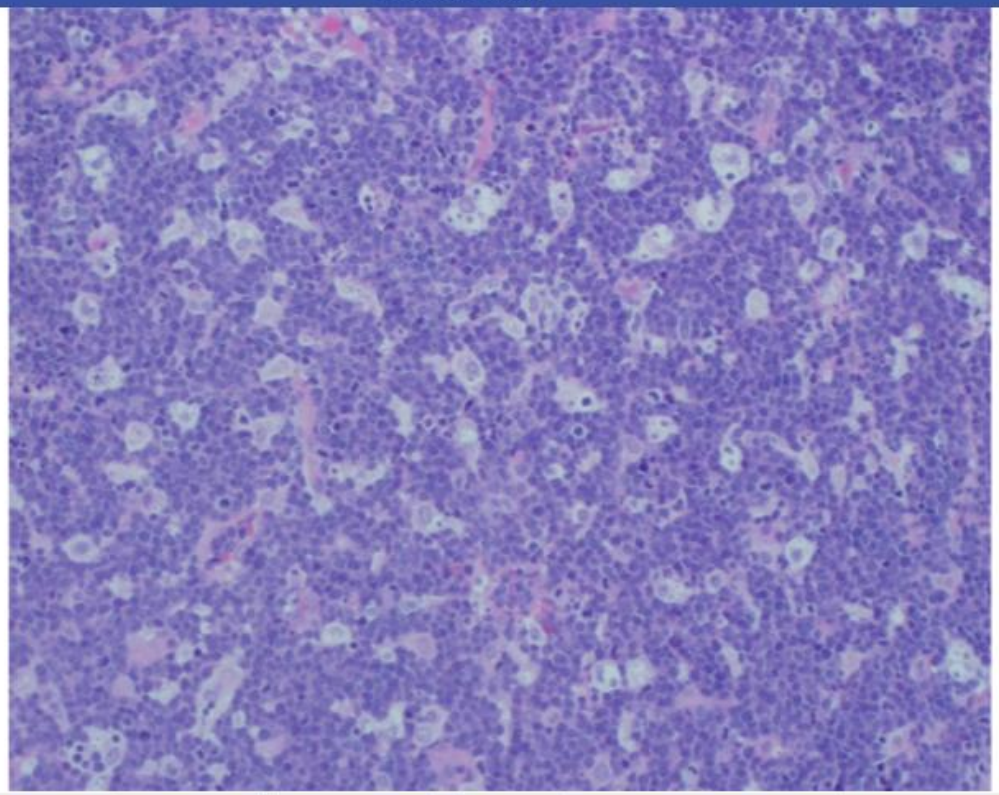

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Item 2 of 34
Question Id: 1786

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A 35-year-old woman comes to the physician complaining of weakness, fatigue, and pallor. She denies heavy menses or melena. Physical examination is unremarkable except for conjunctival pallor. Laboratory results are as follows:

Complete blood count	
Hemoglobin	7.2 g/dL
Erythrocyte count	1.8 million/μL
Mean corpuscular volume	90 fL
Reticulocytes	0.1%
Platelets	280,000 /μL
Leukocyte count	6,700 cells/μL

Iron studies and serum B_{12} and folic acid levels are within normal limits. Bone marrow biopsy shows absence of erythroid precursors but preserved myeloid and megakaryocytic elements. Further workup would most likely show which of the following?

A. Hepatocellular carcinoma
B. Renal cell carcinoma
C. Thymic tumor
D. Cerebellar hemangioblastoma
E. Uterine fibroid

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Complete blood count

Hemoglobin	7.2 g/dL
Erythrocyte count	1.8 million/μL
Mean corpuscular volume	90 fL
Reticulocytes	0.1%
Platelets	280,000 /μL
Leukocyte count	6,700 cells/μL

Iron studies and serum B_{12} and folic acid levels are within normal limits. Bone marrow biopsy shows absence of erythroid precursors but preserved myeloid and megakaryocytic elements. Further workup would most likely show which of the following?

- A. Hepatocellular carcinoma [10%]
- B. Renal cell carcinoma [53%]
- ✔ C. Thymic tumor [23%]
- D. Cerebellar hemangioblastoma [6%]
- E. Uterine fibroid [5%]

Omitted
Correct answer

23%
Answered correctly

6 Seconds
Time Spent

09/06/2018
Last Updated

Explanation

This patient's pallor and fatigue suggest that she is suffering from anemia, which is confirmed by her low erythrocyte count, low percentage of reticulocytes (decreased RBC production), and low hemoglobin. Importantly, her white blood cell and platelet counts are within normal limits and their bone marrow precursors appear normal as well. The most likely diagnosis is pure red cell aplasia (PRCA), a rare form of marrow failure characterized by severe hypoplasia of marrow erythroid elements in the setting of normal granulopoiesis and thrombopoiesis.

The pathogenesis of PRCA often involves the inhibition of erythropoietic precursors and progenitors by IgG autoantibodies or cytotoxic T lymphocytes. It has been associated with immune system diseases such as thymomas and lymphocytic leukemias. When a thymoma is present, removal can occasionally cure PRCA. Thus, all patients with PRCA should undergo a chest CT scan. PRCA can also result from parvovirus B19 infection. This virus preferentially attacks and destroys proerythroblasts. Recent parvovirus infection can be confirmed via the detection of anti-B19 IgM antibodies in the serum.

(Choice A) Hepatocellular carcinoma (HCC) can cause anemia of chronic disease, in which the total iron binding capacity is low. However, this patient's iron studies are within normal limits. HCC tumors may also secrete erythropoietin, although polycythemia is less common.

(Choice B) Renal cell carcinoma (RCC) can cause both anemia of chronic disease and iron deficiency anemia due to chronic hematuria. Some renal cell tumors can produce erythropoietin and cause polycythemia. Thus, anemia, polycythemia, or normal hemoglobin may be present in the setting of RCC. However, selective absence of erythroid precursors in the bone marrow would not occur with RCC. In addition, RCC is rare in younger patients, whereas benign thymomas are more common.

(Choice D) Cerebellar hemangioblastomas can produce erythropoietin and are often associated with polycythemia.

(Choice E) Uterine fibroids can cause bleeding and may result in microcytic hypochromic anemia with iron studies showing low iron and increased total iron binding capacity. However, fibroids can also produce erythropoietin and can cause polycythemia.

Educational objective:
Pure red cell aplasia is a rare form of marrow failure characterized by severe hypoplasia of marrow erythroid elements in the setting of normal

reticulocytes (decreased RBC production), and low hemoglobin. Importantly, her white blood cell and platelet counts are within normal limits and their bone marrow precursors appear normal as well. The most likely diagnosis is pure red cell aplasia (PRCA), a rare form of marrow failure characterized by severe hypoplasia of marrow erythroid elements in the setting of normal granulopoiesis and thrombopoiesis.

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Educational objective:
Pure red cell aplasia is a rare form of marrow failure characterized by severe hypoplasia of marrow erythroid elements in the setting of normal granulopoiesis and thrombopoiesis. Pure red cell aplasia is associated with thymoma, lymphocytic leukemias, and parvovirus B19 infection.

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Item 3 of 34
Question Id: 1954

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A 22-year-old woman comes to the emergency department due to a nosebleed. She had a similar episode yesterday, but the bleeding stopped with prolonged local pressure. On review of systems, the patient has also had easy bruising for the past several months. She has no significant past medical history and takes no medications. On physical examination, her heart and lungs appear normal. The liver span is 8 cm and the spleen is not palpable. There are scattered ecchymoses over her arms and legs. Laboratory results are as follows:

Hematocrit	45%
Platelet count	9,000/mm^3
Leukocytes	5,500/mm^3
Neutrophils	60%
Eosinophils	2%
Lymphocytes	32%
Monocytes	6%
Fibrinogen	250 mg/dL (normal: 150-350 mg/dL)
Prothrombin time	13 sec

HIV and hepatitis C tests are negative. Which of the following is the most likely primary mechanism causing this patient's condition?

A. Bone marrow aplasia
B. Bone marrow infiltration by malignant cells
C. Disseminated intravascular coagulation

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Leukocytes	5,500/mm³
Neutrophils	60%
Eosinophils	2%
Lymphocytes	32%
Monocytes	6%
Fibrinogen	250 mg/dL (normal: 150-350 mg/dL)
Prothrombin time	13 sec

HIV and hepatitis C tests are negative. Which of the following is the most likely primary mechanism causing this patient's condition?

- A. Bone marrow aplasia
- B. Bone marrow infiltration by malignant cells
- C. Disseminated intravascular coagulation
- D. Immune destruction of platelets
- E. Platelet sequestration
- F. von Willebrand disease

Submit

Leukocytes	5,500/mm³
Neutrophils	60%
Eosinophils	2%
Lymphocytes	32%
Monocytes	6%
Fibrinogen	250 mg/dL (normal: 150-350 mg/dL)
Prothrombin time	13 sec

HIV and hepatitis C tests are negative. Which of the following is the most likely primary mechanism causing this patient's condition?

- A. Bone marrow aplasia [1%]
- B. Bone marrow infiltration by malignant cells [2%]
- C. Disseminated intravascular coagulation [3%]
- ✔ D. Immune destruction of platelets [71%]
- E. Platelet sequestration [6%]
- F. von Willebrand disease [14%]

Omitted
Correct answer

71%
Answered correctly

7 Seconds
Time Spent

11/30/2018
Last Updated

Explanation

This patient has recurrent epistaxis, ecchymoses, and marked thrombocytopenia (normal 150,000-400,000/mm^3). She has a normal hematocrit, leukocyte count and differential, fibrinogen level, and prothrombin time/International Normalized Ratio. She takes no medications, and there is no obvious hepatosplenomegaly on physical examination. Taken together, these findings suggest an isolated acquired thrombocytopenia.

Common causes of acquired thrombocytopenia include increased platelet consumption, sequestration, and/or destruction. In this patient, primary **immune thrombocytopenic purpura (ITP)** is the most likely diagnosis as, other than thrombocytopenia (with associated ecchymosis), her physical examination and laboratory findings are unremarkable. ITP is characterized by the **autoimmune** destruction of platelets by anti-platelet antibodies, likely IgG autoantibodies against the platelet membrane glycoproteins GPIIb/IIIa. In children, ITP is typically acute and self-limited, whereas it tends to run an insidious and chronic course in adults. A peripheral blood smear with **isolated** thrombocytopenia and no other platelet abnormalities would help confirm the diagnosis (megakaryocytes can sometimes be seen). Treatment involves systemic immunosuppression (corticosteroids). Secondary ITP is sometimes associated with HIV or hepatitis C infection.

(Choice A) Bone marrow aplasia would cause pancytopenia. It is unlikely that this patient's thrombocytopenia is due to bone marrow failure as the peripheral counts of the hematopoietic cell lines, other than platelets, are normal. Common causes of aplastic anemia include parvovirus and Epstein-Barr virus infections, high-dose chemotherapy, and radiation.

(Choice B) Malignant infiltration of the bone marrow would be expected to cause pancytopenia and extramedullary hematopoiesis within the liver and spleen, leading to hepatosplenomegaly.

(Choice C) If this patient were experiencing accelerated platelet consumption due to disseminated intravascular coagulation, the plasma fibrinogen level would be decreased and the prothrombin time would be elevated due to clotting factor consumption.

(Choice E) Splenic sequestration of platelets typically occurs in disorders that produce splenomegaly, such as portal hypertension; the platelet count usually remains >30,000/mm^3, and abnormal bleeding generally does not occur. Although platelets can undergo splenic sequestration in

antibodies, likely IgG autoantibodies against the platelet membrane glycoproteins GPIIb/IIIa. In children, ITP is typically acute and self-limited, whereas it tends to run an insidious and chronic course in adults. A peripheral blood smear with **isolated** thrombocytopenia and no other platelet abnormalities would help confirm the diagnosis (megakaryocytes can sometimes be seen). Treatment involves systemic immunosuppression (corticosteroids). Secondary ITP is sometimes associated with HIV or hepatitis C infection.

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(Choice E) Splenic sequestration of platelets typically occurs in disorders that produce splenomegaly, such as portal hypertension; the platelet count usually remains >30,000/mm^3, and abnormal bleeding generally does not occur. Although platelets can undergo splenic sequestration in ITP, the primary mechanism responsible for the thrombocytopenia is immune destruction.

(Choice F) In von Willebrand disease, platelet function is impaired because von Willebrand factor, which normally facilitates platelet binding to damaged endothelium, is deficient. The platelet count would be normal (unlike in this patient), and the bleeding time and partial thromboplastin time would be prolonged.

Educational objective:
Autoimmune platelet destruction is a common cause of thrombocytopenia and should be suspected in patients with ecchymoses, petechiae, mucosal bleeding, and no other obvious causes of thrombocytopenia (eg, medications, bone marrow failure).

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Item 4 of 34
Question Id: 1911

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A 34-year-old male notes a lump in his neck that has grown slowly over the past several months. His social history is significant for smoking one pack of cigarettes per day and occasional alcohol use. On review of systems, he denies dysphagia, chest pain, weight loss or fever. Biopsy of the mass reveals abnormal cells with the t(14;18) chromosomal translocation. This chromosomal change is most likely to cause which of the following abnormalities in gene expression?

- A. Bcl2 overexpression
- B. Bcr-abl hybrid formation
- C. C-myc overexpression
- D. Erb-B2 overexpression
- E. p53 inactivation

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Item 4 of 34
Question Id: 1911

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- ✔ A. Bcl2 overexpression [64%]
- B. Bcr-abl hybrid formation [9%]
- C. C-myc overexpression [19%]
- D. Erb-B2 overexpression [2%]
- E. p53 inactivation [3%]

Omitted
Correct answer
A

64%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

This patient has follicular lymphoma, a non-Hodgkin lymphoma of the cleaved and noncleaved B-lymphocytes of the follicular center. The classic cytogenetic abnormality in follicular lymphoma is the t(14;18) translocation, which moves the *Bcl*-2 (B-cell lymphoma-2) protooncogene from chromosome 18 to chromosome 14, near the site of the immunoglobulin heavy chain enhancer element. *Bcl*-2 is considered a protooncogene

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Explanation

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(Choice B) The Bcr-abl hybrid is formed as a result of a reciprocal translocation between chromosomes 9 and 22 (the Philadelphia chromosome). This is the characteristic cytogenetic abnormality in chronic myelogenous leukemia (CML).

(Choice C) C-myc overexpression occurs in many malignancies. The myc oncogene is located on chromosome 8. Translocations between chromosome 8 and chromosomes coding for the immunoglobulin heavy chain (14), the kappa light chain (2), or the lambda light chain (22) may result in Burkitt lymphoma.

(Choice D) ErbB2, HER2 and neu are all names for the same epidermal growth factor receptor, which is overexpressed in many cases of breast cancer.

(Choice E) p53 gene inactivation occurs as one of the two "hits" in many human malignancies. Normally, the p53 protein functions as a tumor suppressor. Li-Fraumeni syndrome is an autosomal dominant cancer syndrome caused by an inherited mutation in p53.

Educational Objective:
Follicular lymphoma is a non-Hodgkin lymphoma of follicular B-lymphocytes. Patients with follicular lymphoma characteristically have a translocation between chromosomes 14 and 18 which causes *Bcl*-2 overexpression. *Bcl*-2 is considered a protooncogene because it has anti-apoptotic effects.

A 24-year-old, HIV-positive, African-American male has a CD 4 count of 200. He is started on dapsone in lieu of trimethoprim-sulfamethoxazole (TMP-SMX) because of a previous adverse reaction. He is also given pneumococcal and influenza vaccines. A few days later, he comes back to the office complaining of fatigue, jaundice, and dark urine. Laboratory studies show:

Complete blood count

Hemoglobin	9.0 g/L
MCV	85 fl
Reticulocytes	7.1%
Platelets	234,000/mm^3
Leukocyte count	5,500/mm^3

Coagulation studies are within normal limits. Peripheral blood smear shows red cell fragments, microspherocytes, and "bite" cells. Which of the following is most likely responsible for his symptoms?

A. Disseminated intravascular coagulation
B. Vaccine-induced hemolysis
C. Enzyme-deficiency anemia
D. Abnormal sickling due to medication
E. Red blood cell cytoskeleton abnormality

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Complete blood count	
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Coagulation studies are within normal limits. Peripheral blood smear shows red cell fragments, microspherocytes, and "bite" cells. Which of the following is most likely responsible for his symptoms?

- A. Disseminated intravascular coagulation [3%]
- B. Vaccine-induced hemolysis [8%]
- ✔ C. Enzyme-deficiency anemia [69%]
- D. Abnormal sickling due to medication [10%]
- E. Red blood cell cytoskeleton abnormality [7%]

Omitted
Correct answer

69%
Answered correctly

5 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

All HIV-positive patients with a CD4 count of < 200 should be prophylactically treated for pneumocystis jiroveci pneumonia. TMP-SMX is the drug of choice for this purpose, but dapsone is an alternative agent in cases of allergy, etc. Possible side effects of dapsone include fever, rash, and methemoglobinemia. Dapsone also puts oxidative stress on the body, so G6PD levels should be checked before administering dapsone in order to prevent hemolytic anemia in patients with this enzyme deficiency.

Common precipitating factors of glucose-6-phosphate dehydrogenase (G6PD) deficiency anemia include:

1. Infections
2. Drugs – dapsone, antimalarials, sulfonamide antibiotics (TMP-SMX)
3. Diabetic ketoacidosis
4. Favism (ingestion of fresh fava beans)

Suspicions of dapsone-induced hemolytic anemia in the context of G6PD deficiency are confirmed by this patient's anemia, reticulocytosis, jaundice, and dark urine. Furthermore, his blood smear shows red cell fragments, microspherocytes, and "bite cells." Bite cells are typical of oxidant-induced damage, such as in G6PD deficiency. Heinz body preparation is also very helpful in the diagnosis—G6PD deficiency will be demonstrated on crystal violet stain as small, irregular, dark purple granules in the red blood cells which are called "Heinz bodies." Bite cells are often the result of the phagocytic removal of Heinz bodies by the splenic monocyte-macrophage system.

(Choice A) Disseminated intravascular coagulation is characterized by thrombocytopenia and a prolonged PT and aPTT.

(Choice B) Hemolytic anemia is not a known complication of either pneumococcal or influenza vaccines.

(Choice D) Abnormal sickling is the hallmark of sickle cell anemia. This form of anemia is genetic. Exacerbations of sickle cell anemia may be caused by deoxygenation and dehydration, but not by dapsone.

(Choice E) Diseases with red blood cell cytoskeleton abnormalities include hereditary spherocytosis, hereditary elliptocytosis, and hereditary stomatocytosis. They would have presented early. This is perhaps a plausible explanation for this patient's symptoms, but not the best choice.

1. Infections
2. Drugs – dapsone, antimalarials, sulfonamide antibiotics (TMP-SMX)
3. Diabetic ketoacidosis
4. Favism (ingestion of fresh fava beans)

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Educational Objective:

- Hemolytic anemia is a possible side effect of dapsone and is most significant in patients deficient for glucose-6-phosphate dehydrogenase (G6PD).
- G6PD deficiency anemia is characterized by episodes of hemolytic anemia precipitated by oxidative stress (drugs, infections). Peripheral smear typically shows bite cells and Heinz bodies (requires special preparation).

Settings

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Question Id: 314

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Rats exposed to high concentrations of carbon tetrachloride suffer rapid and extensive liver damage. Light microscopic examination of affected liver specimens shows fatty change and hepatocyte necrosis. These changes are the result of:

A. Hypoperfusion
B. Hypoxia
C. Abnormal signal transduction
D. Free radical injury
E. Mitochondrial dysfunction

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Rats exposed to high concentrations of carbon tetrachloride suffer rapid and extensive liver damage. Light microscopic examination of affected liver specimens shows fatty change and hepatocyte necrosis. These changes are the result of:

A. Hypoperfusion [1%]
B. Hypoxia [3%]
C. Abnormal signal transduction [2%]
✔ D. Free radical injury [73%]
E. Mitochondrial dysfunction [19%]

Omitted
Correct answer
D

73%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

Carbon tetrachloride (CCl_4) causes free radical injury. Like many other toxic substances, CCl_4 is oxidized by the P450 oxidase system in the liver. The result is the formation of the free radical CCl_3, which reacts with structural lipids of cell membranes. The result is lipid degradation and hydrogen peroxide (H_2O_2) formation. This process is called **lipid peroxidation**. The peroxides go on to form new radicals, continuing the vicious circle of lipid degradation. Carbon tetrachloride cell injury develops rapidly and leads to swelling of the endoplasmic reticulum, destruction of mitochondria, and increased permeability of cell membranes. These processes culminate in hepatocyte necrosis.

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Omitted
Correct answer
D

73%
Answered correctly

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Last Updated

Explanation

Carbon tetrachloride (CCl_4) causes free radical injury. Like many other toxic substances, CCl_4 is oxidized by the P450 oxidase system in the liver. The result is the formation of the free radical CCl_3, which reacts with structural lipids of cell membranes. The result is lipid degradation and hydrogen peroxide (H_2O_2) formation. This process is called **lipid peroxidation**. The peroxides go on to form new radicals, continuing the vicious circle of lipid degradation. Carbon tetrachloride cell injury develops rapidly and leads to swelling of the endoplasmic reticulum, destruction of mitochondria, and increased permeability of cell membranes. These processes culminate in hepatocyte necrosis.

(Choices A and B) Hypoperfusion and hypoxia lead to tissue ischemia and necrosis. Carbon tetrachloride does not affect tissue oxygenation.

(Choice C) Abnormal signal transduction is a mechanism of oncogenesis, as occurs with mutations of the *Ras* proto-oncogene. This mutation increases cell sensitivity to mitogenic influences.

(Choice E) Mitochondrial dysfunction occurs in CCl_4 intoxication as a result of free radical injury.

Educational Objective:
The P450 microsomal oxidase system plays an important role in detoxification. In carbon tetrachloride poisoning, however, it produces free radicals that start a vicious cycle of hepatic injury.

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Item 7 of 34
Question Id: 873

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A 37-year-old man comes to the emergency department due to blood-tinged vomiting and abdominal discomfort. Six months ago, he lost his job as an investment banker and began drinking large amounts of whiskey on a daily basis. He has since been hospitalized several times with alcohol intoxication. His temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, pulse is 84/min, and respirations are 18/min. Physical examination shows a firm, enlarged liver. Peripheral blood smear results show neutrophils with 6-8 nuclear lobes. Which of the following is the most likely explanation for this latter finding?

A. Blood lipid abnormality
B. Chronic blood loss
C. Cobalamin deficiency
D. Folate deficiency
E. Hypothyroidism
F. Myelodysplasia

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Item 7 of 34
Question Id: 873

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 37-year-old man comes to the emergency department due to blood-tinged vomiting and abdominal discomfort. Six months ago, he lost his job as an investment banker and began drinking large amounts of whiskey on a daily basis. He has since been hospitalized several times with alcohol intoxication. His temperature is 36.7 C (98 F), blood pressure is 110/70 mm Hg, pulse is 84/min, and respirations are 18/min. Physical examination shows a firm, enlarged liver. Peripheral blood smear results show neutrophils with 6-8 nuclear lobes. Which of the following is the most likely explanation for this latter finding?

- A. Blood lipid abnormality [1%]
- B. Chronic blood loss [1%]
- C. Cobalamin deficiency [22%]
- ✔ D. Folate deficiency [71%]
- E. Hypothyroidism [0%]
- F. Myelodysplasia [2%]

Omitted
Correct answer
D

71%
Answered correctly

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Explanation

Alcoholism is one of the most common causes of **folate deficiency** anemia due to poor dietary intake and impaired folate absorption, utilization,

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Explanation

Alcoholism is one of the most common causes of **folate deficiency** anemia due to poor dietary intake and impaired folate absorption, utilization, and enterohepatic recycling. A normal individual with a folate-deficient diet can maintain normal red blood cell (RBC) production for months due to folate recycling, whereas a patient who consumes large amounts of alcohol will experience anemia within a few **weeks**. A reduced form of folic acid, tetrahydrofolic acid, is necessary for the synthesis of amino acids, thymidine, and purines. Impaired nucleotide synthesis leads to defective DNA production in blood cell precursors, resulting in abnormal cell division and **megaloblastic** hyperplasia of the bone marrow. The peripheral blood smear shows pancytopenia and **hypersegmented neutrophils** containing nuclei with >5 lobes. RBC abnormalities include ovalocytosis and **macrocytosis**, with a mean corpuscular volume (MCV) >100 μm^3.

(Choice A) Lipid abnormalities such as extreme hypertriglyceridemia can cause acute pancreatitis.

(Choice B) Chronic blood loss causes iron deficiency anemia, which is not characterized by hypersegmented neutrophils.

(Choice C) Vitamin B_{12} (cobalamin) deficiency is typically associated with pernicious anemia, gastrectomy, certain medications, and fish tapeworm infections. Chronic alcohol use can deplete vitamin B_{12} levels; however, given the body's large B_{12} stores, this depletion would take place over a period of many years not months. In addition, there is no mention in this patient of the neurologic symptoms that classically accompany B_{12} deficiency (eg, subacute combined degeneration with paresthesias, ataxia, and loss of proprioception).

(Choice E) Elevated MCV can be present in hypothyroidism, but hypersegmented neutrophils are classically not seen.

(Choice F) Myelodysplasia is a premalignant condition that manifests with pancytopenia, impaired blood cell differentiation, and clonal expansion of mutated hematopoietic cells in the bone marrow. Elevated MCV can be present, but hypersegmented neutrophils are not commonly seen.

Educational objective:
Folic acid deficiency anemia commonly occurs in alcoholism. It is a megaloblastic anemia that can develop within weeks. Peripheral blood smear shows macrocytosis, ovalocytosis, and neutrophils with hypersegmented nuclei.

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Item 7 of 34
Question Id: 873

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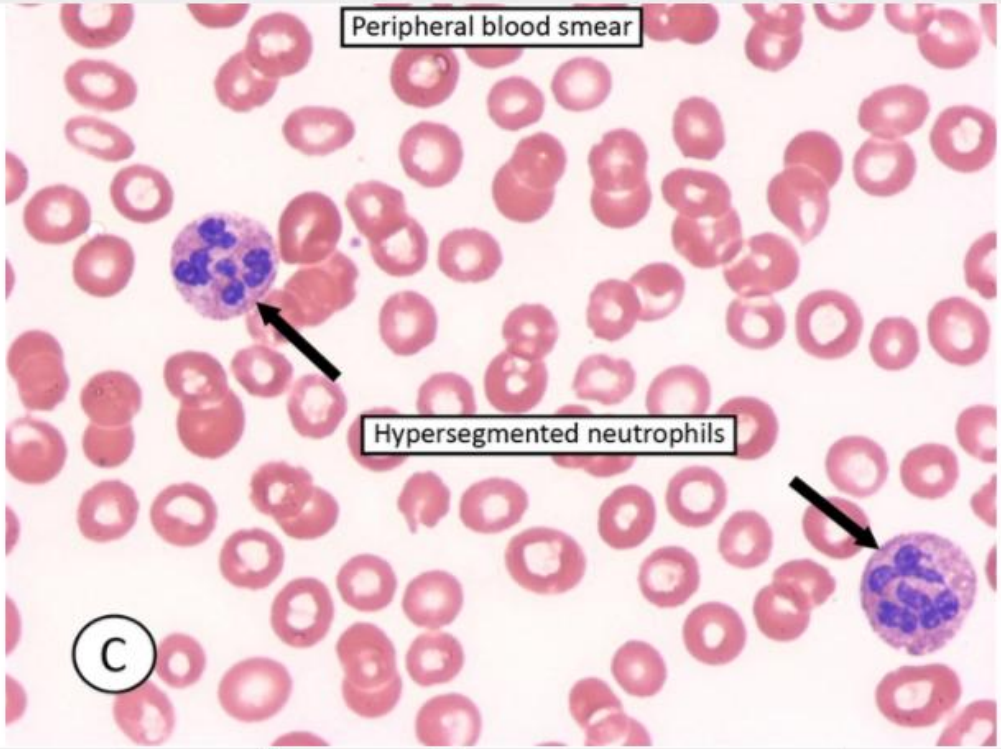
Explanation

Exhibit Display

Hypersegmented neutrophils Hypersegmented neutrophils



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Item 7 of 34
Question Id: 873

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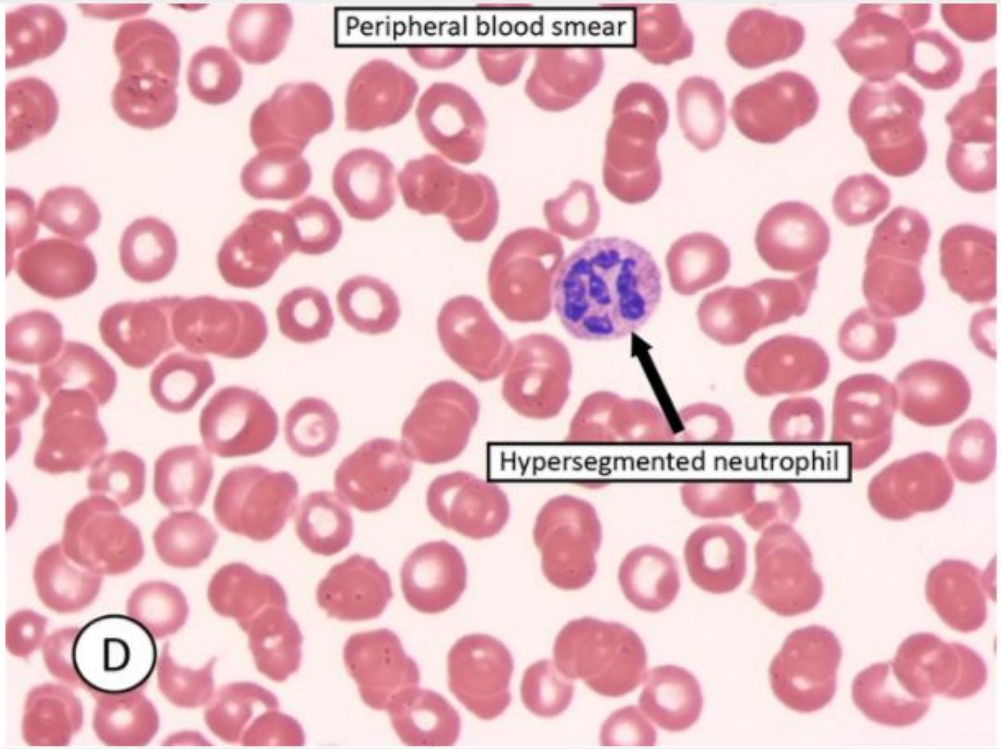
Explanation

Exhibit Display

Hypersegmented neutrophils Hypersegmented neutrophils



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Item 8 of 34
Question Id: 1426

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A 32-year-old African American male is diagnosed with acute prostatitis. He has no significant past medical history. He begins treatment with trimethoprim-sulfamethoxazole, but subsequently develops dark urine and anemia with a high reticulocyte count. Which of the following is the best explanation for the observed findings?

A. Antibody-mediated erythrocyte destruction
B. Hereditary erythrocyte membrane defect
C. Hereditary erythrocyte enzyme deficiency
D. Hemoglobin structure abnormality
E. Microangiopathic hemolytic anemia

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Item 8 of 34
Question Id: 1426

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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- A. Antibody-mediated erythrocyte destruction [7%]
- B. Hereditary erythrocyte membrane defect [3%]
- ✔ C. Hereditary erythrocyte enzyme deficiency [77%]
- D. Hemoglobin structure abnormality [4%]
- E. Microangiopathic hemolytic anemia [6%]

Omitted
Correct answer
C

77%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

This patient is demonstrating signs of hemolysis induced by trimethoprim-sulfamethoxazole (Bactrim, TMP/SMX). This scenario is not an uncommon way for glucose-6-phosphate dehydrogenase (G6PD) deficiency to present. G6PD deficiency is an X-linked disorder that affects mostly males, and is more common in patients of African, Asian and Mediterranean descent. G6PD is an enzyme of the pentose phosphate pathway that in erythrocytes is essential for maintaining adequate concentrations of NADPH. Insufficient NADPH results in an inability to maintain

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This patient is demonstrating signs of hemolysis induced by trimethoprim-sulfamethoxazole (Bactrim, TMP/SMX). This scenario is not an uncommon way for glucose-6-phosphate dehydrogenase (G6PD) deficiency to present. G6PD deficiency is an X-linked disorder that affects mostly males, and is more common in patients of African, Asian and Mediterranean descent. G6PD is an enzyme of the pentose phosphate pathway that in erythrocytes is essential for maintaining adequate concentrations of NADPH. Insufficient NADPH results in an inability to maintain glutathione in the reduced state. This increases the vulnerability of erythrocytes to oxidative stress and manifests with hemolysis induced by infection, drugs (e.g. bactrim, dapsone, antimalarials, nitrofurantoin), or other oxidants (e.g. fava beans).

Hemolytic episodes manifest with symptoms of anemia such as malaise and pallor, indirect bilirubinemia (jaundice), hemoglobinemia and hemoglobinuria (dark-red urine). The level of serum haptoglobin decreases and a reticulocytosis develops to compensate for the increased destruction of RBCs. Patients are generally asymptomatic between episodes.

(Choice A) Autoimmune hemolytic anemias result from extrinsic antibody-mediated hemolysis and are associated with a positive Coombs test. These anemias often accompany SLE and other autoimmune diseases, Hodgkin and non-Hodgkin lymphomas, *Mycoplasma* infections (cold agglutinins), and infectious mononucleosis.

(Choice B) Hereditary spherocytosis is an autosomal dominant defect in RBC structural proteins (spectrin, ankyrin, or protein 4.1) characterized by increased erythrocyte osmotic fragility and MCHC (mean corpuscular hemoglobin concentration) increased above 36 g/dL.

(Choice D) Abnormalities of hemoglobin structure include hemoglobin S (sickle cell disease), C, and E disorders, as well as others. Heterozygotes usually show minimal to no clinical signs, while homozygotes present with hemolytic anemia in addition to other disease-specific complications.

(Choice E) Microangiopathic hemolytic anemia (MAHA) occurs when there is destruction of RBCs within small vessels due to widespread thrombosis. MAHA is associated with disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS).

Educational Objective:

glutathione in the reduced state. This increases the vulnerability of erythrocytes to oxidative stress and manifests with hemolysis induced by infection, drugs (e.g. bactrim, dapsone, antimalarials, nitrofurantoin), or other oxidants (e.g. fava beans).

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Educational Objective:
Glucose-6-phosphate dehydrogenase deficiency is an X-linked disorder of the hexose monophosphate (pentose phosphate) pathway. In affected individuals, the amount of NADPH produced in RBCs is low, which impairs glutathione-mediated inactivation of free radicals. Hemolytic episodes are induced by infections, medications, and other oxidants.

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Item 9 of 34
Question Id: 1879

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A 26-year-old Caucasian female is found to have a single amino acid substitution (glutamine for arginine) near the protein C cleavage site in her coagulation factor V gene product. The patient is at greatest risk for developing which of the following conditions?

A. Petechiae and ecchymoses
B. Recurrent hemarthroses
C. Renal artery stenosis
D. Splenic infarction
E. Pulmonary thromboembolism

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Item 9 of 34
Question Id: 1879

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 26-year-old Caucasian female is found to have a single amino acid substitution (glutamine for arginine) near the protein C cleavage site in her coagulation factor V gene product. The patient is at greatest risk for developing which of the following conditions?

A. Petechiae and ecchymoses [14%]
B. Recurrent hemarthroses [12%]
C. Renal artery stenosis [1%]
D. Splenic infarction [5%]
✔ E. Pulmonary thromboembolism [65%]

Omitted
Correct answer
E

65%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

The major clinical manifestations of factor V Leiden include deep vein thrombosis (DVT), cerebral vein thrombosis, and recurrent pregnancy loss. Because pulmonary thromboembolism occurs in approximately 50% of all individuals with untreated DVTs, the young woman presented here is at significant risk of developing a pulmonary thromboembolism at some point in her lifetime.

Factor V Leiden is the most common cause of inherited thrombophilia, with the heterozygote prevalence of this genetic mutation ranging from 1-

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Factor V Leiden is the most common cause of inherited thrombophilia, with the heterozygote prevalence of this genetic mutation ranging from 1-9% in Caucasian populations worldwide. Heterozygote carriers of factor V Leiden have five to ten times the risk of developing a thrombosis, while homozygote carriers of factor V Leiden have fifty to one hundred times the risk of developing a thrombosis.

Factor V Leiden causes thrombophilia through two pathophysiological mechanisms. In normal hemostasis, activated protein C (APC) restricts clot formation by proteolytically inactivating factors Va and VIIIa. Factor Va Leiden has reduced susceptibility to cleavage by APC, however. Because factor Va is a cofactor in the conversion of prothrombin to thrombin, persistently circulating factor Va Leiden results in increased thrombin production. Additionally, factor V Leiden is unable to support APC anticoagulant activity. This combination of increased coagulation and decreased anticoagulation produces the hypercoagulable state seen in those with factor V Leiden.

(Choice A) Petechiae and ecchymoses are more consistent with qualitative or quantitative platelet abnormalities than factor V Leiden.

(Choice B) Recurrent hemarthroses are suggestive of hemophilia (factor VIII or IX deficiency), not factor V Leiden.

(Choice C) Renal artery stenosis is primarily caused by atherosclerosis and fibromuscular disease, not thrombosis. Moreover, factor V Leiden is associated with an increased risk of deep venous (not arterial) thrombosis.

(Choice D) Major causes of splenic infarction include sickle cell anemia, infectious endocarditis, and myeloproliferative disorders. Moreover, the factor V Leiden mutation is associated with deep venous (not arterial) thrombosis.

Educational Objective:
One to nine percent of Caucasians worldwide are heterozygote carriers of factor V Leiden, which is modified to resist activated protein C. The resulting hypercoagulable state predisposes to deep vein thromboses, which are the source of most pulmonary emboli.

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Item 10 of 34
Question Id: 336

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A 73-year-old man comes to the office due to blood in his urine. He has noted bright red blood at the end of micturition on several occasions but has had no urinary frequency or pain with urination. The patient has a history of hypertension and chronic bronchitis. He has smoked a pack of cigarettes daily for 30 years. Temperature is 37 C (98.6 F). Abdominal, external genital, and rectal examinations are unremarkable. Urinalysis shows hematuria. Urine cytology is positive for malignant cells. Cystoscopy is planned for visualization and biopsy of suspected urinary tract cancer. Which of the following features would be most suggestive of a poor prognosis?

A. High-grade intraepithelial lesion
B. Involvement of the muscular layer
C. Location at the anterior bladder wall
D. Papillary morphology
E. Tumor size >2 cm

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Item 10 of 34
Question Id: 336

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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A. High-grade intraepithelial lesion [9%]
✔ B. Involvement of the muscular layer [77%]
C. Location at the anterior bladder wall [3%]
D. Papillary morphology [4%]
E. Tumor size >2 cm [5%]

Omitted
Correct answer
B

77%
Answered correctly

3 Seconds
Time Spent

10/05/2018
Last Updated

Explanation

This patient with a significant smoking history has developed painless gross hematuria, which raises suspicion for bladder cancer. **Urothelial (transitional cell) carcinomas** arising from the transitional epithelium lining the bladder are the most common type of bladder cancer; squamous cell and adenocarcinomas may occur but are significantly less common. Urothelial cancer typically grows as an erythematous papillary, nodular,

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Explanation

This patient with a significant smoking history has developed painless gross hematuria, which raises suspicion for bladder cancer. **Urothelial (transitional cell) carcinomas** arising from the transitional epithelium lining the bladder are the most common type of bladder cancer; squamous cell and adenocarcinomas may occur but are significantly less common. Urothelial cancer typically grows as an erythematous papillary, nodular, or sessile mass and is easily diagnosed on cystoscopy. Microscopy may show cells resembling normal bladder epithelium but with irregular architecture, pleomorphism, hyperchromatic nuclei, and **atypical mitoses**.

Tumor stage is the most important factor for determining prognosis in urothelial carcinoma and is based on the **depth of invasion** into the bladder wall and the degree of spread to other tissues. Tumor penetration through the mucosa and lamina propria **into the muscular layer** (indicating stage T2 or higher in the Tumor, Node, Metastasis [TNM] system) carries an **unfavorable prognosis**.

(Choice A) Tumor grade, or the degree of cellular abnormality, also influences prognosis but to a lesser extent than staging. High-grade intraepithelial lesions (**carcinoma in situ**), despite their high degree of cellular abnormality, have a relatively favorable prognosis as they have not invaded the basement membrane.

(Choice C) Urothelial tumors at the bladder neck may have an elevated risk of recurrence, but, in general, tumor location within the bladder has only a minor effect on prognosis.

(Choice D) Tumors with papillary morphology are more likely to extend into the bladder lumen rather than penetrate into the bladder wall. However, these tumors can become invasive, and papillary morphology itself does not directly influence prognosis.

(Choice E) Larger tumors are associated with worse prognosis; however, depth of tumor invasion is a much more important prognostic factor than tumor size.

Educational objective:
Urothelial (transitional cell) carcinoma is the most common type of bladder cancer. Tumor stage is the most important factor for determining prognosis and is based on the depth of invasion into the bladder wall and the degree of spread to other tissues. Tumor invasion into the muscular

Tumor stage is the most important factor for determining prognosis in urothelial carcinoma and is based on the **depth of invasion** into the bladder wall and the degree of spread to other tissues. Tumor penetration through the mucosa and lamina propria **into the muscular layer** (indicating stage T2 or higher in the Tumor, Node, Metastasis [TNM] system) carries an **unfavorable prognosis**.

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(Choice E) Larger tumors are associated with worse prognosis; however, depth of tumor invasion is a much more important prognostic factor than tumor size.

Educational objective:
Urothelial (transitional cell) carcinoma is the most common type of bladder cancer. Tumor stage is the most important factor for determining prognosis and is based on the depth of invasion into the bladder wall and the degree of spread to other tissues. Tumor invasion into the muscular layer of the bladder wall carries an unfavorable prognosis.

References

- Diagnosis and staging of bladder cancer.

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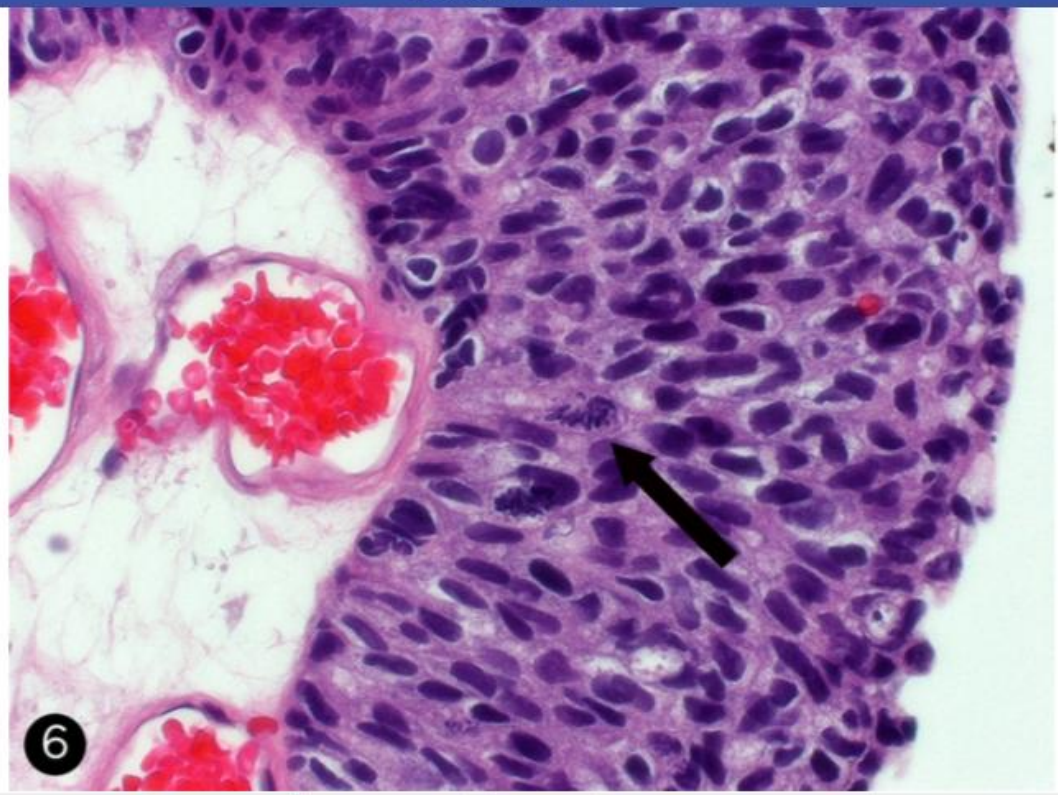

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Item 11 of 34
Question Id: 1880

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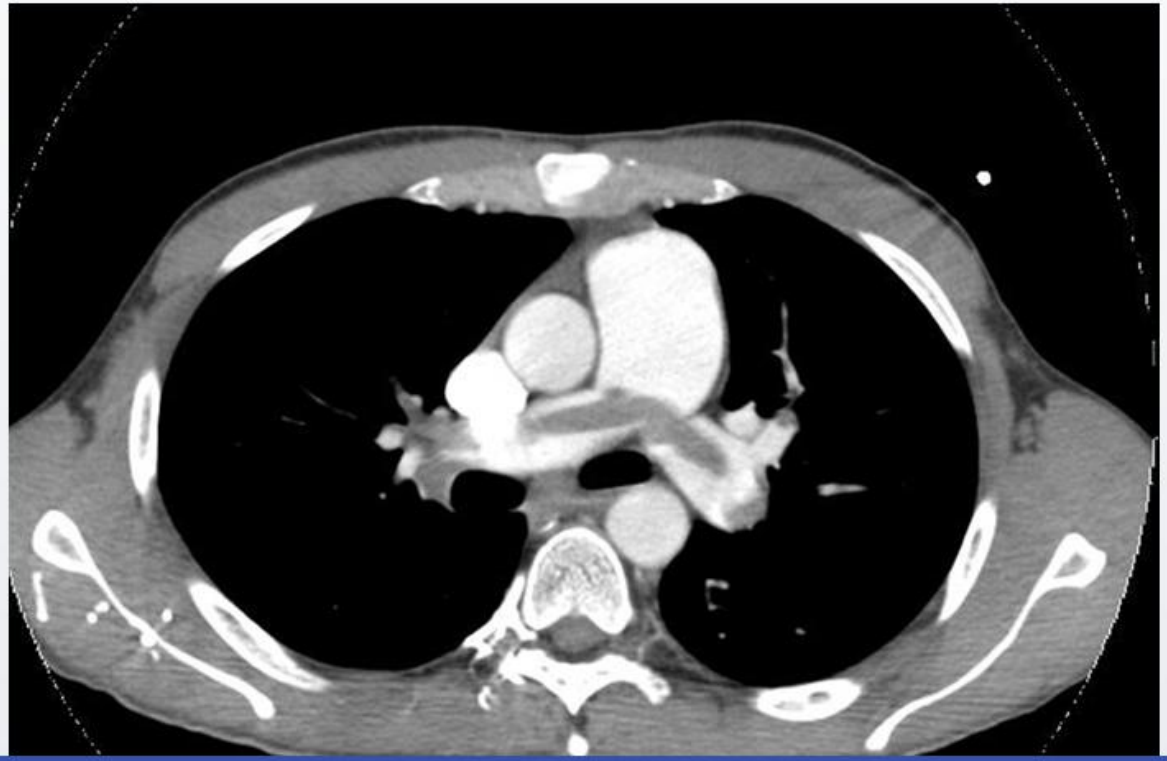
A 72-year-old man comes to the emergency department due to severe chest tightness and dyspnea that started 20 minutes ago at a family dinner. He has never experienced similar symptoms before. The patient's medical conditions include hypertension, hyperlipidemia, type 2 diabetes mellitus, and prostate cancer. He takes multiple medications and has no drug allergies. The patient smoked a pack of cigarettes daily for 30 years and stopped smoking 10 years ago. Chest CT scan with contrast is shown in the image below.



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Question Id: 1880

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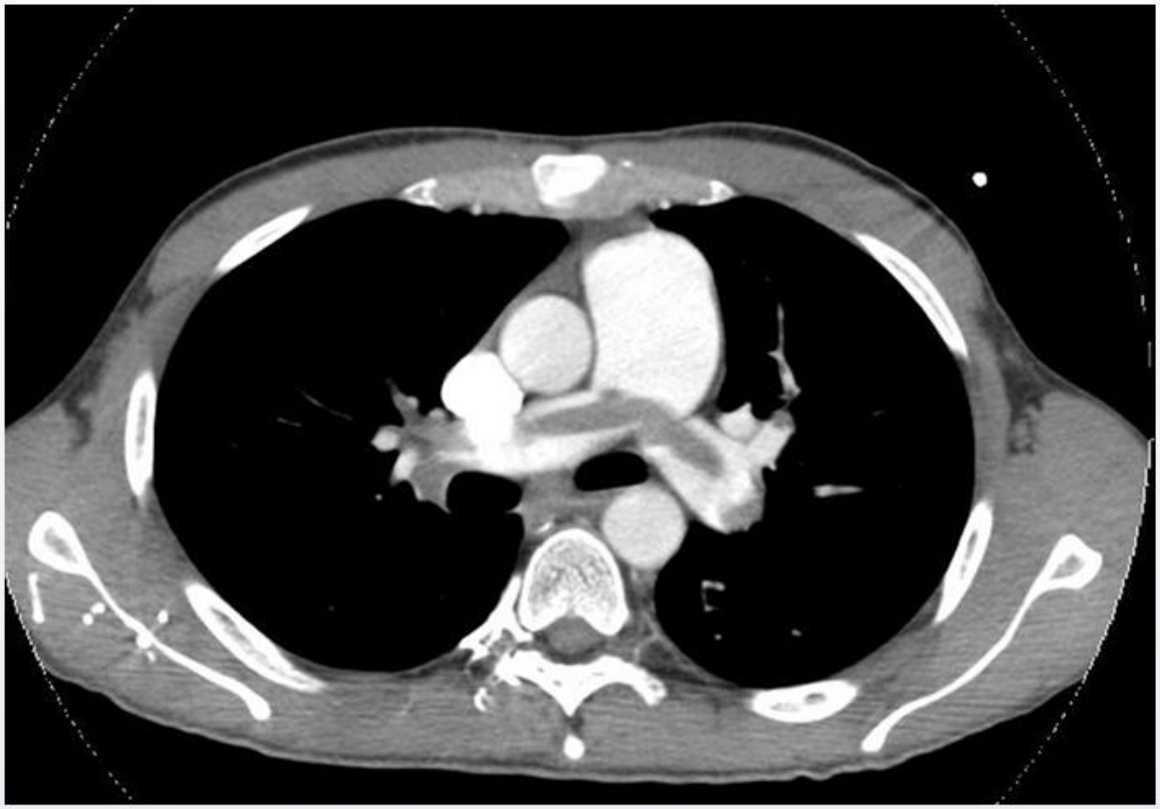
30 years and stopped smoking 10 years ago. Chest CT scan with contrast is shown in the image below.



Which of the following factors most likely contributed to this patient's current condition?

A. Atherosclerosis

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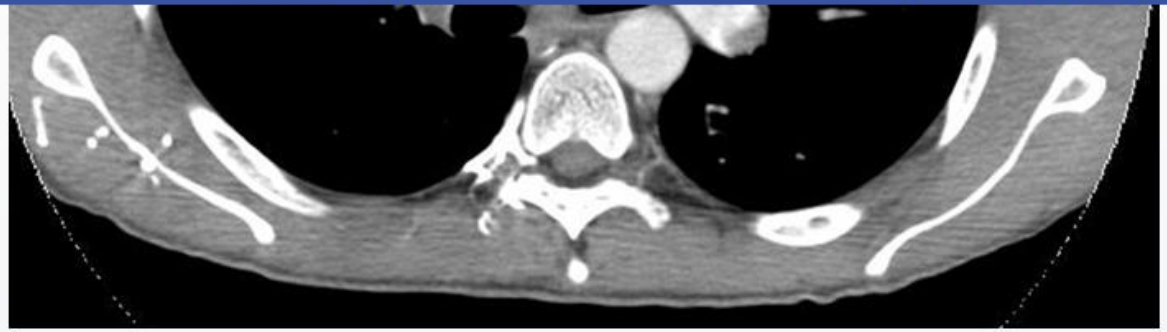

Which of the following factors most likely contributed to this patient's current condition?

A. Atherosclerosis
B. Fluid overload
C. Hypercoagulability
D. Intimal tear
E. Noninfectious vasculitis
F. Pulmonary bleb rupture
G. Pulmonary metastasis

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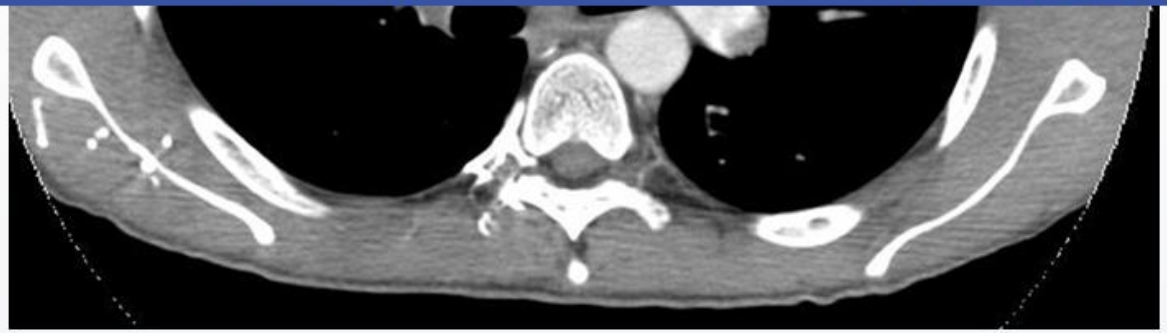

Which of the following factors most likely contributed to this patient's current condition?

- A. Atherosclerosis [18%]
- B. Fluid overload [1%]
- ✔ C. Hypercoagulability [63%]
- D. Intimal tear [11%]
- E. Noninfectious vasculitis [0%]
- F. Pulmonary bleb rupture [2%]
- G. Pulmonary metastasis [1%]

Omitted
Correct answer

63%
Answered correctly

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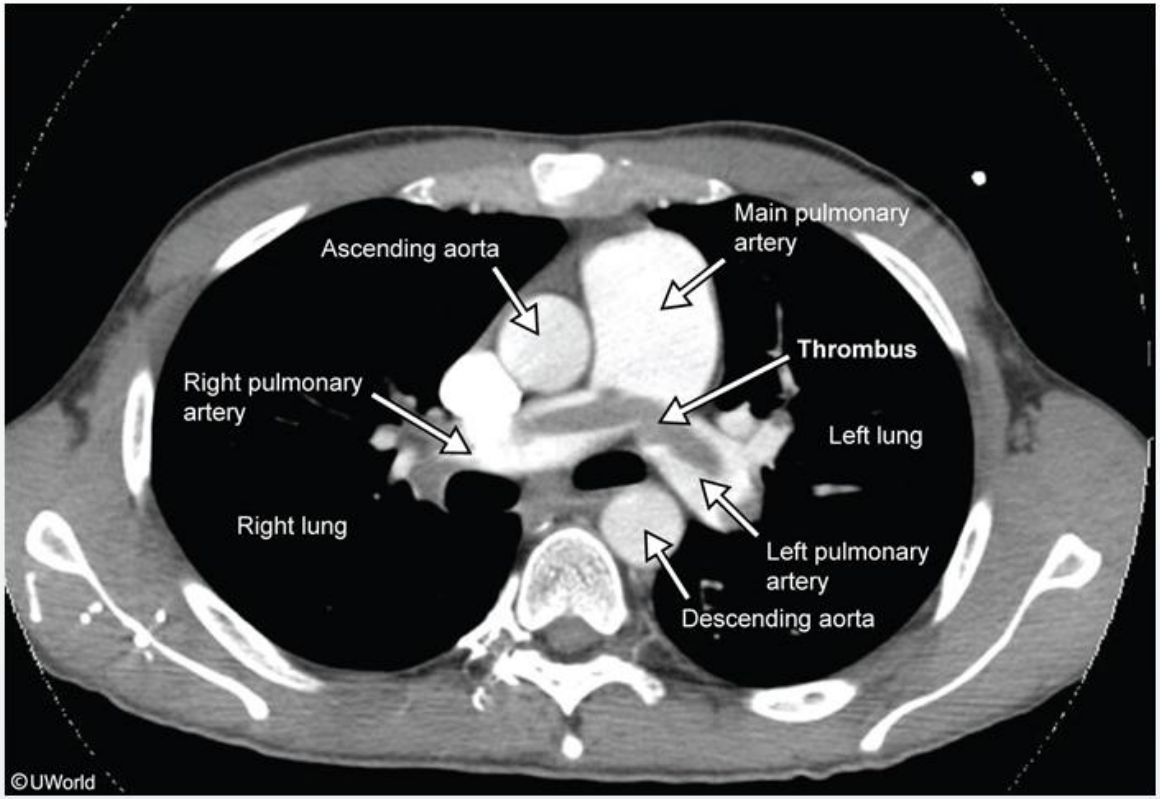

This patient is experiencing sudden-onset chest tightness and dyspnea, and CT scan of the chest shows a **saddle pulmonary embolism** (PE) straddling the bifurcation of the main pulmonary artery. The main pulmonary artery, usually comparable in diameter to the ascending aorta, is significantly dilated due to the proximal increase in hydrostatic pressure from the PE. Saddle PE can result in sudden cardiac death or severe hypotension, but many patients can be hemodynamically stable on presentation.

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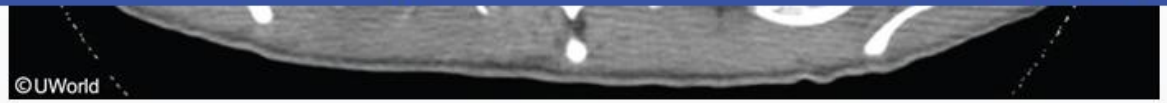

This patient is experiencing sudden-onset chest tightness and dyspnea, and CT scan of the chest shows a **saddle pulmonary embolism** (PE) straddling the bifurcation of the main pulmonary artery. The main pulmonary artery, usually comparable in diameter to the ascending aorta, is significantly dilated due to the proximal increase in hydrostatic pressure from the PE. Saddle PE can result in sudden cardiac death or severe hypotension, but many patients can be hemodynamically stable on presentation.

Venous thromboembolism (VTE) (ie, PE or deep venous thrombosis) results from the **Virchow triad** of endothelial injury, venous stasis, and a **hypercoagulable** state. **Malignancy** (eg, prostate cancer) induces a hypercoagulable state and is a strong risk factor for VTE. Active **smoking** is also a risk factor as it contributes to endothelial injury and a hypercoagulable state. Age plays a role as well, as older individuals tend to be more **sedentary** and are more prone to venous stasis.

(Choice A) Atherosclerosis primarily affects the higher pressure arteries in the systemic circulation (eg, aorta, popliteal arteries, carotid arteries) and the coronary arteries. Significant atherosclerosis in the relatively low-pressure pulmonary arteries is rare.

(Choice B) Fluid overload causes pulmonary edema, typically appearing as alveolar ground glass opacities on CT scan. This patient's lungs appear clear of airspace disease.

(Choice D) An intimal tear can lead to **aortic dissection**, which classically manifests as severe chest pain radiating to the back. Pulmonary artery dissection is extremely rare.

(Choice E) Pulmonary vasculitis (eg, granulomatosis with polyangiitis) could cause dyspnea and chest tightness but would demonstrate an interstitial pattern on CT scan, sometimes leading to **pulmonary hemorrhage**.

(Choice F) Rupture of **pulmonary blebs** (thin-walled, air-filled subpleural structures) leads to pneumothorax.

(Choice G) For **pulmonary metastasis** to cause significant dyspnea, multiple lesions would likely be present. There is no evidence of lung masses on this patient's CT scan.

(Choice A) Atherosclerosis primarily affects the higher pressure arteries in the systemic circulation (eg, aorta, popliteal arteries, carotid arteries) and the coronary arteries. Significant atherosclerosis in the relatively low-pressure pulmonary arteries is rare.

(Choice B) Fluid overload causes pulmonary edema, typically appearing as alveolar ground glass opacities on CT scan. This patient's lungs appear clear of airspace disease.

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(Choice F) Rupture of **pulmonary blebs** (thin-walled, air-filled subpleural structures) leads to pneumothorax.

(Choice G) For **pulmonary metastasis** to cause significant dyspnea, multiple lesions would likely be present. There is no evidence of lung masses on this patient's CT scan.

Educational objective:
Saddle pulmonary embolism straddles the bifurcation of the main pulmonary artery. Venous thromboembolism (ie, pulmonary embolism or deep vein thrombosis) arises due to the Virchow triad of endothelial injury, venous stasis, and a hypercoagulable state. Malignancy causes a hypercoagulable state and is a strong risk factor for venous thromboembolism.

References

- Saddle pulmonary embolism diagnosed by CT angiography: frequency, clinical features and outcome.
- Saddle pulmonary embolism: is it as bad as it looks? A community hospital experience.

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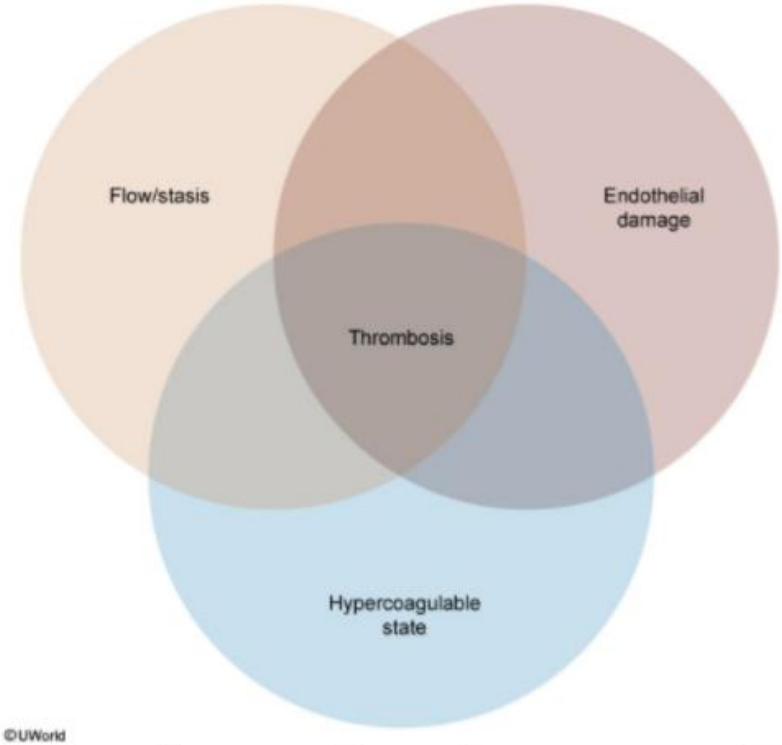
Descending aorta

Exhibit Display

Virchow triad



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(Choice F) Rupture of pulmonary blebs (thin-walled, air-filled subpleural structures) leads to pneumothorax.

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A 9-year-old girl is brought to the emergency department due to prolonged epistaxis. The girl says that she picked her nose immediately before the bleeding started. Her parents decided to bring her to the emergency department after the epistaxis persisted for 20 minutes despite constant compression of the nasal alae. The patient has had frequent nosebleeds that often last >10 minutes. Her family history is significant for a grandfather who had an unspecified bleeding disorder. Given the history of prolonged, recurrent nosebleeds, laboratory tests are ordered, and results are as follows:

Hematocrit	43%
Bleeding time	prolonged
Partial thromboplastin time (PTT)	prolonged
Prothrombin time (PT)	normal
Thrombin time (TT)	normal
D-dimer	normal

Which of the following is the most likely diagnosis?

A. Disseminated intravascular coagulopathy
B. Dysfibrinogenemia
C. Factor XIII deficiency
D. Hemophilia A
E. Hemophilia B

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Hematocrit	43%
Bleeding time	prolonged
Partial thromboplastin time (PTT)	prolonged
Prothrombin time (PT)	normal
Thrombin time (TT)	normal
D-dimer	normal

Which of the following is the most likely diagnosis?

- A. Disseminated intravascular coagulopathy
- B. Dysfibrinogenemia
- C. Factor XIII deficiency
- D. Hemophilia A
- E. Hemophilia B
- F. Vitamin K deficiency
- G. von Willebrand disease

Submit

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Hematocrit	43%
Bleeding time	prolonged
Partial thromboplastin time (PTT)	prolonged
Prothrombin time (PT)	normal
Thrombin time (TT)	normal
D-dimer	normal

Which of the following is the most likely diagnosis?

- A. Disseminated intravascular coagulopathy [0%]
- B. Dysfibrinogenemia [0%]
- C. Factor XIII deficiency [4%]
- D. Hemophilia A [9%]
- E. Hemophilia B [3%]
- F. Vitamin K deficiency [1%]
- ✔ G. von Willebrand disease [80%]

Omitted
Correct answer

80%
Answered correctly

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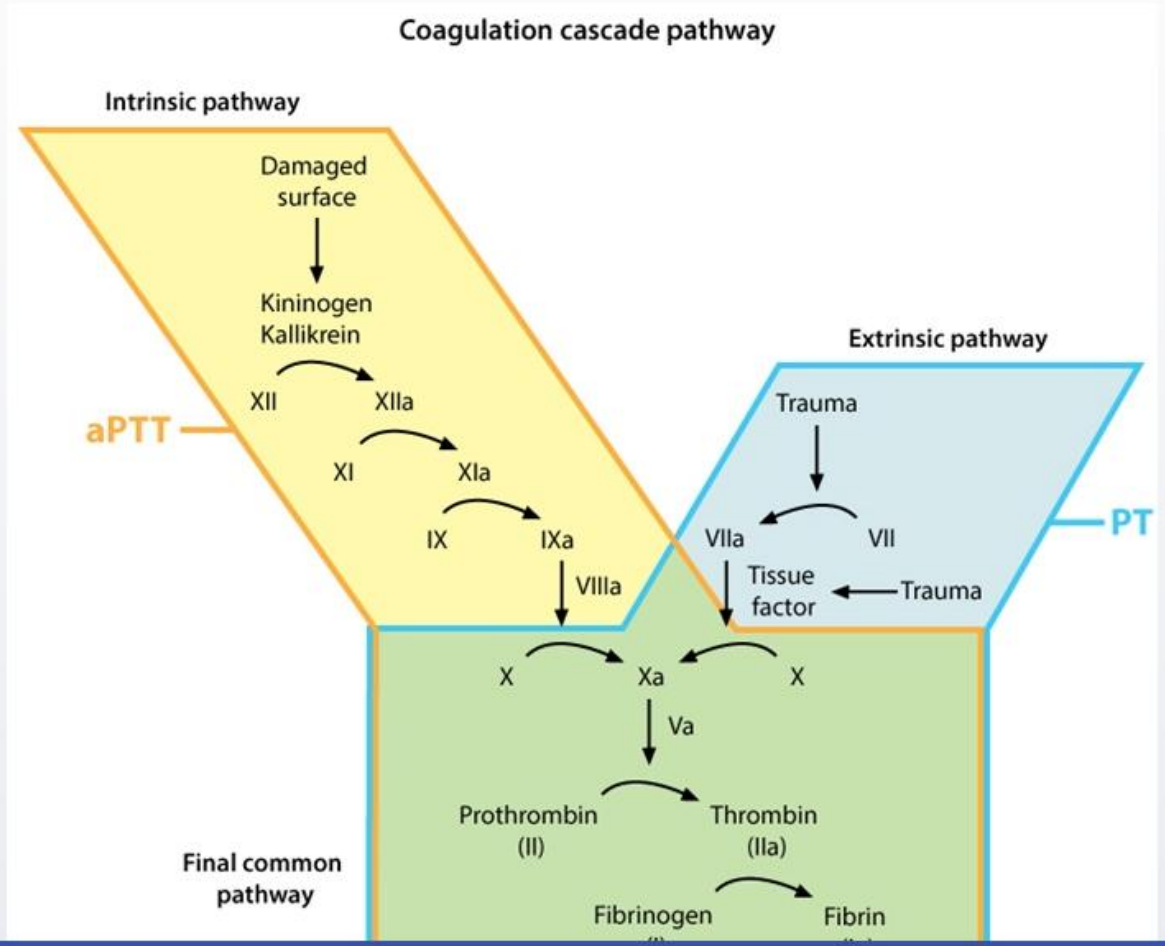

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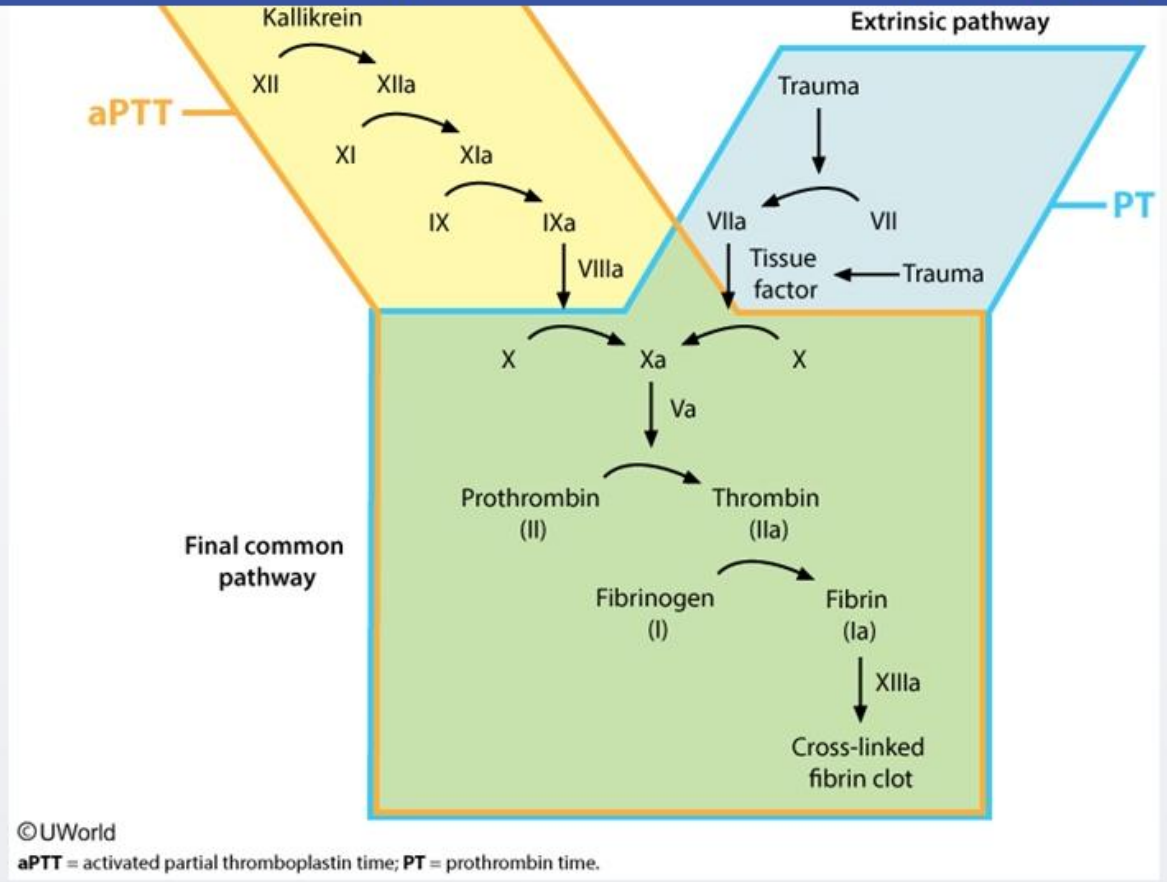

aPTT = activated partial thromboplastin time; **PT** = prothrombin time.

This patient has a normal prothrombin time (PT) and thrombin time (TT) and a **prolonged partial thromboplastin time (PTT)**, indicating a defect in the intrinsic pathway (coagulation factors VIII, IX, XI, or XII). **Bleeding time** is a test of **platelet function** and is prolonged by qualitative and

aPTT = activated partial thromboplastin time; PT = prothrombin time.

This patient has a normal prothrombin time (PT) and thrombin time (TT) and a **prolonged partial thromboplastin time (PTT)**, indicating a defect in the intrinsic pathway (coagulation factors VIII, IX, XI, or XII). **Bleeding time** is a test of **platelet function** and is prolonged by qualitative and quantitative platelet defects. The term "bleeding time" refers to this particular test and not the duration of bleeding, which can be prolonged from other coagulopathies.

von Willebrand disease (vWD) will cause both a prolonged PTT and bleeding time. **von Willebrand factor (vWF)** is produced by endothelial cells and megakaryocytes and functions as a **carrier protein for factor VIII** and as a **mediator of platelet adhesion** to the endothelium. Absence of vWF leads to impaired platelet function and coagulation pathway abnormalities. vWD is inherited in an autosomal dominant fashion with variable penetrance and is the **most common heritable bleeding disorder**.

(Choice A) Disseminated intravascular coagulopathy (DIC) is a consumptive coagulopathy most commonly seen in septic shock. PT, PTT, and bleeding time are prolonged, and the D-dimer, a degradation product of cross-linked fibrin, is elevated.

(Choice B) Dysfibrinogenemias are inherited abnormalities in the fibrinogen molecule that can cause excessive bleeding or thrombophilia. TT, PT, and PTT are abnormal in this condition, but bleeding time is unaffected.

(Choice C) Factor XIII is a transglutaminase that cross-links fibrin polymers, thereby stabilizing clots. Factor XIII deficiency causes spontaneous or excessive bleeding, but it would not prolong the bleeding time, PT, or PTT.

(Choice D) Hemophilia A is an X-linked hereditary deficiency of factor VIII that causes coagulopathy with a prolonged PTT but shows normal bleeding time.

(Choice E) Hemophilia B is an X-linked hereditary deficiency of factor IX that causes coagulopathy with a prolonged PTT but shows normal bleeding time.

(Choice F) Vitamin K is required for activation of clotting factors II, VII, IX, and X. Vitamin K deficiency causes a coagulopathy that primarily prolongs PT, with PTT prolongation occurring in severe cases. Bleeding time is not affected.

Educational objective:

with variable penetrance and is the **most common heritable bleeding disorder**.

(Choice A) Disseminated intravascular coagulopathy (DIC) is a consumptive coagulopathy most commonly seen in septic shock. PT, PTT, and bleeding time are prolonged, and the D-dimer, a degradation product of cross-linked fibrin, is elevated.

(Choice B) Dysfibrinogenemias are inherited abnormalities in the fibrinogen molecule that can cause excessive bleeding or thrombophilia. TT, PT, and PTT are abnormal in this condition, but bleeding time is unaffected.

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Educational objective:
von Willebrand disease is the most common inherited bleeding disorder. It has an autosomal dominant pattern of inheritance and variable penetrance. Absence of von Willebrand factor leads to impaired platelet function (prolonged bleeding time) and coagulation pathway abnormalities due to decreased factor VIII activity (prolonged partial thromboplastin time).

References

- Diagnosis and Management of Von Willebrand disease: guidelines for primary care
- Of von Willebrand factor and platelets.

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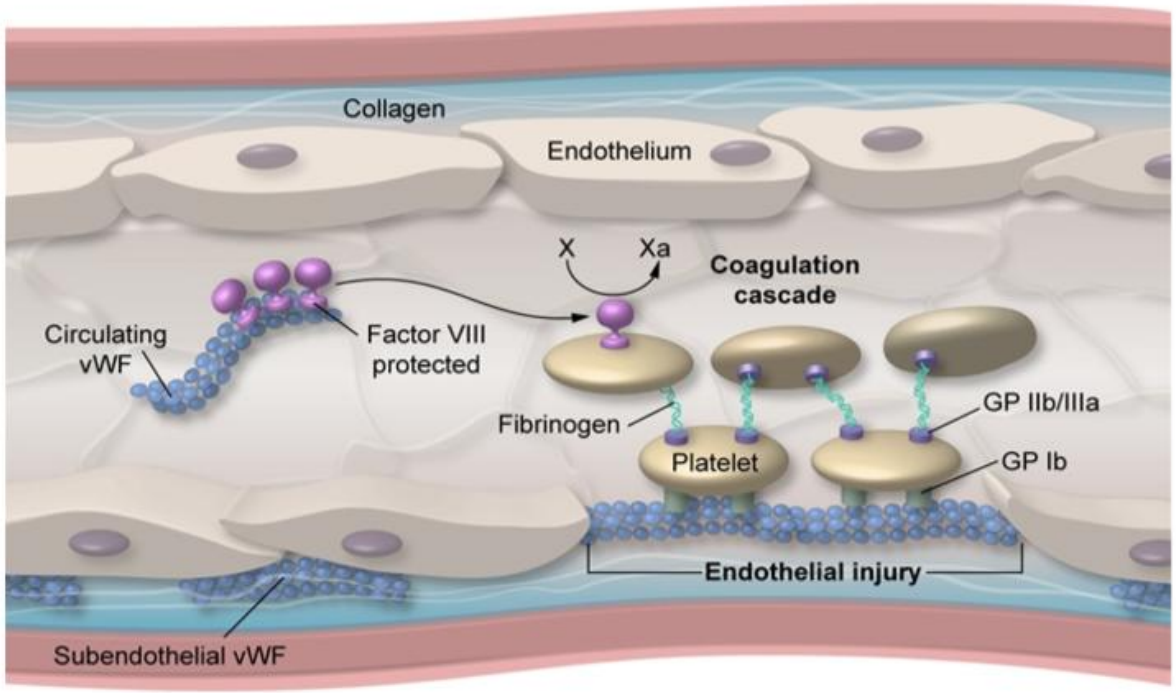
Platelet adhesion & activation via vWF



GP = glycoprotein; vWF = von Willebrand factor.

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bleeding time are prolonged, and the D-dimer, a degradation product of cross-linked fibrin, is elevated.

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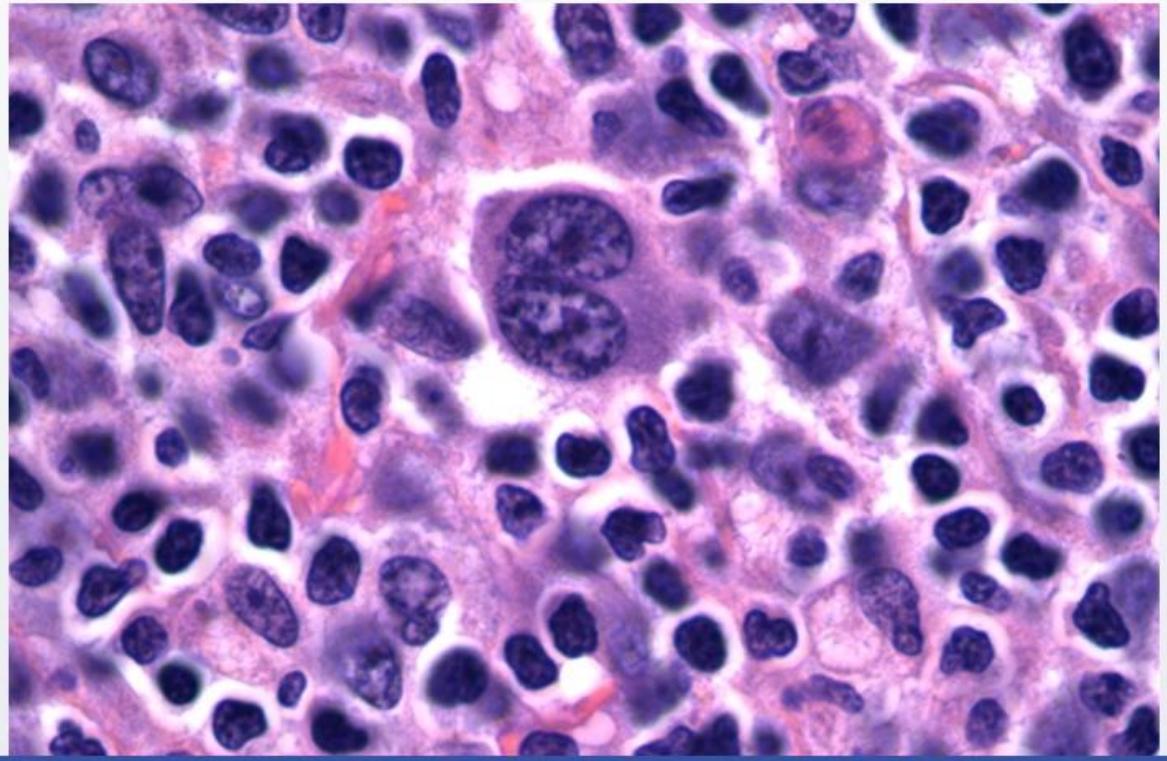
A 28-year-old previously healthy man comes to the office due to episodic fevers, night sweats, and weight loss for several months. He emigrated from Kenya with his family at age 14. He does not use tobacco, alcohol, or illicit drugs. The patient works as a driving instructor and volunteers at a homeless shelter. His temperature is 37.2 C (99 F). Physical examination is normal with the exception of cervical lymphadenopathy. A lymph node biopsy is performed, and a histopathology slide is shown in the image below.



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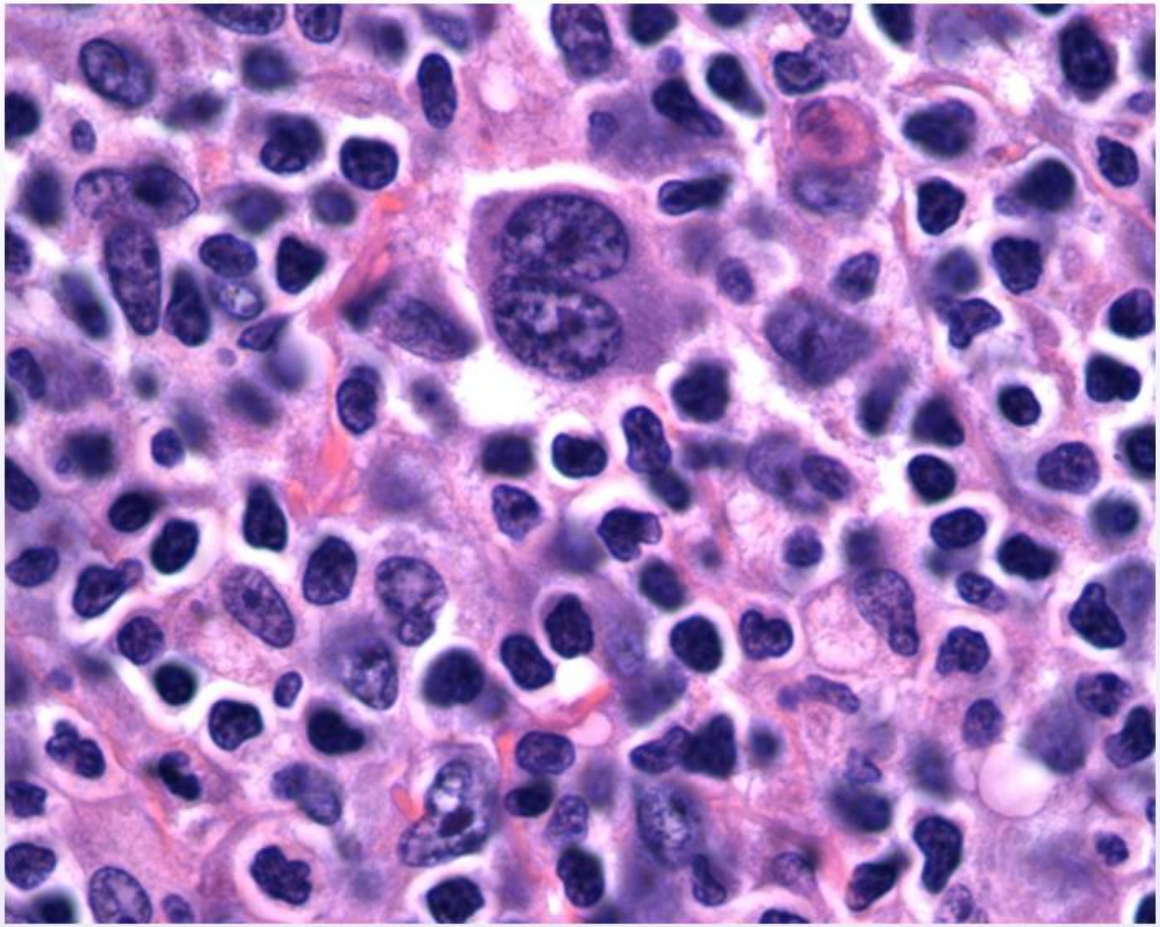

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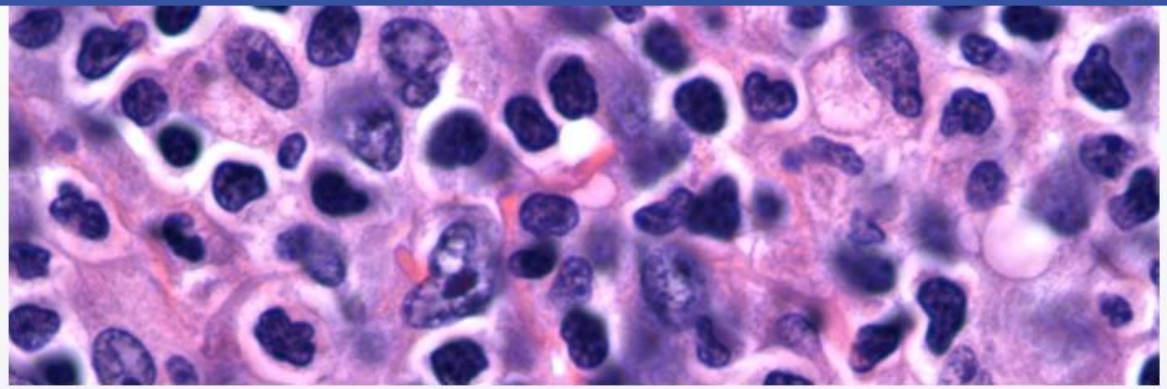

Which of the following is the most likely diagnosis?

A. Burkitt lymphoma
B. Follicular lymphoma
C. Hodgkin lymphoma
D. Large B-cell lymphoma
E. Multiple myeloma
F. Tuberculosis

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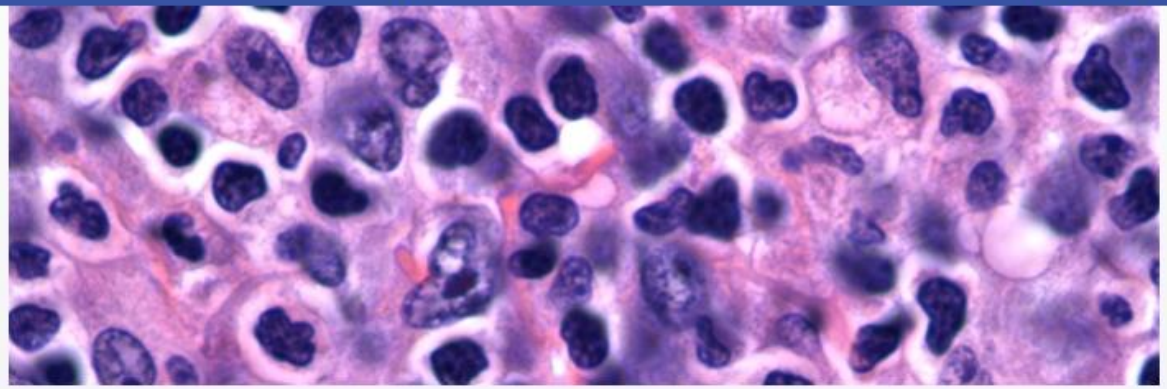

Which of the following is the most likely diagnosis?

- A. Burkitt lymphoma [11%]
- B. Follicular lymphoma [1%]
- ✔ C. Hodgkin lymphoma [83%]
- D. Large B-cell lymphoma [1%]
- E. Multiple myeloma [0%]
- F. Tuberculosis [1%]

Omitted
Correct answer

83%
Answered correctly

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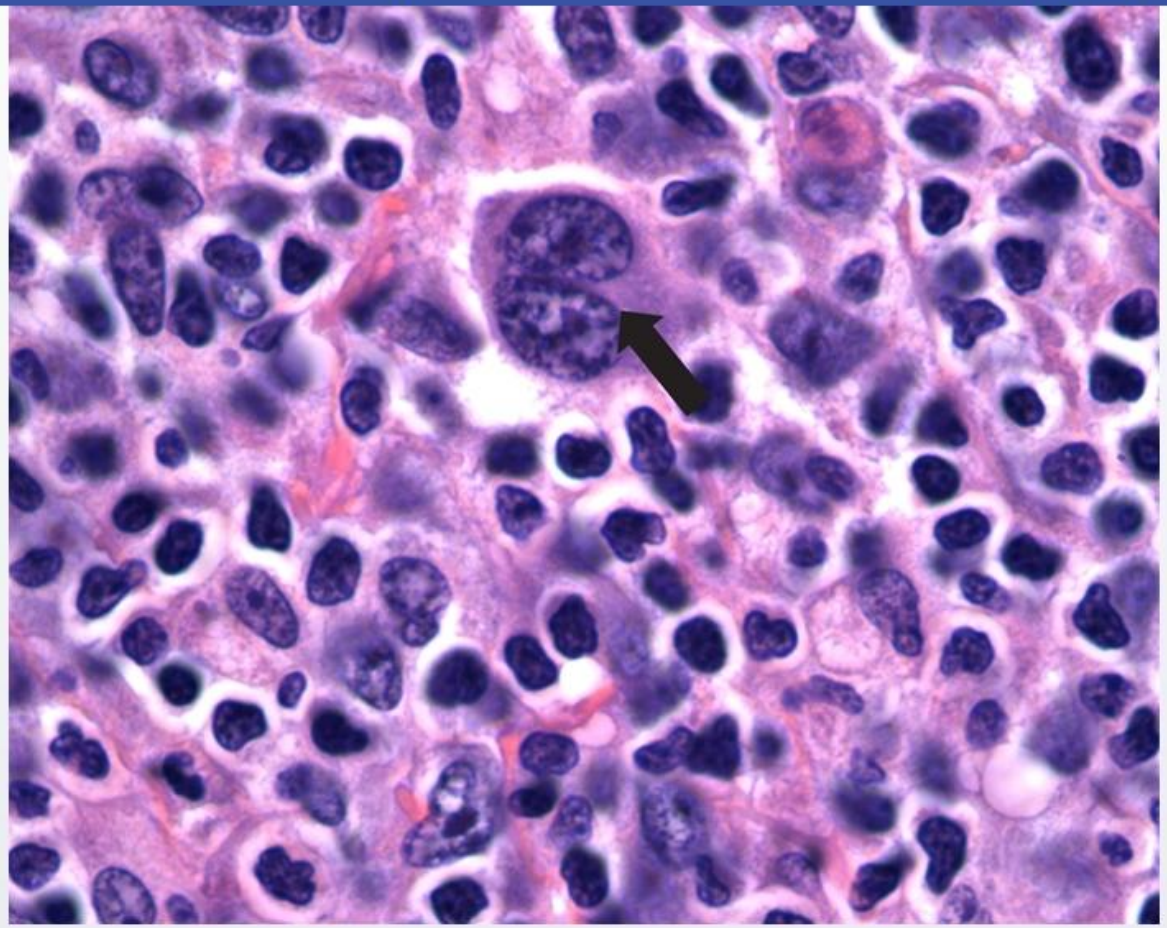

This patient most likely has classic **Hodgkin lymphoma (HL)**. The typical presentation is either nontender **lymphadenopathy** or

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This patient most likely has classic **Hodgkin lymphoma (HL)**. The typical presentation is either nontender **lymphadenopathy** or lymphadenopathy incidentally detected on routine chest x-ray. Many patients develop associated systemic **B symptoms** (fevers, night sweats, weight loss). HL has a **bimodal age distribution** with a peak in the 20s (or younger in some countries) and another in the 60s. The complete blood count and peripheral blood smear are usually unremarkable. A **lymph node biopsy** can definitively distinguish this malignancy from benign causes of lymphadenopathy. The key to diagnosing classic HL is detecting the characteristic **Reed-Sternberg** (RS) cell (arrow) on hematoxylin and eosin preparation. RS cells have ample cytoplasm, bilobed or double nuclei, and inclusion-like eosinophilic nucleoli. RS cells are seen against a background of lymphocytes, histiocytes, and eosinophils in classical HL.

(Choice A) Burkitt lymphoma is a high-grade lymphoma that often presents as a mass in the abdomen, pelvis, or jaw (in endemic cases in Africa with a peak incidence in boys around age 5). However, histology would show a monotonous population of medium-sized lymphocytes with many tingible body macrophages, giving a **"starry sky" appearance**. High numbers of mitotic cells and apoptotic bodies would be seen.

(Choice B) Follicular lymphoma shows aggregates of closely packed lymph node follicles. Two major cell types, centrocytes (small cleaved cells) and centroblasts (large noncleaved cells), are observed. Older adults tend to be affected. Waxing and waning painless lymphadenopathy (typically without B symptoms) is common.

(Choice D) The histological presentation of large B-cell lymphoma is diffuse sheets of large lymphocytes with nuclei at least 5 times the size of small lymphocytes. No RS cells are seen.

(Choice E) Multiple myeloma, a plasma cell dyscrasia characterized by proliferation of mature and immature plasma cells (similar in appearance to normal plasma cells), is predominantly a disease of the elderly. It is characterized by osteolytic lesions, although spread to nodal and extranodal sites can occur.

(Choice F) Tuberculosis is on the differential diagnosis for this patient, who is from Kenya, volunteers at homeless shelters, and has had night

blood count and peripheral blood smear are usually unremarkable. A **lymph node biopsy** can definitively distinguish this malignancy from benign causes of lymphadenopathy. The key to diagnosing classic HL is detecting the characteristic **Reed-Sternberg** (RS) cell (arrow) on hematoxylin and eosin preparation. RS cells have ample cytoplasm, bilobed or double nuclei, and inclusion-like eosinophilic nucleoli. RS cells are seen against a background of lymphocytes, histiocytes, and eosinophils in classical HL.

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(Choice E) Multiple myeloma, a plasma cell dyscrasia characterized by proliferation of mature and immature plasma cells (similar in appearance to normal plasma cells), is predominantly a disease of the elderly. It is characterized by osteolytic lesions, although spread to nodal and extranodal sites can occur.

(Choice F) Tuberculosis is on the differential diagnosis for this patient, who is from Kenya, volunteers at homeless shelters, and has had night sweats and weight loss. However, histology in tuberculosis would show caseating granulomas, not RS cells.

Educational objective:
The presence of Reed-Sternberg (RS) cells on lymph node biopsy is diagnostic of classic Hodgkin lymphoma. RS cells have abundant cytoplasm, bilobed or double nuclei, and inclusion-like eosinophilic nucleoli.

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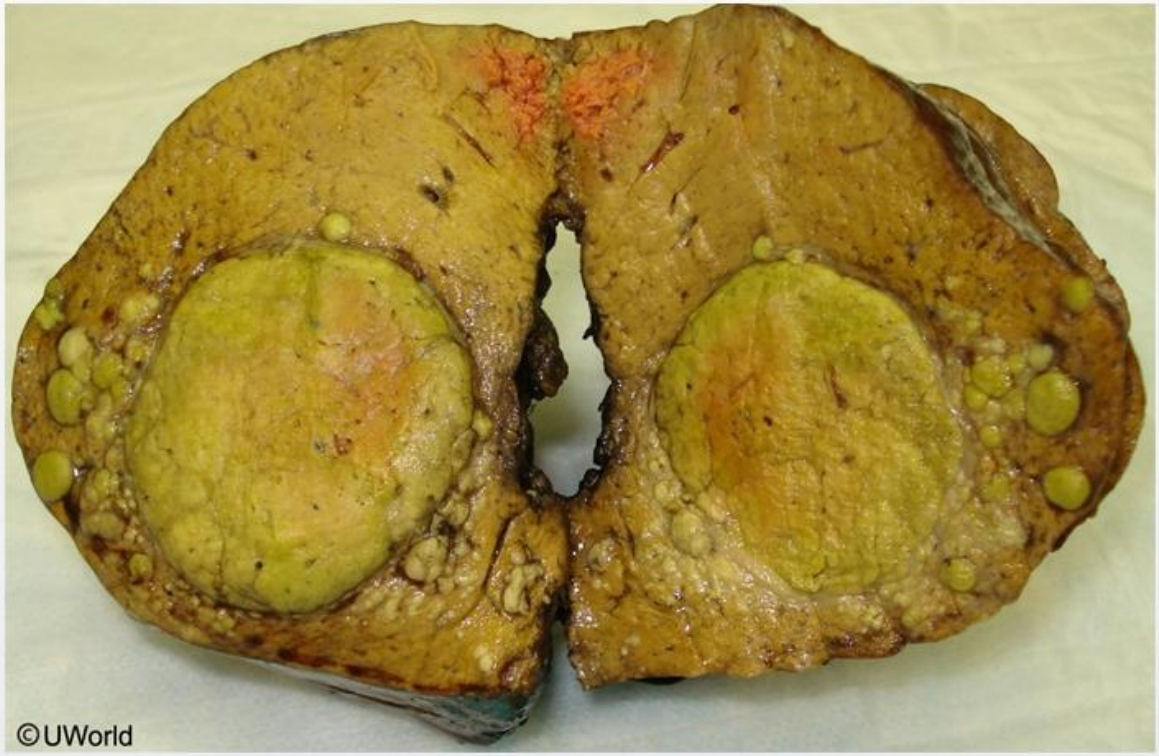
A 64-year-old man is brought to the hospital by ambulance after being found unresponsive by his brother. Despite resuscitative efforts, he dies shortly thereafter. The family reports that the patient had 2 months of progressive fatigue and an unintentional weight loss prior to the episode. Autopsy examination reveals a massive pulmonary embolus, and a cross-section of the liver shows the following:



Genomic analysis of the hepatic lesions demonstrates intranuclear fragments of foreign DNA. These fragments most likely belong to which of the

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Question Id: 58

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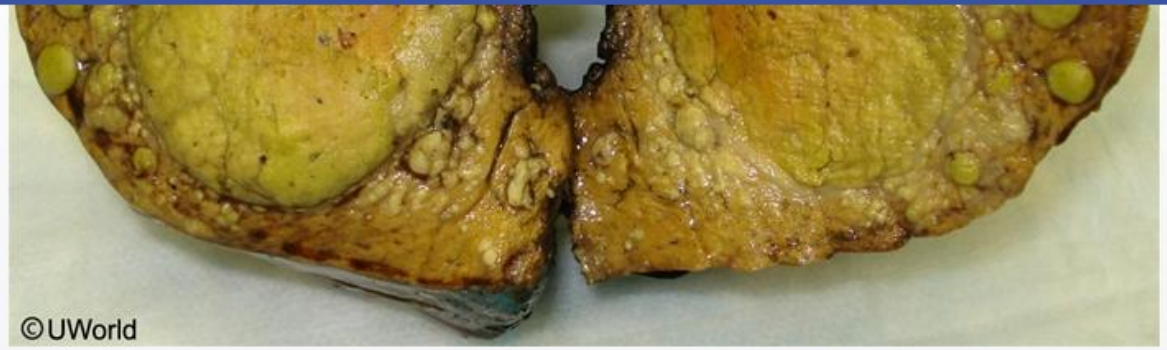

Genomic analysis of the hepatic lesions demonstrates intranuclear fragments of foreign DNA. These fragments most likely belong to which of the following pathogens?

A. Cytomegalovirus
B. *Entamoeba histolytica*
C. Epstein-Barr virus
D. Hepatitis B virus
E. Hepatitis C virus
F. Human papilloma virus

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Question Id: 58

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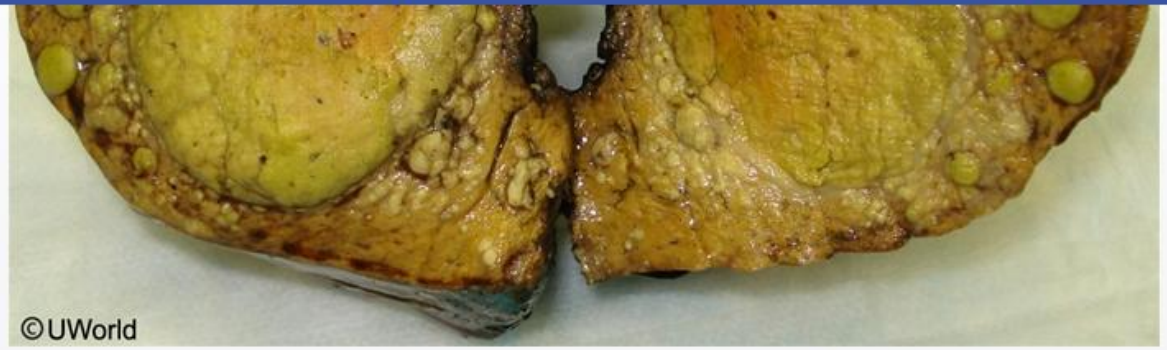

Genomic analysis of the hepatic lesions demonstrates intranuclear fragments of foreign DNA. These fragments most likely belong to which of the following pathogens?

A. Cytomegalovirus [5%]
B. *Entamoeba histolytica* [12%]
C. Epstein-Barr virus [5%]
✔ D. Hepatitis B virus [52%]
E. Hepatitis C virus [22%]
F. Human papilloma virus [0%]

Omitted
Correct answer

52%
Answered correctly

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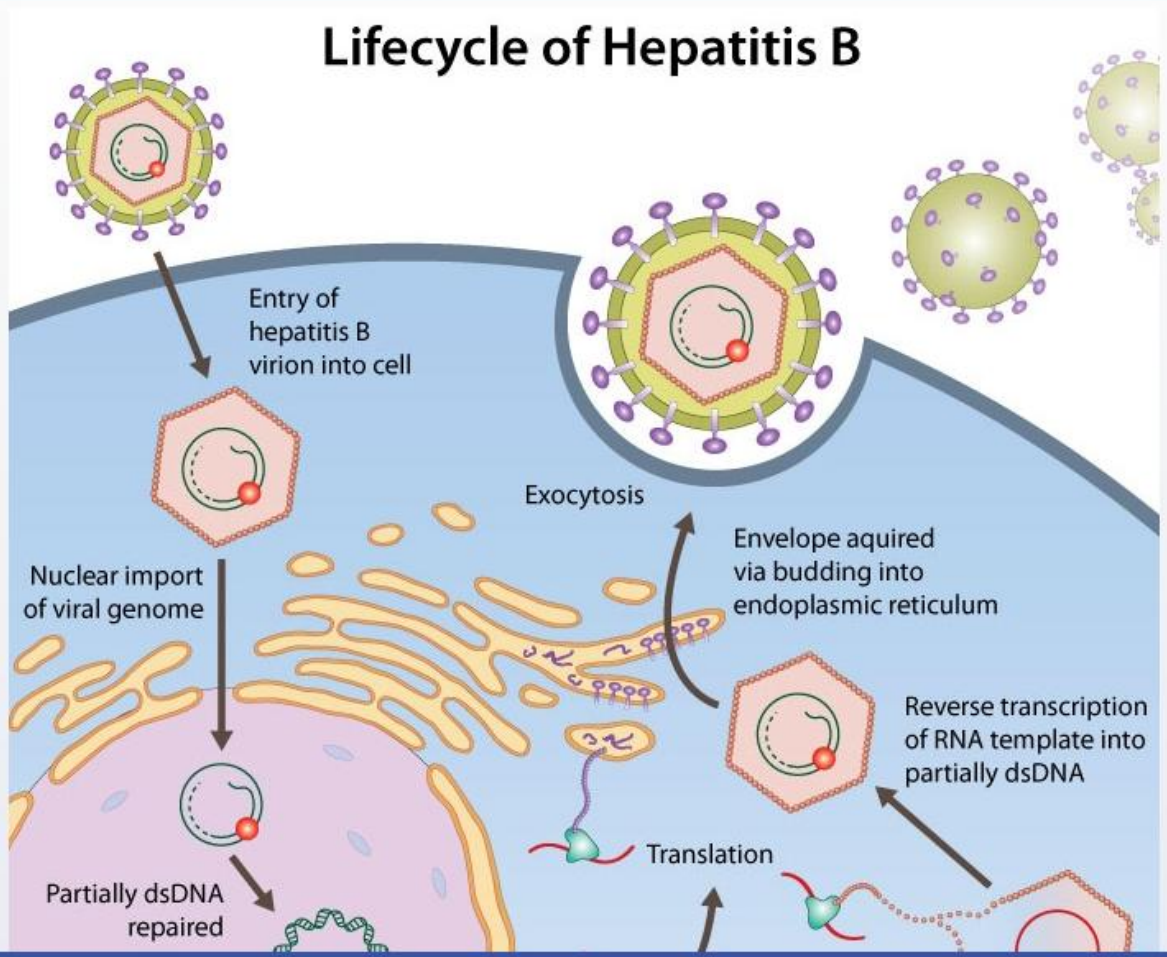

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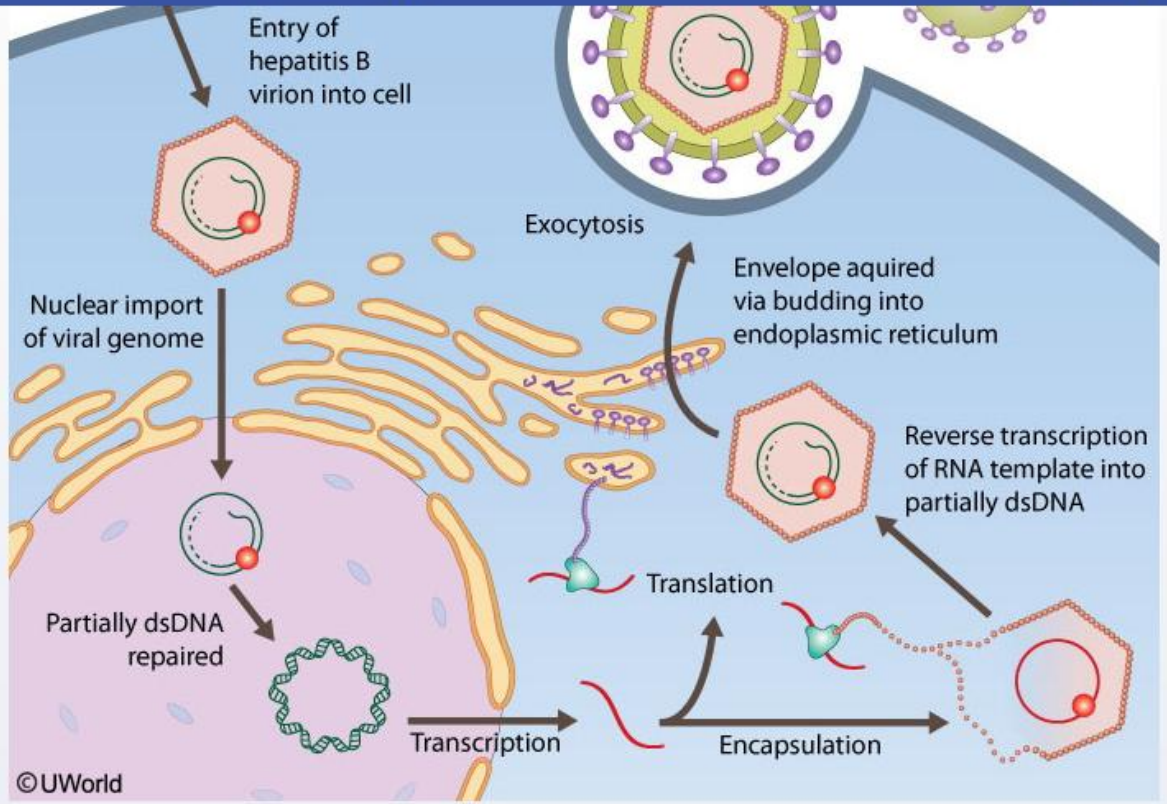

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections dramatically increase the risk of **hepatocellular carcinoma** (HCC). Ongoing infection with either virus leads to **increased hepatocyte turnover** and the generation of local inflammatory cytokines, which can result in genetic mutations that lead to malignant transformation. However, **HBV** has several additional mechanisms that promote HCC, including the following:

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections dramatically increase the risk of **hepatocellular carcinoma** (HCC). Ongoing infection with either virus leads to **increased hepatocyte turnover** and the generation of local inflammatory cytokines, which can result in genetic mutations that lead to malignant transformation. However, **HBV** has several additional mechanisms that promote HCC, including the following:

- **Integration into the host genome** – Nearly 90% of patients with chronic HBV who develop HCC have evidence of HBV DNA in the chromosome of tumor cells. HBV is a partially double-stranded DNA virus that is repaired by host cell machinery into a covalently closed circular DNA strand. Although it is not required for viral replication (unlike HIV), HBV DNA is often inserted into the cellular genome by host topoisomerase I. Integration into regions that control cell growth and differentiation can result in insertional mutagenesis.
- **Production of oncogenic viral proteins** – HBV produces a viral protein called **HBx** that is a transcriptional activator of several genes associated with cellular growth. It also interferes with the function of p53, an important tumor-suppressor protein.

(Choices A and C) Cytomegalovirus and Epstein-Barr virus are members of the *Herpesviridae* family. Both have double-stranded DNA genomes and cause acute infection followed by latent infection. Cytomegalovirus is not particularly associated with cancer, but Epstein-Barr infection is linked to nasopharyngeal carcinoma and hematologic malignancies. However, neither virus incorporates its genome into the host cell.

(Choice B) *Entamoeba histolytica* is a protozoal infection that is typically acquired by ingesting contaminated food or water in developing countries. A minority of patients develops invasive disease with liver abscess. This usually presents with fever and right-upper quadrant pain. The organism does not incorporate its genome into host cells.

(Choice E) Chronic HCV infection dramatically increases the risk of HCC. However, HCV is an RNA virus (that does not have reverse transcriptase) and is unable to integrate into the host genome.

(Choice F) Human papilloma virus is a double-stranded DNA virus of the papillomavirus family. HPV produces oncogenic proteins and is able to integrate into the host chromosome. However, HPV is not linked with liver cancer; it typically causes cervical and oropharyngeal cancer.

Educational objective:

topoisomerase I. Integration into regions that control cell growth and differentiation can result in insertional mutagenesis.

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Educational objective:
Both hepatitis B (HBV) and hepatitis C virus infections increase the risk of hepatocellular carcinoma due to chronic hepatic inflammation and cell turnover. HBV is also carcinogenic due to the production of oncogenic proteins and the insertion of the HBV genome into the host chromosome.

References

- Role of hepatitis B virus DNA integration in human hepatocarcinogenesis.

A 20-year-old man is brought to the emergency department (ED) due to a day of fevers, headache, and neck pain. He has no significant past medical history. Temperature is 38.7 C (101.6 F), blood pressure is 120/72 mm Hg, pulse is 112/min, and respirations are 26/min. On physical examination, neck stiffness and a truncal petechial rash are present. Cerebrospinal fluid (CSF) analysis shows the following:

Glucose	30 mg/dL
Protein	180 mg/dL
Leukocytes	1,500/mm^3
Neutrophils	70%

CSF gram stain shows gram-negative diplococci. While in the ED, the patient's hemodynamic status deteriorates rapidly. His blood pressure drops to 80/50 mm Hg, and he starts to bleed from the venous access sites. Which of the following findings is most likely to be seen on this patient's peripheral smear?

- A. Acanthocytes
- B. Bite cells
- C. Schistocytes
- D. Spherocytes
- E. Target cells
- F. Teardrop cells

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Neutrophils	70%

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- A. Acanthocytes [5%]
- B. Bite cells [3%]
- ✔ C. Schistocytes [81%]
- D. Spherocytes [2%]
- E. Target cells [3%]
- F. Teardrop cells [3%]

Omitted
Correct answer

81%
Answered correctly

4 Seconds
Time Spent

11/10/2018
Last Updated

Explanation

This patient likely has sepsis from meningococcal meningitis, given his clinical findings (fever, headache, neck stiffness, rash) and cerebrospinal (CSF) analysis results (elevated protein, low glucose, leukocytosis, gram-negative diplococci). Bleeding from venous puncture sites is highly suggestive of **disseminated intravascular coagulopathy** (DIC) (associated with sepsis and also seen with acute pancreatitis and burn injury, among others).

In DIC due to gram-negative **sepsis**, the coagulation cascade is activated by bacterial **endotoxins**, leading to widespread fibrin deposition and consumption of coagulation factors and platelets, with eventual **bleeding**. The excess fibrin strands exert shearing forces on circulating erythrocytes, resulting in **schistocytes** (fragmented erythrocytes) on peripheral smear. Laboratory values in DIC typically show decreased platelet count, fibrinogen, and factor V and VIII levels, with prolonged prothrombin and partial thromboplastin times.

(Choice A) **Acanthocytes** are cells with irregularly spaced surface projections that vary in length and width. Spur cells are the extreme form of acanthocytosis. These cells are typical of abetalipoproteinemia.

(Choice B) **Bite cells** are typical of oxidant-induced damage, as found in glucose-6-phosphate dehydrogenase deficiency. Bite cells occur when the splenic monocyte-macrophage system removes Heinz bodies from erythrocytes.

(Choice D) **Spherocytes** are small, round erythrocytes without normal central pallor. They are commonly seen in hereditary spherocytosis, but they are also present in autoimmune hemolytic anemia, burns, and blood samples that are not fresh.

(Choice E) **Target cells**, which have a "bull's-eye" morphology with a central concentration of hemoglobin surrounded by a colorless area, can be seen in many conditions, including obstructive liver disease, thalassemia, iron deficiency anemia, and asplenia. Although meningococcal infection is associated with asplenia, it can develop with intact splenic function, such as in this patient who has no past medical history suggesting asplenia.

(Choice F) **Teardrop cells** are typically seen in myelofibrosis. When bone marrow is replaced with fibrosis (or metastatic cancer), red blood cells must squeeze through the fibrous strands, later appearing in the peripheral smear as characteristic teardrop cells.

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Educational objective:
Disseminated intravascular coagulation (DIC) is a common complication of gram-negative bacterial sepsis, acute pancreatitis, and burn injury. In gram-negative sepsis, DIC results from activation of the coagulation cascade by bacterial endotoxins, causing the formation of microemboli. Peripheral smear shows fragmented erythrocytes (schistocytes) and thrombocytopenia. Laboratory tests show decreased fibrinogen levels and prolonged prothrombin and partial thromboplastin times.

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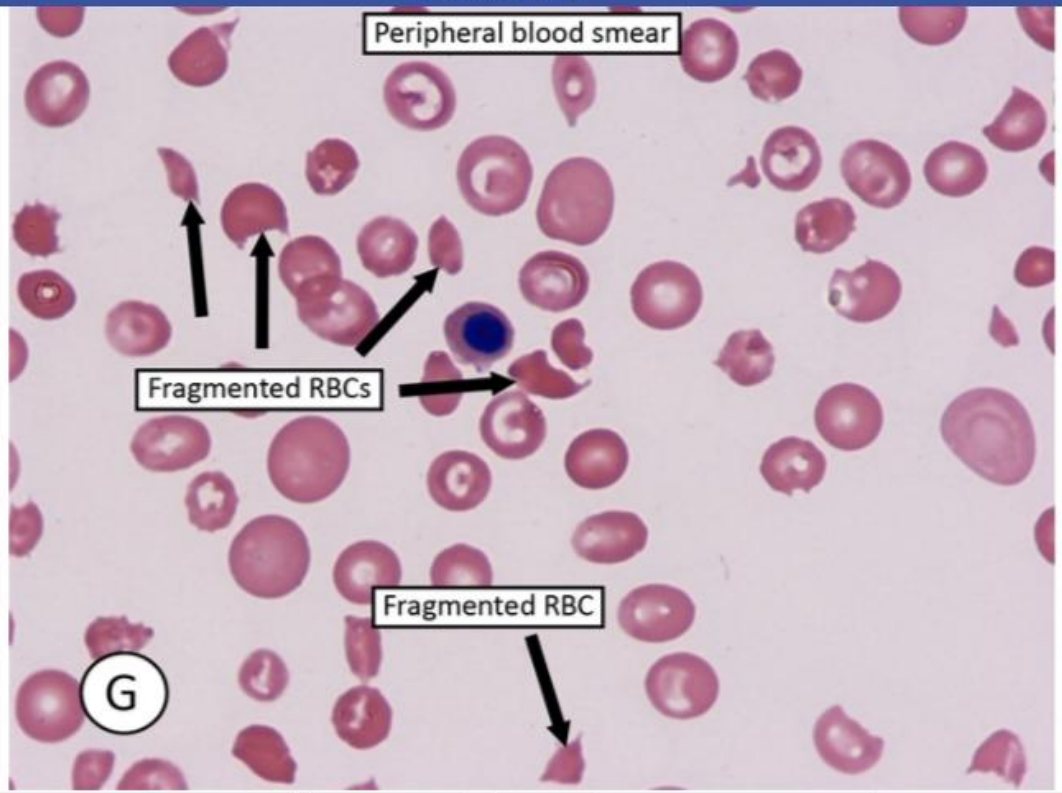

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must squeeze through the fibrous strands, later appearing in the peripheral smear as characteristic teardrop cells.

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Item 16 of 34
Question Id: 1088

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A 72-year-old woman comes to the office for a routine follow-up appointment. She has no symptoms and her past medical history is insignificant. Her temperature is 36.7 C (98 F), blood pressure is 110/80 mm Hg, and pulse is 76/min and irregular. ECG shows atrial fibrillation with no ischemic changes. Anticoagulation therapy with warfarin is initiated for stroke prevention. Two days later, the patient is hospitalized with severe skin and subcutaneous fat necrosis. Drug effects on which of the following processes are most likely responsible for this patient's skin findings?

A. Factor IX synthesis
B. Factor VIIa activity
C. Factor XIa activity
D. Fibrinogen conversion
E. Protein C activity
F. Prothrombin conversion

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Item 16 of 34
Question Id: 1088

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- A. Factor IX synthesis [2%]
- B. Factor VIIa activity [6%]
- C. Factor XIa activity [0%]
- D. Fibrinogen conversion [2%]
- ✔ E. Protein C activity [83%]
- F. Prothrombin conversion [2%]

Omitted
Correct answer
E

83%
Answered correctly

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Last Updated

Explanation

This patient has **warfarin-induced skin necrosis**, a rare but important complication of warfarin initiation. It is thought to be due to a **transient hypercoagulable state** that can occur during the **first few days** of warfarin therapy.

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Explanation

This patient has **warfarin-induced skin necrosis**, a rare but important complication of warfarin initiation. It is thought to be due to a **transient hypercoagulable state** that can occur during the **first few days** of warfarin therapy.

The overall anticoagulant effect of **warfarin** is due primarily to its inhibition of the vitamin K-dependent gamma-carboxylation of clotting factors II, VII, IX, and X ("vitamin K-dependent clotting factors"). However, warfarin also decreases carboxylation of proteins C and S, which normally exert an anticoagulant effect (through proteolysis and deactivation of factors V and VIII). **Protein C** has a **short half-life**, so its anticoagulant activity is reduced quickly when warfarin therapy is initiated, by about 50% within the first day. During this time, the vitamin K-dependent clotting factors II, IX, and X continue to exert a procoagulant effect as they have longer half-lives (factor VII has a short half-life similar to protein C).

This difference in half-lives translates into a transient hypercoagulable state:

Decreased protein C (anticoagulant) activity → procoagulant effect
Persistent clotting factor II, IX, and X activity → procoagulant effect

Thrombosis and clot can interrupt blood flow to the skin and lead to skin necrosis. For this reason, overlapping coadministration of heparin **("heparin bridge")** is commonly used when warfarin is initiated. The risk of warfarin-induced skin necrosis is increased in patients with a preexisting protein C deficiency, as well as in those started on a large loading dose of warfarin.

(Choice A) Warfarin affects coagulation factor carboxylation, not synthesis.

(Choice B) Factor VII inhibition by warfarin has an anticoagulant effect.

(Choice C) Warfarin does not have a major direct effect on factor XI activity that would cause skin necrosis.

(Choices D and F) Fibrinogen and prothrombin activity may be impacted downstream, but this is not the primary process affected by warfarin.

Educational objective:

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Educational objective:
Warfarin inhibits proteins C and S (natural anticoagulants present in blood), which can lead to skin necrosis, particularly in patients with protein C or S deficiency. This complication is usually seen in the first few days of warfarin therapy.

References

- Coumadin-induced skin necrosis in a 64 year-old female despite LMWH bridging therapy.

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Question Id: 7643

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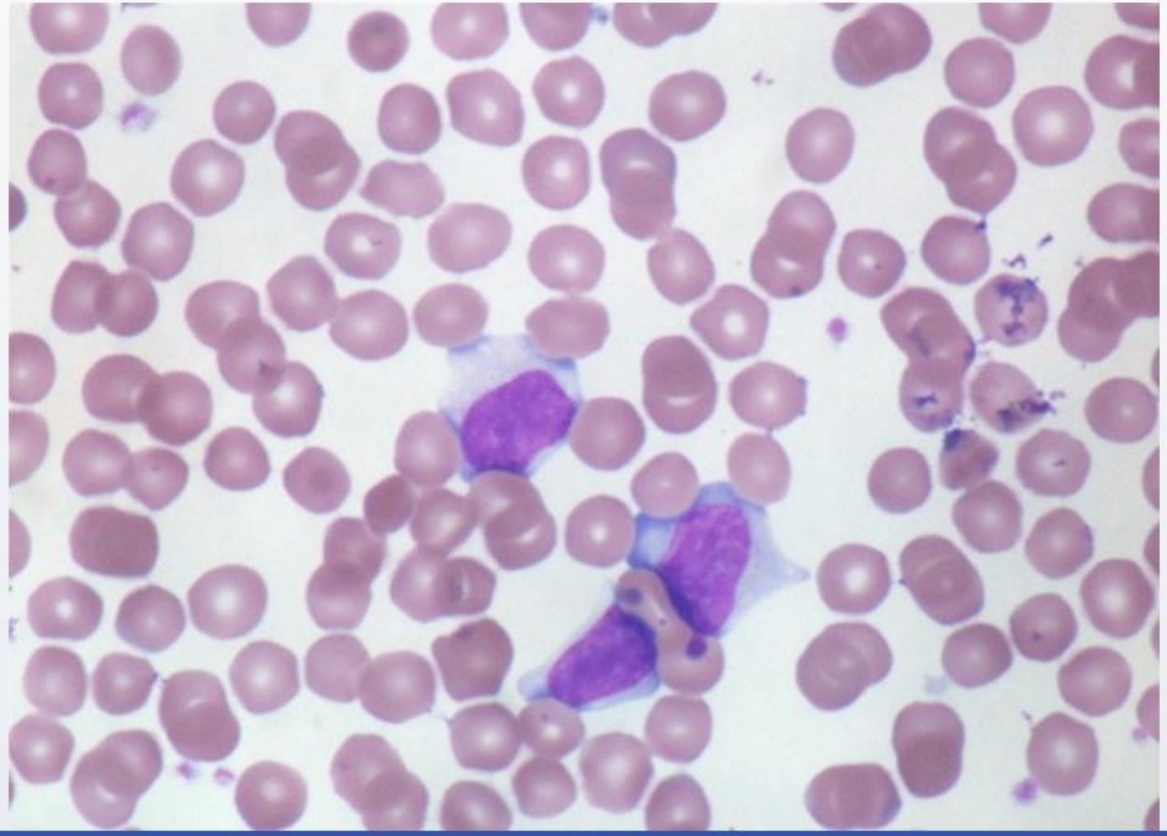
A 15-year-old woman is being evaluated for persistent fever and sore throat. Physical examination reveals anterior and posterior cervical lymphadenopathy and splenomegaly. Her peripheral blood smear is shown below.



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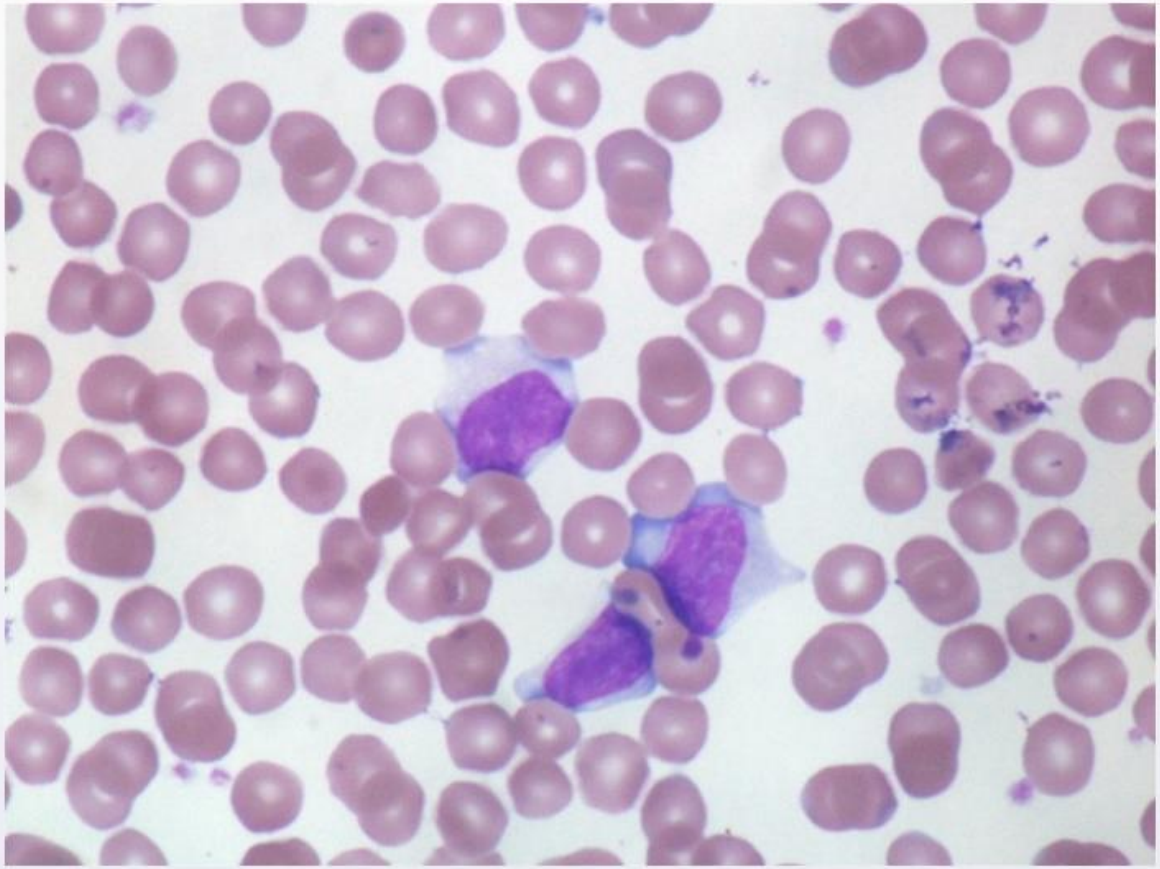

The atypical cells are most likely which of the following?

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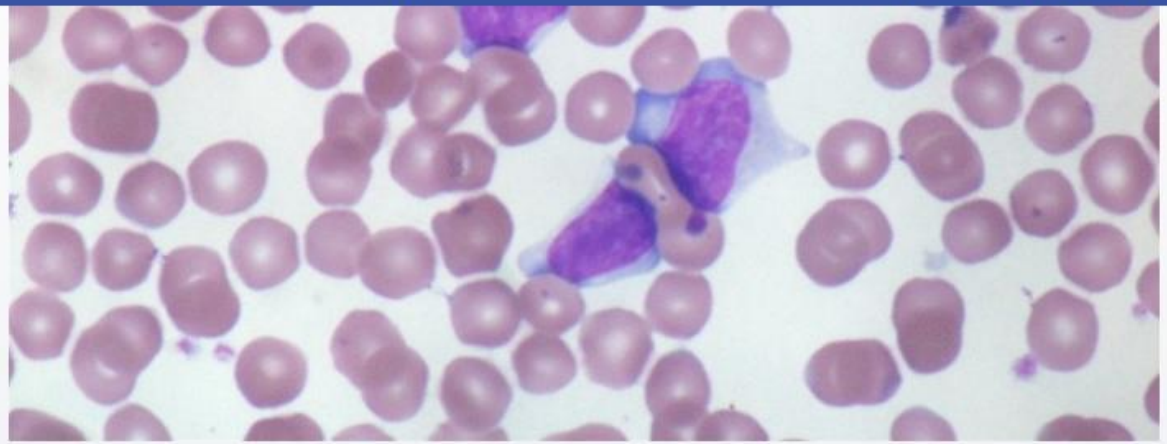

The atypical cells are most likely which of the following?

- A. Activated CD8+ cytotoxic lymphocytes
- B. Activated CD4+ helper lymphocytes
- C. Proliferating CD21+ lymphocytes
- D. Activated plasma cells
- E. CD14+ inflammatory cells

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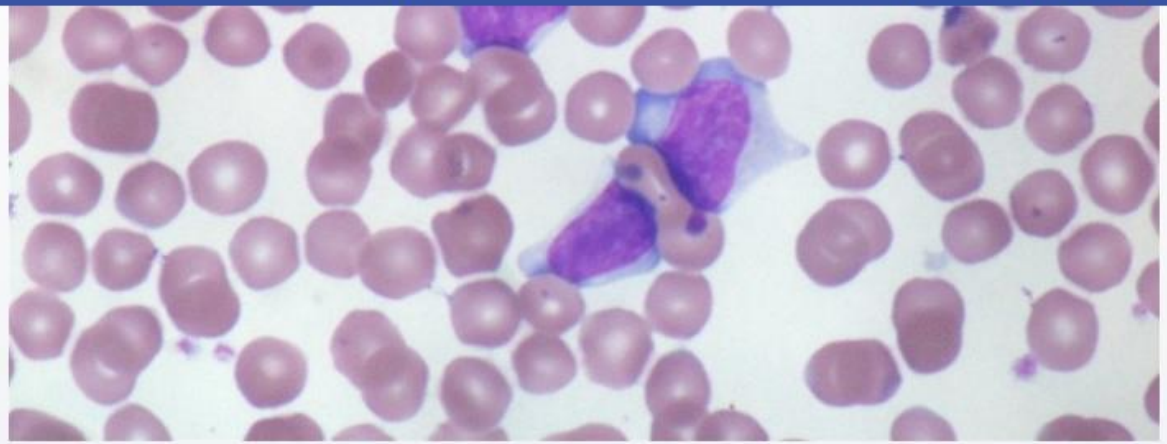

The atypical cells are most likely which of the following?

- A. Activated CD8+ cytotoxic lymphocytes [46%] ✔
- B. Activated CD4+ helper lymphocytes [12%]
- C. Proliferating CD21+ lymphocytes [27%]
- D. Activated plasma cells [9%]
- E. CD14+ inflammatory cells [4%]

Omitted
Correct answer

46%
Answered correctly

9 Seconds
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Item 17 of 34
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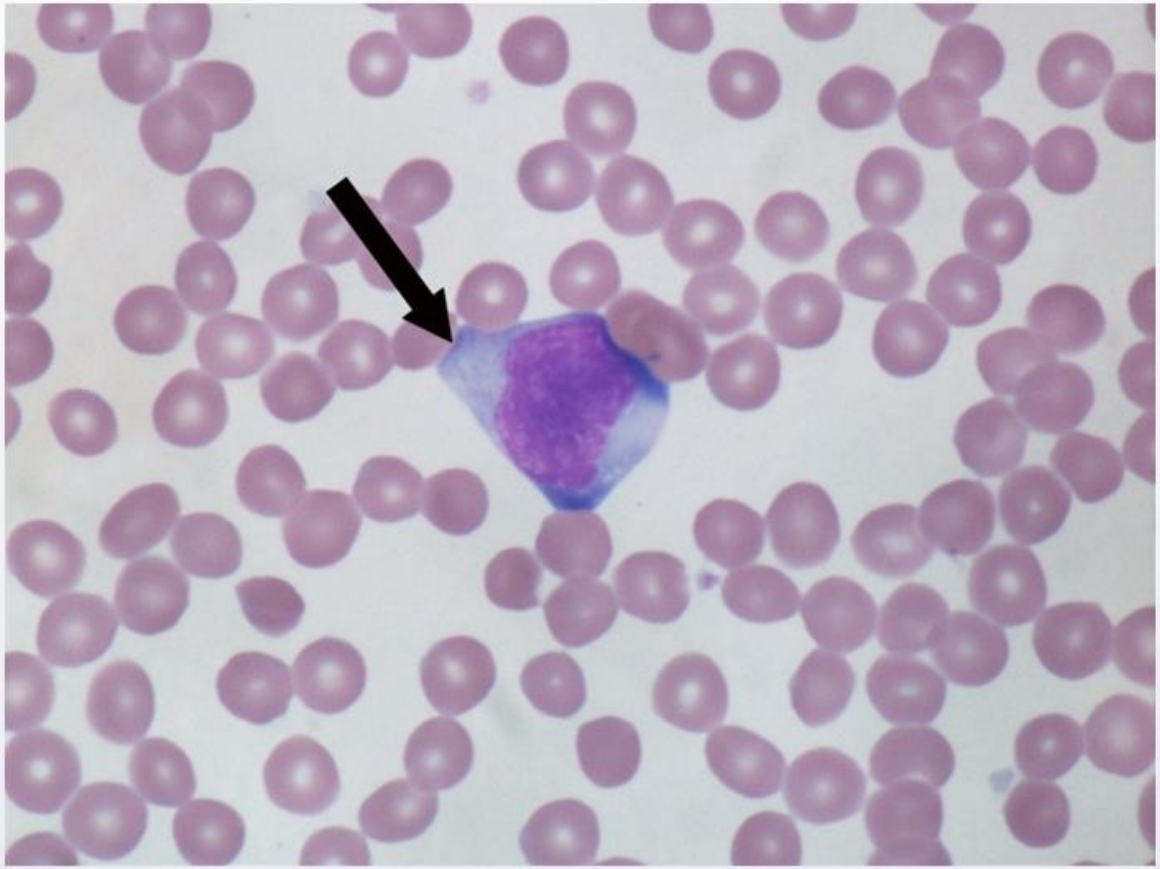

Infectious mononucleosis (IM) is a disease characterized by sore throat, malaise, lymphadenopathy, myalgias, splenomegaly, and fever. The

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Infectious mononucleosis (IM) is a disease characterized by sore throat, malaise, lymphadenopathy, myalgias, splenomegaly, and fever. The causative agent in IM is the Epstein-Barr virus. After infecting the pharyngeal mucosa and tonsillar crypts, the virus gains access to the bloodstream where it preferentially infects B-lymphocytes by binding to the CD21 cell surface receptor. Cytotoxic T-lymphocytes (CD8+) clonally expand in response to the EBV infected B-lymphocytes in an effort to destroy the virally-infected cells. These reactive (atypical) CD8+ T-lymphocytes may be seen on peripheral blood smear in IM. They classically appear as cells much larger than quiescent lymphocytes with abundant cytoplasm, an eccentrically-placed nucleus, and a cell membrane that appears to conform to the borders of neighboring cells.

(Choice B) The proportion of CD4+ helper lymphocytes to CD8+ cytotoxic lymphocytes is decreased in active EBV infection.

(Choice C) CD21 is the receptor for the C3d complement component and is found on the surface of mature B-lymphocytes. B-lymphocytes also proliferate during the acute phase of EBV infection in IM, but they represent only a small fraction (~5%) of the atypical lymphocytes seen on peripheral blood smear.

(Choice D) Activated plasma cells appear histologically as ovoid cells with abundant cytoplasm and an eccentric nucleus. The nucleus in active plasma cells classically has a wagon wheel appearance. A zone of perinuclear clearing within the cytoplasm may also be noted, corresponding to the active Golgi body.

(Choice E) CD14 is a cell surface marker characteristically expressed on monocytes and macrophages; it serves as a receptor for lipopolysaccharide (LPS). Binding of LPS to this receptor results in activation of the macrophage.

Educational objective:
Atypical lymphocytes observed in the peripheral blood smears of patients with infectious mononucleosis represent activated CD8+ cytotoxic T-lymphocytes. These activated T-lymphocytes function to destroy virally-infected B-lymphocytes.

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Question Id: 1084

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A research scientist injects hepatocellular carcinoma cells into the liver parenchyma of an experimental guinea pig. Serial observations show that the tumor cells progressively proliferate and invade the liver parenchyma to form a large mass. After some time, malignant cells begin to penetrate the vascular basement membrane to gain access to the circulation. During the process of basement membrane invasion, expression of which of the following substances is most likely to be increased in the tumor cells?

- A. Acid hydrolase
- B. Alkaline phosphatase
- C. Carboxypeptidase
- D. E-cadherin
- E. Hyaluronic acid
- F. Metalloproteinase

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Item 18 of 34
Question Id: 1084

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A research scientist injects hepatocellular carcinoma cells into the liver parenchyma of an experimental guinea pig. Serial observations show that the tumor cells progressively proliferate and invade the liver parenchyma to form a large mass. After some time, malignant cells begin to penetrate the vascular basement membrane to gain access to the circulation. During the process of basement membrane invasion, expression of which of the following substances is most likely to be increased in the tumor cells?

A. Acid hydrolase [3%]
B. Alkaline phosphatase [3%]
C. Carboxypeptidase [2%]
D. E-cadherin [19%]
E. Hyaluronic acid [4%]
✔ F. Metalloproteinase [66%]

Omitted
Correct answer
F

66%
Answered correctly

2 Seconds
Time Spent

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Explanation

Metalloproteinases are zinc-containing enzymes that degrade components of the extracellular matrix (ECM) and basement membrane, which are composed primarily of laminin and collagens IV and VII. These enzymes participate in many physiologic processes, such as tissue remodeling

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Explanation

Metalloproteinases are zinc-containing enzymes that degrade components of the extracellular matrix (ECM) and basement membrane, which are composed primarily of laminin and collagens IV and VII. These enzymes participate in many physiologic processes, such as tissue remodeling and embryogenesis. They also facilitate **basement membrane penetration**, which distinguishes an invasive tumor from carcinoma in situ and includes the following steps:

1. Tumor cells **detach** from surrounding cells in a process commonly determined by decreased (rather than increased) expression of adhesion molecules, including **E-cadherins (Choice D)**
2. Tumor cells **adhere** to the basement membrane; this is facilitated by increased expression of **laminin** and other adhesion molecules
3. Tumor cells **invade** the basement membrane via enhanced secretion of **proteolytic enzymes** (eg, **metalloproteinases**, cathepsin D protease)

(Choice A) Acid hydrolases, which function at acidic pH, are primarily degradative lysosomal enzymes.

(Choice B) In humans, alkaline phosphatase is concentrated in liver cells; elevated levels suggest an obstructive biliary process.

(Choice C) Carboxypeptidases cleave peptide bonds at the carboxy-terminal; some participate in the synthesis of insulin and neuropeptides.

(Choice E) Hyaluronic acid is an ECM component.

Educational objective:
Metalloproteinases are zinc-containing enzymes that degrade the extracellular matrix. They participate in normal tissue remodeling and in tumor invasion through the basement membrane and connective tissue.

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Item 19 of 34
Question Id: 614

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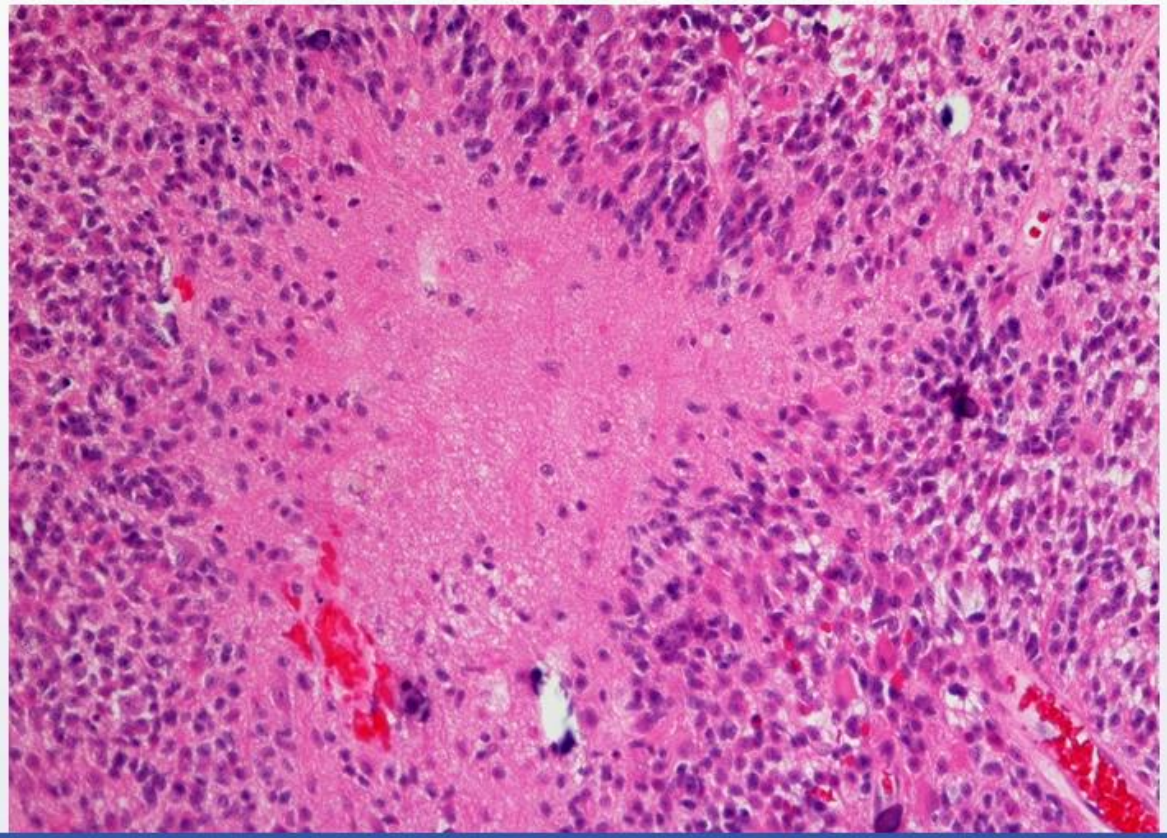
A 64-year-old man complaining of a new-onset headache is diagnosed with an intracranial mass after abnormal magnetic resonance imaging of his brain. The mass is biopsied, and light microscopy of the tissue specimen is shown in the image below.



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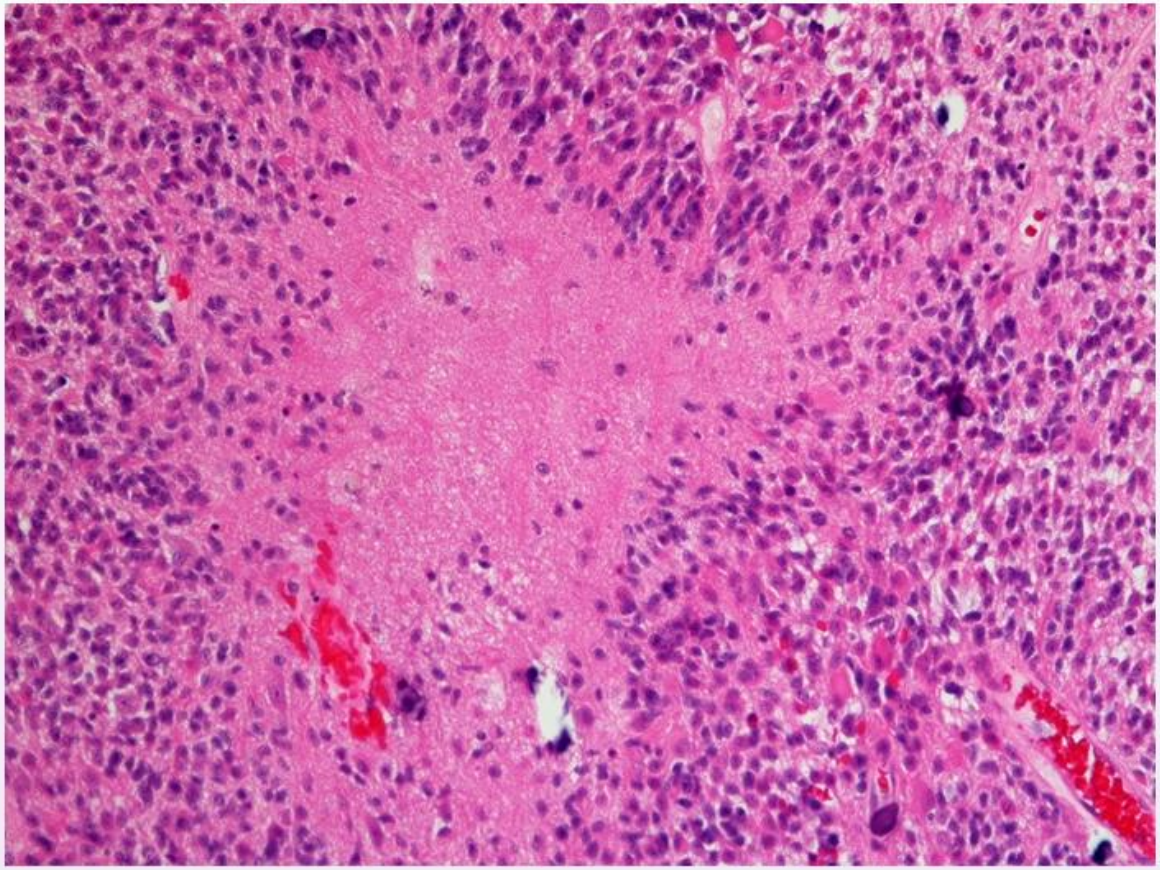

Which of the following histological findings is most characteristic of this lesion?

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Question Id: 614

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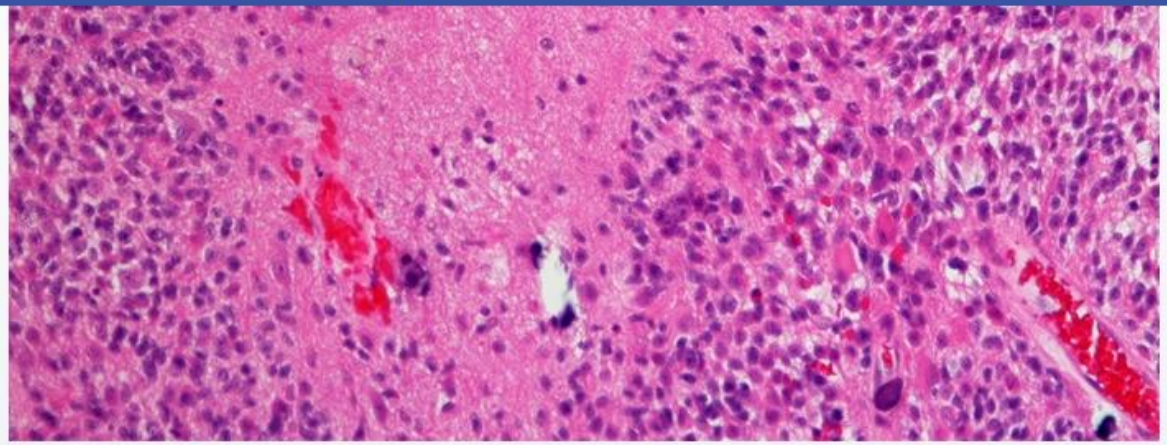

Which of the following histological findings is most characteristic of this lesion?

A. Cyst formation and rare mitoses
B. Necrosis and vascular proliferation
C. Inflammatory cell infiltrate and reticulin deposits
D. Microscopic to massive calcium deposition
E. Exclusive infratentorial location

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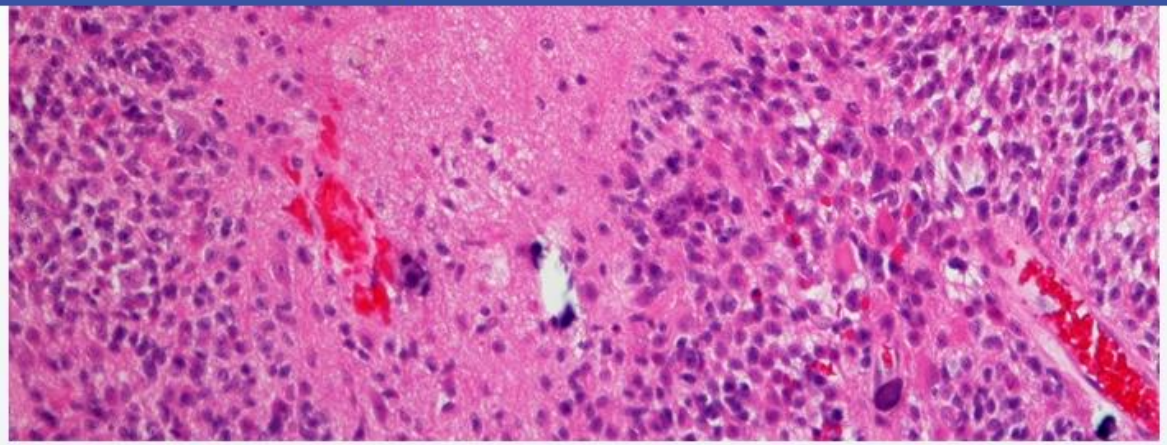

Which of the following histological findings is most characteristic of this lesion?

- A. Cyst formation and rare mitoses [4%]
- ✔ B. Necrosis and vascular proliferation [67%]
- C. Inflammatory cell infiltrate and reticulin deposits [19%]
- D. Microscopic to massive calcium deposition [5%]
- E. Exclusive infratentorial location [2%]

Omitted
Correct answer

67%
Answered correctly

11 Seconds
Time Spent

10/21/2018
Last Updated

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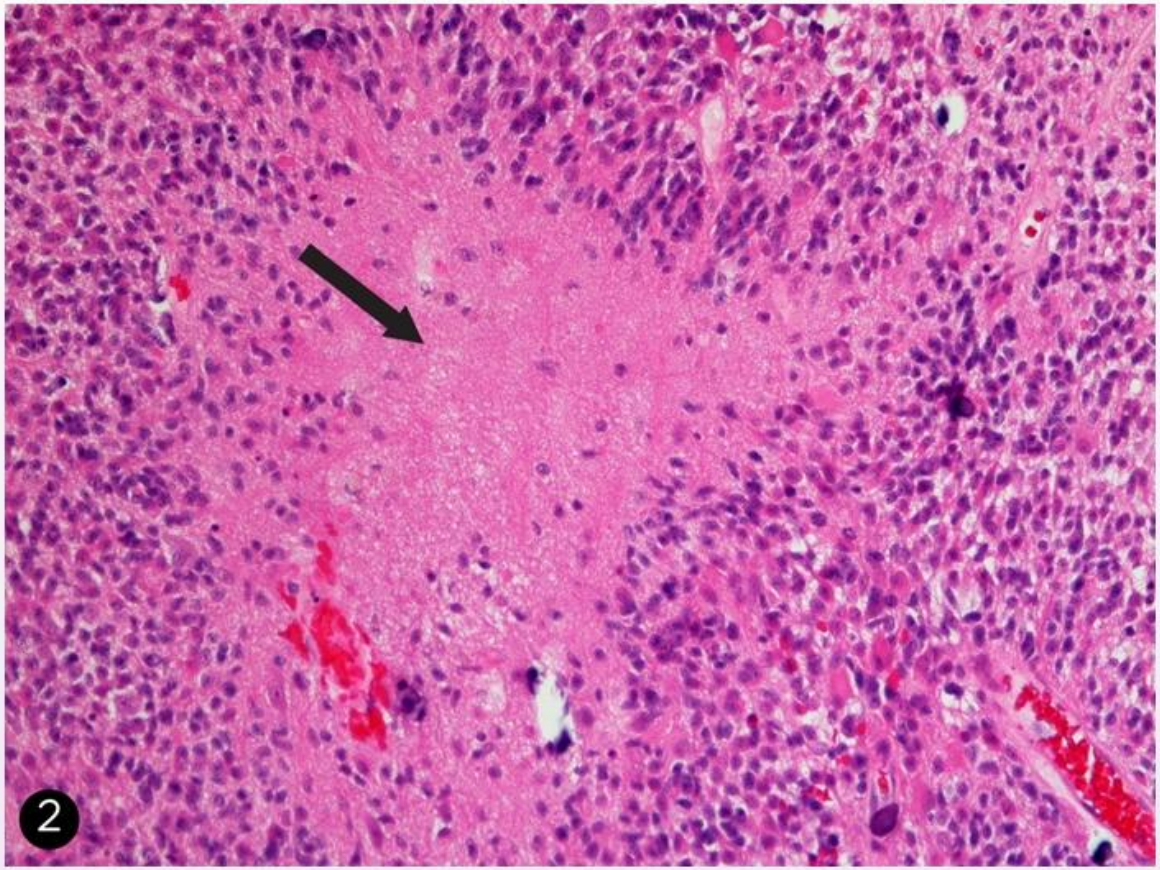
Explanation



This image shows an area of necrosis (arrow) surrounded by columns of tumor cells (pseudopalisading necrosis). Capillaries are seen at the

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This image shows an area of necrosis (arrow) surrounded by columns of tumor cells (pseudopalisading necrosis). Capillaries are seen at the periphery. Both features are characteristic of glioblastoma multiforme (GBM), the most common primary brain neoplasm in adults.

Glioblastoma multiforme	
Criteria	**Description**
Age of onset	40-70 years
Cell of origin	Astrocyte
Location	• Frontal & temporal lobes, basal ganglia • Commonly **crosses the midline** (butterfly distribution)
Macroscopic appearance	• Areas of necrosis & hemorrhage (variegated appearance, thus termed multiforme) • Poorly demarcated from the surrounding tissue
Microscopic appearance	• **Pseudopalisading necrosis** (foci of necrosis surrounded by tumor cells) • New vessel formation • Small round cells, bizarre giant cells, large number of mitoses

Location	• Frontal & temporal lobes, basal ganglia • Commonly **crosses the midline** (butterfly distribution)
Macroscopic appearance	• Areas of necrosis & hemorrhage (variegated appearance, thus termed multiforme) • Poorly demarcated from the surrounding tissue
Microscopic appearance	• **Pseudopalisading necrosis** (foci of necrosis surrounded by tumor cells) • New vessel formation • Small round cells, bizarre giant cells, large number of mitoses
Symptoms	Headache, seizure, mental status change, focal neurologic symptoms
Prognosis	• Highly malignant • Patients usually die within 1 to 2 years of diagnosis

(Choice A) Cyst formation and rare mitoses indicate a **colloid cyst**, a pathologically benign tumor usually found in the third ventricle. Although colloid cysts are benign, they can cause lethal obstructive hydrocephalus.

(Choice C) Reticulin deposits and chronic inflammatory infiltrates are seen in pleomorphic xanthoastrocytoma, an astrocytoma found in children and young adults. Pleomorphic xanthoastrocytoma can progress to GBM (very rarely).

(Choice D) **Meningiomas** are tumors of the meninges that have a whorled pattern of growth. Laminar calcifications called psammoma bodies are often present.

Prognosis	• Highly malignant • Patients usually die within 1 to 2 years of diagnosis

(Choice A) Cyst formation and rare mitoses indicate a **colloid cyst**, a pathologically benign tumor usually found in the third ventricle. Although colloid cysts are benign, they can cause lethal obstructive hydrocephalus.

(Choice C) Reticulin deposits and chronic inflammatory infiltrates are seen in pleomorphic xanthoastrocytoma, an astrocytoma found in children and young adults. Pleomorphic xanthoastrocytoma can progress to GBM (very rarely).

(Choice D) **Meningiomas** are tumors of the meninges that have a whorled pattern of growth. Laminar calcifications called psammoma bodies are often present.

(Choice E) Glioblastoma multiforme is usually located within the hemispheres (above the tentorium), commonly in the frontal and temporal lobes. Infratentorial brain tumors are much more common in children than adults. Pilocytic astrocytomas and medulloblastomas are the most common brain tumors of childhood.

Educational objective:
Glioblastoma multiforme is the most common primary brain tumor in adults. Areas of necrosis and hemorrhage are seen on gross examination. Light microscopy showing pseudopalisading tumor cells around areas of necrosis is diagnostic.

References

- 'Pseudopalisading' necrosis in glioblastoma: a familiar morphologic feature that links vascular pathology, hypoxia, and angiogenesis.

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Item 20 of 34
Question Id: 345

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A 32-year-old woman comes to the office for evaluation of a breast lump. She noticed the lump a few months ago but thinks it might be getting larger. The patient has a history of right lower limb amputation at age 17 due to osteosarcoma. The patient's mother died of an adrenal tumor, and her younger sister died of leukemia. Examination of the left breast shows a 5-cm, firm immobile mass with irregular borders. Which of the following gene mutations is the most likely etiology for this patient's condition?

A. *APC*
B. *BRCA1*
C. *NF2*
D. *TP53*
E. *RB1*

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Question Id: 345

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A 32-year-old woman comes to the office for evaluation of a breast lump. She noticed the lump a few months ago but thinks it might be getting larger. The patient has a history of right lower limb amputation at age 17 due to osteosarcoma. The patient's mother died of an adrenal tumor, and her younger sister died of leukemia. Examination of the left breast shows a 5-cm, firm immobile mass with irregular borders. Which of the following gene mutations is the most likely etiology for this patient's condition?

A. *APC* [2%]
B. *BRCA1* [20%]
C. *NF2* [1%]
✔ D. *TP53* [58%]
E. *RB1* [16%]

Omitted
Correct answer
D

58%
Answered correctly

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Explanation

Common hereditary cancer syndromes			
Syndrome	Gene	Associated neoplasms	Pathogenesis

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Common hereditary cancer syndromes			
Syndrome	**Gene**	**Associated neoplasms**	**Pathogenesis**
Lynch syndrome	*MSH2, MLH1, MSH6, PMS2*	• Colorectal cancer • Endometrial cancer • Ovarian cancer	• **Autosomal dominant** • Caused by **inactivating** mutation in corresponding **tumor suppressor gene** • Deletion of remaining normal allele (**second hit**) leads to loss of heterozygosity & **malignant transformation**
Familial adenomatous polyposis	*APC*	• Colorectal cancer • Desmoids & osteomas • Brain tumors	
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	
Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	
		• Parathyroid	

		• Brain tumors	
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	• **Autosomal dominant** • Caused by **inactivating** mutation in corresponding **tumor suppressor gene** • Deletion of remaining normal allele (**second hit**) leads to loss of heterozygosity & **malignant transformation**
Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	
Multiple endocrine neoplasia type 1	*MEN1*	• Parathyroid adenomas • Pituitary adenomas • Pancreatic adenomas	
Multiple endocrine neoplasia type 2	*RET*	• Medullary thyroid cancer • Pheochromocytoma • Parathyroid hyperplasia (*MEN2A*)	• **Autosomal dominant** • **Activating** (gain-of-function) mutation in proto-oncogene • **Continuous stimulation** of cell division predisposes to tumor growth

A history of **sarcoma, leukemia, adrenal,** and **breast cancer** is suggestive of **Li-Fraumeni syndrome**. Cancers of the **brain** are also common.

		• Pancreatic adenomas	
Multiple endocrine neoplasia type 2	*RET*	• Medullary thyroid cancer • Pheochromocytoma • Parathyroid hyperplasia (*MEN2A*)	• **Autosomal dominant** • **Activating** (gain-of-function) mutation in proto-oncogene • **Continuous stimulation** of cell division predisposes to tumor growth

A history of **sarcoma, leukemia, adrenal,** and **breast cancer** is suggestive of **Li-Fraumeni syndrome**. Cancers of the **brain** are also common. The syndrome is the result of an **autosomal dominant** mutation in *TP53*, a gene that codes for the tumor suppressor protein **p53**. Patients with this disorder are genetically predisposed to cancer development at a **young** age. Patients with Li-Fraumeni syndrome inherit one mutated allele of *TP53*, but somatic mutation of the second allele is needed for tumor development (**2-hit hypothesis**).

p53 plays an essential role in maintaining the integrity of the human genome by causing cells with mutant DNA to arrest in the **G1/S stage** of the cell cycle until the damage is repaired. Normally, cells with irreversible DNA damage are not allowed to divide and proceed to apoptosis. Without a functioning p53 protein, the defective cells divide unchecked and become cancerous.

(Choice A) The adenomatous polyposis coli (*APC*) gene mutation is found in patients with familial polyposis syndromes, sporadic colon cancer, and melanomas. *APC* is responsible for maintaining low levels of β-catenin (oncogenic protein) and for intercellular adhesion.

(Choice B) Mutation of the *BRCA1* tumor suppressor gene increases the risk for breast and ovarian cancers, and it is the most common hereditary breast cancer. This mutation is not associated with sarcomas, leukemia, or brain tumors.

(Choice C) *NF2* is a tumor suppressor gene. Mutation of *NF2* increases the risk for developing neurofibromatosis type 2. Patients present with bilateral acoustic neuromas (schwannomas of the cerebellopontine angle). Symptoms include bilateral hearing loss, vertigo, and tinnitus.

(Choice E) *RB1* is a tumor suppressor gene that codes for the Rb protein, which regulates the G1-S checkpoint of the cell cycle. Mutation of *RB1*

The syndrome is the result of an **autosomal dominant** mutation in *TP53*, a gene that codes for the tumor suppressor protein **p53**. Patients with this disorder are genetically predisposed to cancer development at a **young** age. Patients with Li-Fraumeni syndrome inherit one mutated allele of *TP53*, but somatic mutation of the second allele is needed for tumor development (**2-hit hypothesis**).

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(Choice E) *RB1* is a tumor suppressor gene that codes for the Rb protein, which regulates the G1-S checkpoint of the cell cycle. Mutation of *RB1* predisposes to the development of **retinoblastomas** and osteosarcomas, but not breast cancer or leukemia. The 2-hit hypothesis has been proposed to account for hereditary retinoblastoma.

Educational objective:
Li-Fraumeni syndrome is caused by an autosomal dominant mutation in the tumor suppressor gene *TP53*. Leukemia, sarcomas, and tumors of the breast, brain, and adrenal cortex are most common.

References

- Revisiting Li-Fraumeni Syndrome From TP53 Mutation Carriers.

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The syndrome is the result of an **autosomal dominant** mutation in *TP53*, a gene that codes for the tumor suppressor protein **p53**. Patients with

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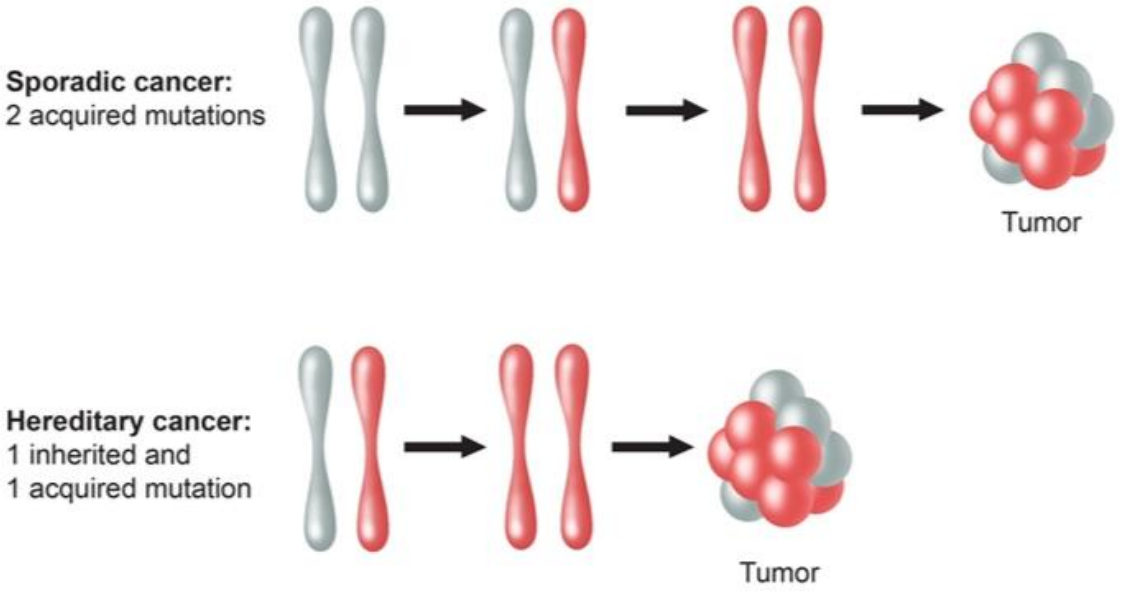
Knudson's 2-Hit Hypothesis

Both copies of the gene must be knocked out in order to promote malignancy



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The syndrome is the result of an **autosomal dominant** mutation in *TP53*, a gene that codes for the tumor suppressor protein **p53**. Patients with

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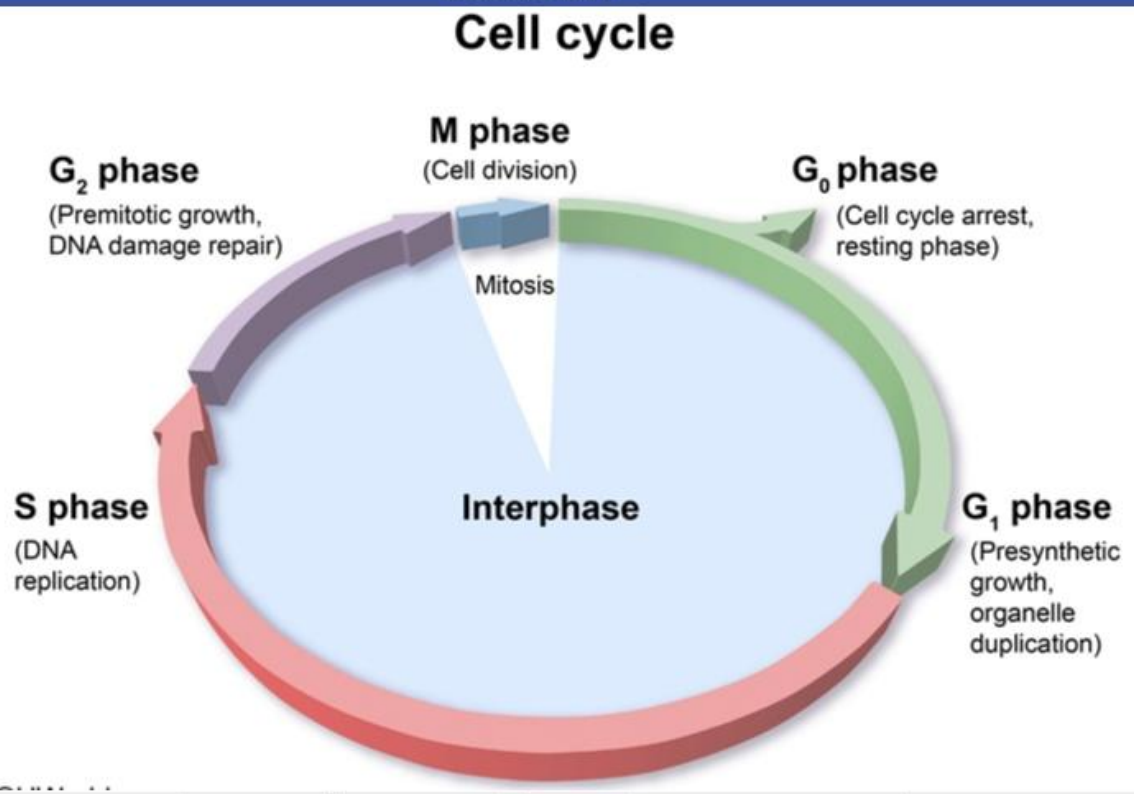

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Item 21 of 34
Question Id: 1298

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A 50-year-old woman with a history of systemic lupus erythematosus is admitted to the hospital with fever, chills, and burning pain when urinating. She quickly becomes hypotensive despite aggressive resuscitation. Urine and blood cultures grow Gram-negative rods. One hour after admission, she starts bleeding from venipuncture sites.

Laboratory results are as follows:

Complete blood count	
Hemoglobin	9.0 g/dL
Platelets	68,000 /μL
Leukocytes	24,500 /μL
Coagulation studies	
Prothrombin time	23 sec
Partial thromboplastin time	60 sec
Plasma fibrinogen	100 mg/dL (150-350 mg/dL)

Which of the following is the most likely diagnosis?

A. Immune thrombocytopenic purpura
B. Thrombotic thrombocytopenic purpura
C. Disseminated intravascular coagulation
D. von Willebrand disease

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Hemoglobin	9.0 g/dL
Platelets	68,000 /µL
Leukocytes	24,500 /µL

Coagulation studies

Prothrombin time	23 sec
Partial thromboplastin time	60 sec
Plasma fibrinogen	100 mg/dL (150-350 mg/dL)

Which of the following is the most likely diagnosis?

- A. Immune thrombocytopenic purpura
- B. Thrombotic thrombocytopenic purpura
- C. Disseminated intravascular coagulation
- D. von Willebrand disease
- E. Autoimmune hemolytic anemia
- F. Paroxysmal nocturnal hemoglobinuria

Submit

Hemoglobin	9.0 g/dL
Platelets	68,000 /µL
Leukocytes	24,500 /µL

Coagulation studies

Prothrombin time	23 sec
Partial thromboplastin time	60 sec
Plasma fibrinogen	100 mg/dL (150-350 mg/dL)

Which of the following is the most likely diagnosis?

- A. Immune thrombocytopenic purpura [6%]
- B. Thrombotic thrombocytopenic purpura [3%]
- ✔ C. Disseminated intravascular coagulation [85%]
- D. von Willebrand disease [1%]
- E. Autoimmune hemolytic anemia [2%]
- F. Paroxysmal nocturnal hemoglobinuria [0%]

Omitted
Correct answer

85%
Answered correctly

9 Seconds
Time Spent

10/04/2018
Last Updated

	Platelet Count	Prothrombin time	Partial thromboplastin time	Plasma fibrinogen values	Peripheral blood smear
von Willebrand disease	Normal	Normal	↑	Normal	Normal
Immune thrombocytopenic purpura	↓	Normal	Normal	Normal	Isolated thrombocytopenia
TTP-HUS	↓	Normal	Normal	Normal	RBC fragmentation
Disseminated intravascular coagulation	↓	↑	↑	↓	RBC fragmentation

This patient has a urinary tract infection complicated by septicemia, as documented by the urine and blood cultures positive for Gram-negative rods. Disseminated intravascular coagulation (DIC) is a common complication associated with sepsis, particularly in Gram-negative infections. DIC occurs due to the exposure of blood to procoagulants that initiate intravascular thrombosis, which is followed by compensatory thrombolysis. The result is consumption of coagulation factors, coagulopathy, and bleeding.

DIC should be suspected in any sick patient who has both an elevated prothrombin time (PT) and partial thromboplastin time (PTT). In addition to elevated PT and PTT, platelet and fibrinogen levels are decreased. Fibrin degradation products (FDP), particularly D-dimer, are also elevated in DIC (indicating lyses of cross-linked fibrin).

(Choice A) In immune (idiopathic) thrombocytopenic purpura (ITP), thrombocytopenia is the only peripheral blood abnormality and fever is absent. Thrombocytopenia occurs secondary to the production of autoantibodies that target platelets and megakaryocytes. Coagulation studies such as PT and PTT are normal. Spontaneous bleeding is very uncommon unless the platelet count is < 10,000 /μL.

(Choice B) Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are two points on a disease spectrum

DIC should be suspected in any sick patient who has both an elevated prothrombin time (PT) and partial thromboplastin time (PTT). In addition to elevated PT and PTT, platelet and fibrinogen levels are decreased. Fibrin degradation products (FDP), particularly D-dimer, are also elevated in DIC (indicating lyses of cross-linked fibrin).

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(Choice B) Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are two points on a disease spectrum characterized by the pentad of fever, neurologic manifestations, acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. TTP often occurs in adults with predominant neurologic symptoms; HUS usually occurs in children and has predominant renal involvement. TTP-HUS involves the isolated activation of platelets and does not affect the coagulation cascade (unlike in DIC). Patients with TTP-HUS do not bleed as coagulation factor levels are usually normal.

(Choice D) von Willebrand disease (vWD) is a mild inherited bleeding disorder that presents with easy bruising and prolonged bleeding from mucosal surfaces (eg, excessive epistaxis or menstruation). In vWD, von Willebrand factor is deficient, causing impaired platelet adhesion (increased bleeding time). von Willebrand factor also protects factor VIII from degradation, and thus vWD also causes factor VIII deficiency and PTT elevation.

(Choice E) Autoimmune hemolytic anemia is associated with either warm or cold antibodies that cause hemolytic anemia. Coagulopathy is not a component of autoimmune hemolytic anemia.

(Choice F) Paroxysmal nocturnal hemoglobinuria is a complement-activated hemolytic anemia that is commonly associated with thrombocytopenia and leukopenia. This patient has leukocytosis secondary to sepsis.

Educational objective:

DIC	TTP- HUS
Patients bleed	Usually do not bleed

(Choice B) Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are two points on a disease spectrum characterized by the pentad of fever, neurologic manifestations, acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia. TTP often occurs in adults with predominant neurologic symptoms; HUS usually occurs in children and has predominant renal involvement. TTP-HUS involves the isolated activation of platelets and does not affect the coagulation cascade (unlike in DIC). Patients with TTP-HUS do not bleed as coagulation factor levels are usually normal.

(Choice D) von Willebrand disease (vWD) is a mild inherited bleeding disorder that presents with easy bruising and prolonged bleeding from mucosal surfaces (eg, excessive epistaxis or menstruation). In vWD, von Willebrand factor is deficient, causing impaired platelet adhesion (increased bleeding time). von Willebrand factor also protects factor VIII from degradation, and thus vWD also causes factor VIII deficiency and PTT elevation.

(Choice E) Autoimmune hemolytic anemia is associated with either warm or cold antibodies that cause hemolytic anemia. Coagulopathy is not a component of autoimmune hemolytic anemia.

(Choice F) Paroxysmal nocturnal hemoglobinuria is a complement-activated hemolytic anemia that is commonly associated with thrombocytopenia and leukopenia. This patient has leukocytosis secondary to sepsis.

Educational objective:

DIC	TTP- HUS
Patients bleed	Usually do not bleed
Coagulation cascade is activated	Only platelets are activated
PT and PTT are prolonged	Normal PT and PTT
Low fibrinogen and increased FDP	Normal fibrinogen

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Item 22 of 34
Question Id: 1757

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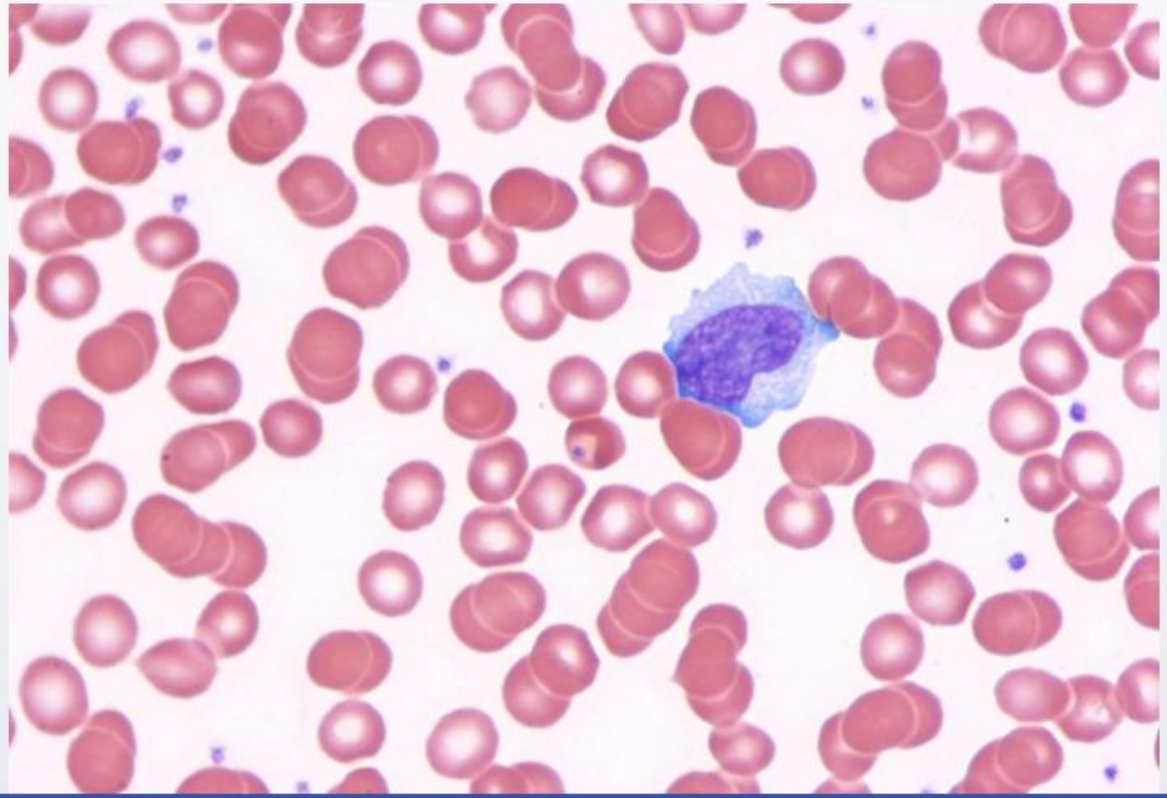
A 16-year-old previously healthy boy is brought to the office due to fever, malaise, and sore throat. The patient says that he gets tired even by simply getting out of bed. Physical examination shows palatal petechiae, cervical lymphadenopathy, and splenomegaly. His peripheral blood smear is shown in the image below.



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Item 22 of 34
Question Id: 1757

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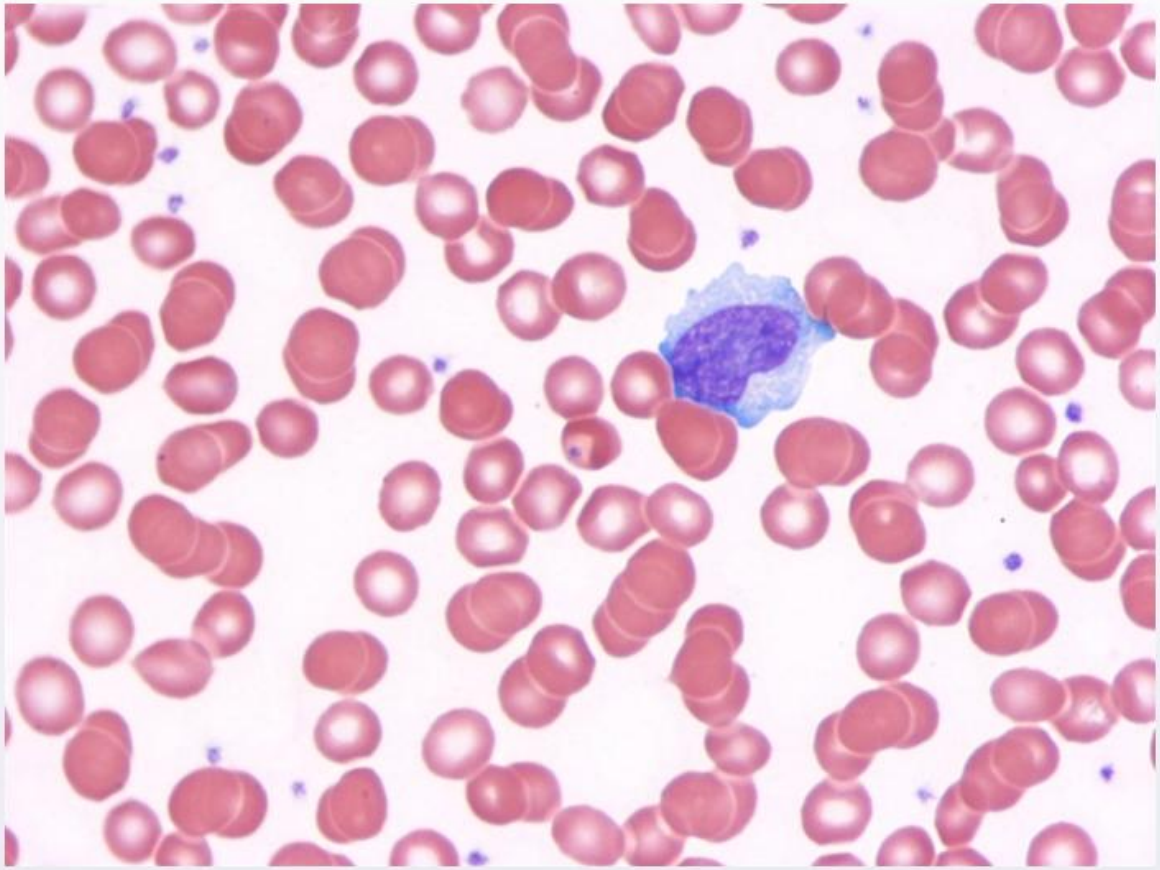
Smear is shown in the image below:



Horse erythrocytes agglutinate when exposed to the patient's serum. The agent causing this patient's disease is most strongly associated with

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Item 22 of 34
Question Id: 1757

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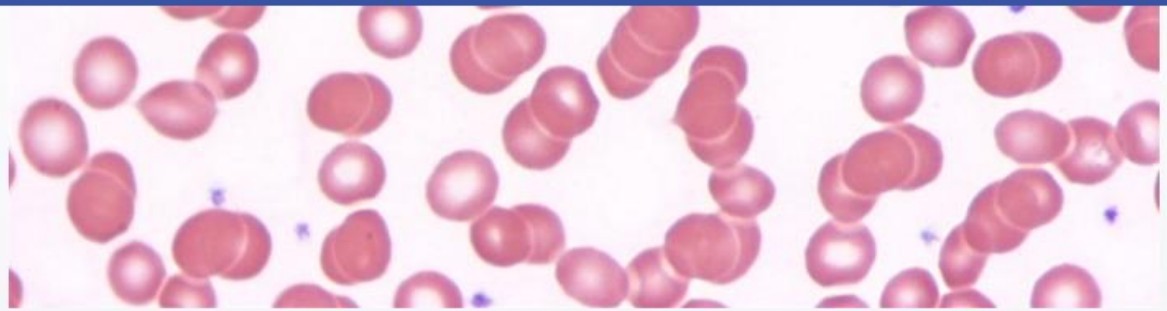

Horse erythrocytes agglutinate when exposed to the patient's serum. The agent causing this patient's disease is most strongly associated with which of the following malignancies?

- A. Acute myeloid leukemia
- B. Cervical carcinoma
- C. Hepatocellular carcinoma
- D. Kaposi sarcoma
- E. Mucosa-associated lymphoid tissue tumor
- F. Multiple myeloma
- G. Nasopharyngeal carcinoma

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Item 22 of 34
Question Id: 1757

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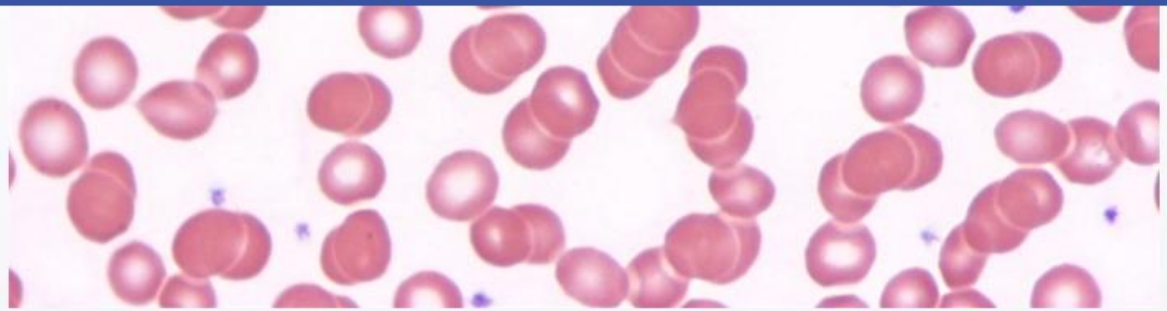

Horse erythrocytes agglutinate when exposed to the patient's serum. The agent causing this patient's disease is most strongly associated with which of the following malignancies?

- A. Acute myeloid leukemia [8%]
- B. Cervical carcinoma [0%]
- C. Hepatocellular carcinoma [0%]
- D. Kaposi sarcoma [3%]
- E. Mucosa-associated lymphoid tissue tumor [4%]
- F. Multiple myeloma [9%]
- ✔ G. Nasopharyngeal carcinoma [72%]

Omitted
Correct answer

72%

14 Seconds

12/06/2018

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Item 22 of 34
Question Id: 1757

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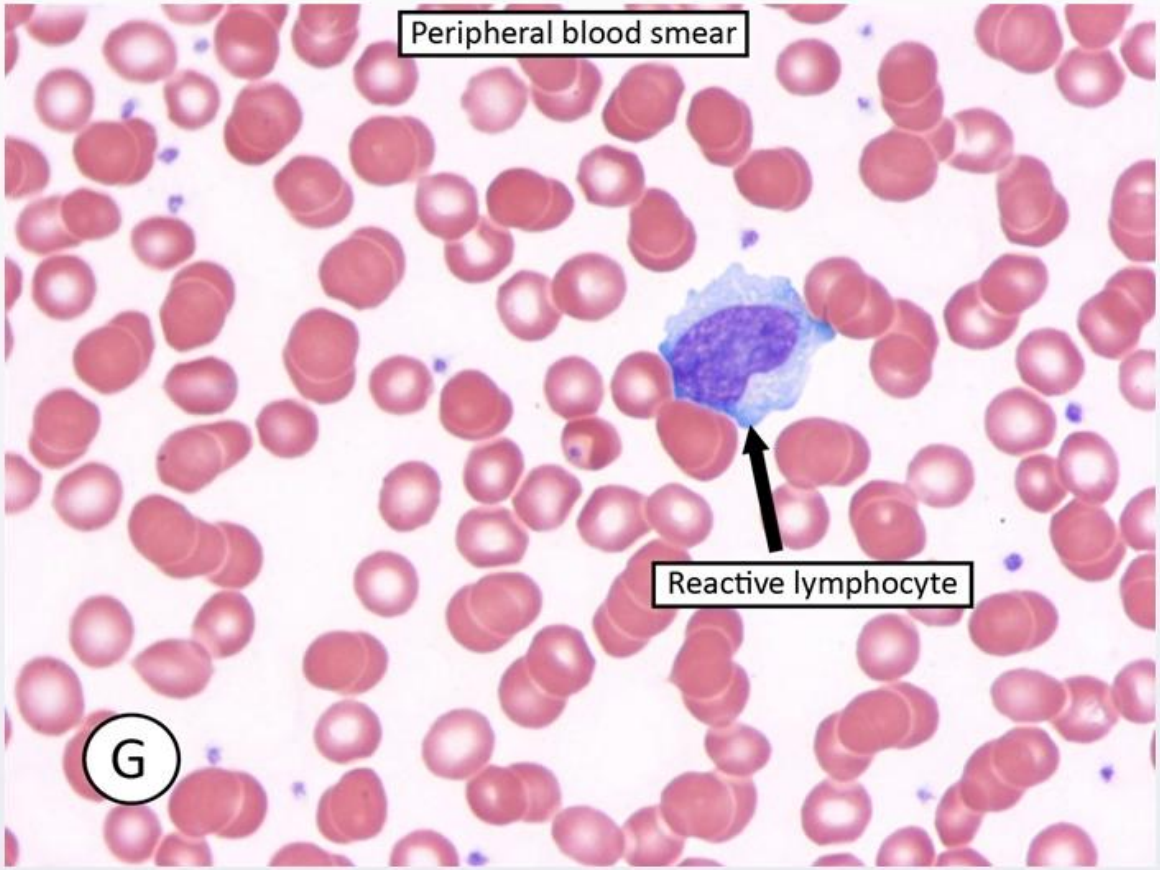

Sore throat, moderate to high fever, palatal petechiae, **lymphadenopathy** (commonly posterior cervical or auricular), splenomegaly, and **atypical**

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Sore throat, moderate to high fever, palatal petechiae, **lymphadenopathy** (commonly posterior cervical or auricular), splenomegaly, and **atypical** (reactive) **lymphocytosis** are classic signs and symptoms of **infectious mononucleosis**, a disease common among teenagers and young adults. Ninety percent of cases of infectious mononucleosis are caused by the **Epstein-Barr virus** (EBV); however, cytomegalovirus, HIV, and *Toxoplasma* are some of the other agents known to cause non-EBV infectious mononucleosis. EBV infection induces **heterophile antibodies**, which react to antigens from animal erythrocytes (sheep in the Paul-Bunnell test and horse in the Monospot test). The heterophile antibody tests are sensitive and specific for EBV-associated infectious mononucleosis.

EBV replicates primarily in B lymphocytes and is also associated with **malignancies**, including **Burkitt lymphoma** (especially the endemic African type) and **nasopharyngeal carcinoma**. Many disorders in immunocompromised patients are caused by EBV, including central nervous system lymphoma in HIV-positive patients and post-transplant lymphoproliferative disorder (PTLD) in allograft recipients.

(Choices A and F) There is no classic association between acute myeloid leukemia or multiple myeloma and viral infection.

(Choice B) Cervical carcinoma is strongly associated with human papillomavirus (types 16, 18, 31, and 33) infection.

(Choice C) Chronic infection with either hepatitis B or C virus significantly increases the risk of hepatocellular carcinoma.

(Choice D) Kaposi sarcoma is strongly associated with HIV and human herpes virus type 8 infections.

(Choice E) Gastric adenocarcinoma and mucosa-associated lymphoid tissue tumor (MALToma) are associated with *Helicobacter pylori* infection.

Educational objective:
Epstein-Barr virus causes infectious mononucleosis in teenagers and young adults. It is also associated with a number of malignant conditions, including Burkitt lymphoma and nasopharyngeal carcinoma.

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Item 23 of 34
Question Id: 941

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A 6-year-old boy is brought to the emergency department due to bleeding after a dental extraction earlier this morning. The patient's past medical history is significant for painful swelling of his knee joints after minor trauma. Aspiration of the joints during several occasions yielded frank blood, and he was diagnosed with hemarthrosis. He has no known allergies. Currently, hemostasis in this patient most likely can be achieved by the administration of which of the following?

A. Factor XII
B. Fibrinogen
C. Protein C
D. Thrombin
E. Urokinase

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Item 23 of 34
Question Id: 941

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A 6-year-old boy is brought to the emergency department due to bleeding after a dental extraction earlier this morning. The patient's past medical history is significant for painful swelling of his knee joints after minor trauma. Aspiration of the joints during several occasions yielded frank blood, and he was diagnosed with hemarthrosis. He has no known allergies. Currently, hemostasis in this patient most likely can be achieved by the administration of which of the following?

- A. Factor XII [15%]
- B. Fibrinogen [15%]
- C. Protein C [9%]
- ✔ D. Thrombin [57%]
- E. Urokinase [2%]

Omitted
Correct answer
D

57%
Answered correctly

3 Seconds
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12/25/2018
Last Updated

Explanation

Coagulation cascade pathway

Intrinsic pathway

Block Time Remaining: 00:02:13
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Item 23 of 34
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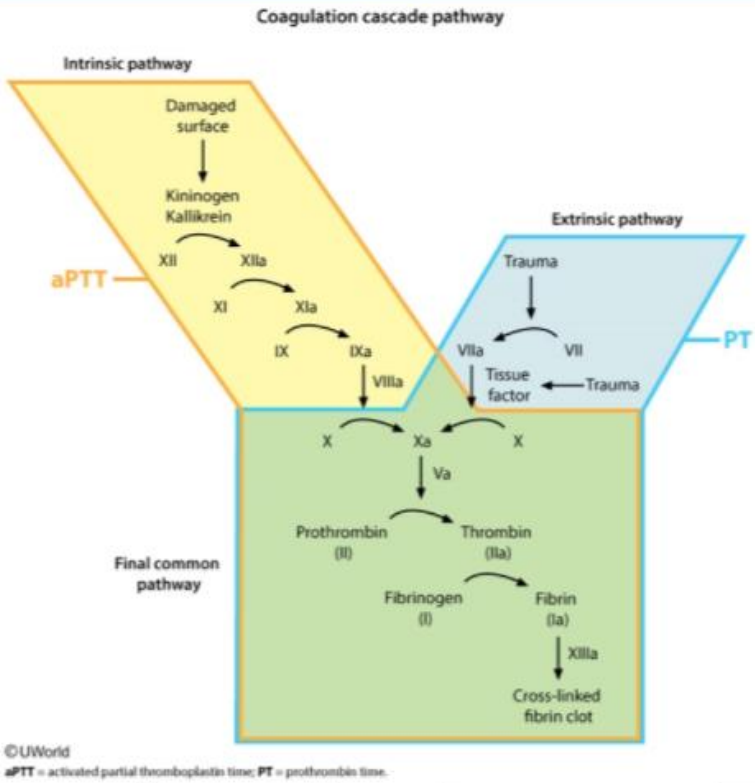

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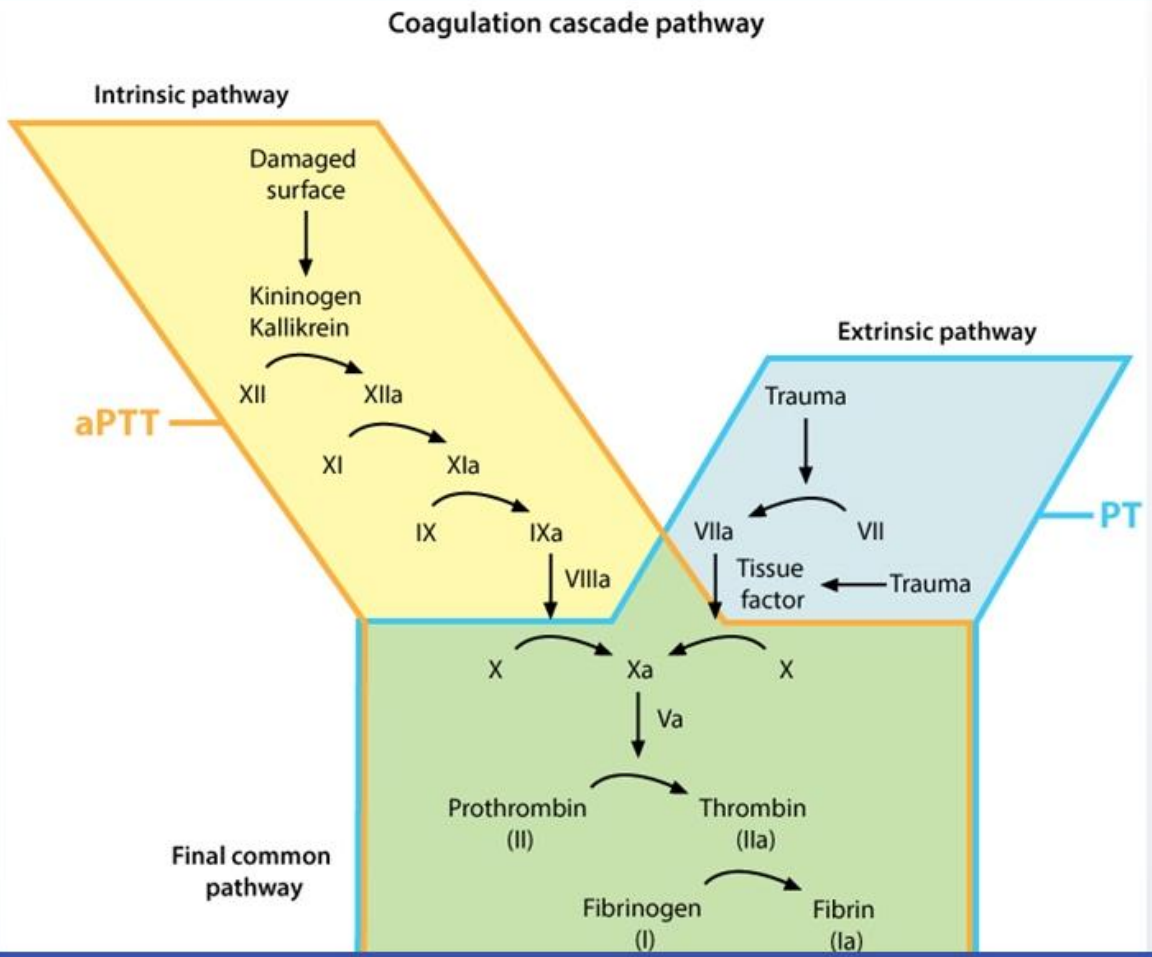

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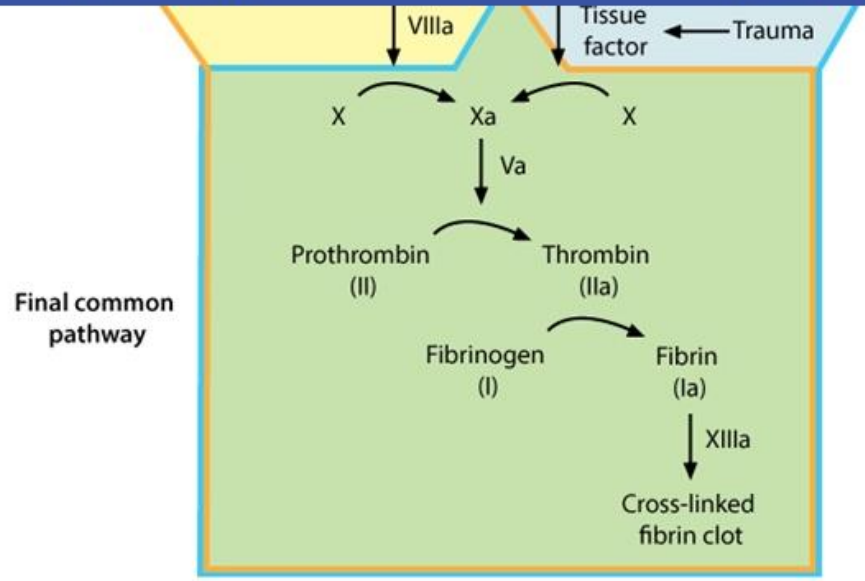

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aPTT = activated partial thromboplastin time; **PT** = prothrombin time.

A history of prolonged bleeding following procedures (eg, dental extractions, surgeries) and spontaneous hemorrhages into the joints (hemarthrosis) is typical for **hemophilia**, an X-linked recessive bleeding disorder due to decreased levels of factor VIII (hemophilia A) or factor IX (hemophilia B).

Factors VIII and IX are components of the **intrinsic** coagulation pathway and activate factor X; activated factor X (Xa) then catalyzes the conversion of prothrombin (factor II) into thrombin as part of the final common pathway. In the absence of factors VIII or IX, activation of factor X and subsequent conversion of prothrombin into thrombin do not occur. Administration of **thrombin**, however, will make up for the deficiency and lead to blood clotting. In practice, prothrombin complex concentrates (containing factors II, VII, IX, and X, which lead to thrombin formation) were used for management of hemophilia B, although thrombogenic risks have limited their application

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In both types of hemophilia, the bleeding time and platelet count are normal. The prothrombin time (PT) is also normal as it tests the **e**xtrinsic clotting pathway and reflects the function of factors II, V, VII, and X (mnemonic: P**e**T). However, the activated partial thromboplastin time (PTT) is prolonged as it assesses the activity of factors II, V, VIII, IX, X, XI and XII, the **i**ntrinsic clotting pathway (mnemonic: P**i**TT). Diagnoses of hemophilia A and B are made by measuring plasma levels of factors VIII and IX, respectively.

(Choice A) Factor XII (Hageman) is synthesized by the liver and is activated by endothelial injury. It triggers the intrinsic coagulation pathway by activating factor XI. The addition of factor XII does not clot the blood of patients with hemophilia because the downstream clotting factors VIII or IX are deficient.

(Choice B) Fibrinogen is a protein synthesized by the liver. Thrombin mediates cleavage of fibrinogen to form fibrin, the main component of thrombi; therefore, without thrombin, fibrinogen administration alone would not be helpful.

(Choice C) Protein C is a vitamin K-dependent factor synthesized in the liver. It is a physiologic anticoagulant that degrades factors Va and VIIIa.

(Choice E) Urokinase is a thrombolytic agent used for treatment of myocardial infarction and pulmonary embolism. It acts by converting plasminogen to plasmin, which then breaks down fibrinogen and fibrin into their respective degradation products. The addition of urokinase would prevent thrombosis.

Educational objective:
Bleeding after a tooth extraction and history of hemarthrosis are suggestive of hemophilia. Decreased levels of factor VIII or IX lead to failure to

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Educational objective:
Bleeding after a tooth extraction and history of hemarthrosis are suggestive of hemophilia. Decreased levels of factor VIII or IX lead to failure to convert prothrombin into thrombin and deficient thrombus formation. The addition of thrombin to the blood of a patient with hemophilia results in clotting.

References

- Prothrombin complex concentrates in emergency bleeding disorders.

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Item 24 of 34
Question Id: 1293

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A 40-year-old man with end-stage renal disease due to type 1 diabetes mellitus is hospitalized for initiation of hemodialysis. A tunneled dialysis catheter is inserted into the right internal jugular vein. Before he is able to undergo dialysis treatment, the patient develops bleeding around the catheter exit site that is difficult to control. He has not been treated recently with anticoagulants. Further evaluation of this patient would most likely show which of the following laboratory abnormalities?

	Prothrombin time	Activated partial thromboplastin time	Platelet count	Bleeding Time
A.	Normal	Normal	Normal	Prolonged
B.	Normal	Prolonged	Normal	Prolonged
C.	Normal	Prolonged	Normal	Normal
D.	Prolonged	Prolonged	Decreased	Prolonged
E.	Prolonged	Prolonged	Normal	Normal

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Item 24 of 34
Question Id: 1293

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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	Prothrombin time	Activated partial thromboplastin time	Platelet count	Bleeding Time
✔ A. [29%]	Normal	Normal	Normal	Prolonged
B. [15%]	Normal	Prolonged	Normal	Prolonged
C. [8%]	Normal	Prolonged	Normal	Normal
D. [34%]	Prolonged	Prolonged	Decreased	Prolonged
E. [12%]	Prolonged	Prolonged	Normal	Normal

Omitted
Correct answer
A

29%
Answered correctly

3 Seconds
Time Spent

11/06/2018
Last Updated

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Laboratory characteristics of coagulopathies				
	PT	**aPTT**	**Platelet count**	**Bleeding time**
Hemophilia A & B	Normal	↑	Normal	Normal
von Willebrand factor deficiency	Normal	Normal or ↑	Normal	↑
Disseminated intravascular coagulation	↑	↑	↓	↑
Uremic platelet dysfunction	Normal	Normal	Normal	↑
Heparin administration	Normal	↑	Normal (except in heparin-induced thrombocytopenia)	Normal
Warfarin use	↑	↑ (weak effect)	Normal	Normal

Hemophilia A & B	Normal	↑	Normal	Normal
von Willebrand factor deficiency	Normal	Normal or ↑	Normal	↑
Disseminated intravascular coagulation	↑	↑	↓	↑
Uremic platelet dysfunction	Normal	Normal	Normal	↑
Heparin administration	Normal	↑	Normal (except in heparin-induced thrombocytopenia)	Normal
Warfarin use	↑	↑ (weak effect)	Normal	Normal
Immune thrombocytopenia	Normal	Normal	↓	↑

aPTT = activated partial thromboplastin time; PT = prothrombin time.

Excessive bleeding is common in patients with significant renal dysfunction due in part to the accumulation of **uremic toxins** in the circulation. These toxins impair platelet aggregation and adhesion, resulting in a **qualitative platelet disorder** characterized by **prolonged bleeding time**.

Warfarin use	↑	↑ (weak effect)	Normal	Normal
Immune thrombocytopenia	Normal	Normal	↓	↑

aPTT = activated partial thromboplastin time; **PT** = prothrombin time.

Excessive bleeding is common in patients with significant renal dysfunction due in part to the accumulation of **uremic toxins** in the circulation. These toxins impair platelet aggregation and adhesion, resulting in a **qualitative platelet disorder** characterized by **prolonged bleeding time** with normal platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT). Uremic bleeding can be improved with **dialysis** as it removes the toxins and partially reverses the bleeding abnormality.

(Choice B) von Willebrand factor (vWF) acts as a bridge between glycoprotein 1b receptors and subendothelial collagen, allowing platelets to bind to damaged vessels. vWF deficiency results in platelet dysfunction with a prolonged bleeding time and normal platelet count. Since vWF also protects factor VIII from degradation, vWF deficiency can result in decreased factor VIII and prolonged aPTT.

(Choice C) Isolated aPTT prolongation is seen with hemophilia A, an X-linked disorder caused by factor VIII deficiency. Heparin use also prolongs the aPTT via antithrombin-associated inhibition of factors II and X (PT is usually normal due to the addition of heparin neutralizers in the PT reagent).

(Choice D) Disseminated intravascular coagulation is a consumptive coagulopathy associated with decreased platelet count and increased bleeding time, aPTT, and PT.

(Choice E) Warfarin inhibits vitamin K-dependent clotting factors (II, VII, IX, and X). Warfarin prolongs both PT and aPTT, but PT is increased much more than aPTT. Platelet count and bleeding time are normal.

Education objective:

Excessive bleeding is common in patients with significant renal dysfunction due in part to the accumulation of **uremic toxins** in the circulation. These toxins impair platelet aggregation and adhesion, resulting in a **qualitative platelet disorder** characterized by **prolonged bleeding time** with normal platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT). Uremic bleeding can be improved with **dialysis** as it removes the toxins and partially reverses the bleeding abnormality.

(Choice B) von Willebrand factor (vWF) acts as a bridge between glycoprotein 1b receptors and subendothelial collagen, allowing platelets to bind to damaged vessels. vWF deficiency results in platelet dysfunction with a prolonged bleeding time and normal platelet count. Since vWF also protects factor VIII from degradation, vWF deficiency can result in decreased factor VIII and prolonged aPTT.

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(Choice D) Disseminated intravascular coagulation is a consumptive coagulopathy associated with decreased platelet count and increased bleeding time, aPTT, and PT.

(Choice E) Warfarin inhibits vitamin K-dependent clotting factors (II, VII, IX, and X). Warfarin prolongs both PT and aPTT, but PT is increased much more than aPTT. Platelet count and bleeding time are normal.

Education objective:
Abnormal bleeding in patients with uremia is due to a qualitative platelet disorder that causes prolonged bleeding time with normal platelet count, prothrombin time, and activated partial thromboplastin time.

References

- Coagulation assays and anticoagulant monitoring.

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Item 25 of 34
Question Id: 465

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A 32-year-old Caucasian woman experiences three episodes of deep venous thrombosis in a six year period. She has a history of pulmonary embolism as well. The patient's partial thromboplastin time (PTT) is within normal limits, and remains unchanged when activated protein C is added to her plasma. The most likely cause of this patient's problem is:

A. Immune
B. Nutritional
C. Inherited
D. Infectious
E. Neoplastic

Submit

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Item 25 of 34
Question Id: 465

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 32-year-old Caucasian woman experiences three episodes of deep venous thrombosis in a six year period. She has a history of pulmonary embolism as well. The patient's partial thromboplastin time (PTT) is within normal limits, and remains unchanged when activated protein C is added to her plasma. The most likely cause of this patient's problem is:

A. Immune [18%]
B. Nutritional [4%]
✔ C. Inherited [70%]
D. Infectious [1%]
E. Neoplastic [5%]

Omitted
Correct answer
C

70%
Answered correctly

3 Seconds
Time Spent

02/06/2019
Last Updated

Explanation

This is a young patient with recurrent deep venous thromboses, features indicative of a hypercoagulable state. Inherited causes of hypercoagulability must be considered in all patients under age 50 who present with thromboses in the absence of any obvious explanation for an acquired prothrombotic state.

The patient's plasma is resistant to the normally antithrombotic effects of activated protein C. Thus, the most likely diagnosis is a mutation in the

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Explanation

This is a young patient with recurrent deep venous thromboses, features indicative of a hypercoagulable state. Inherited causes of hypercoagulability must be considered in all patients under age 50 who present with thromboses in the absence of any obvious explanation for an acquired prothrombotic state.

The patient's plasma is resistant to the normally antithrombotic effects of activated protein C. Thus, the most likely diagnosis is a mutation in the factor V gene, which renders factor Va resistant to inactivation by activated protein C. Approximately 2–15% of Caucasians carry a specific factor V mutation, the Leiden mutation. The factor V Leiden mutation and mutations in the prothrombin gene are the most common inherited causes of hypercoagulability. Activated protein C resistance (factor V Leiden mutation) is detected in approximately 20% (range 12–40%) of patients with abnormal venous thromboses.

(Choice A) Antiphospholipid antibody syndrome is a common immune cause of hypercoagulability. This condition is defined by the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies) plus one or more of the following: venous thromboembolism, arterial thromboembolism, or frequent fetal loss. Unlike the patient in the vignette, patients with antiphospholipid antibody syndrome typically have a prolonged baseline aPTT. Lupus anticoagulants are the most common cause of aPTT prolongation.

(Choice B) Folic acid deficiency can cause hyperhomocysteinemia, which is a prothrombotic state. However, activated protein C resistance is not seen with this condition.

(Choice D) Endovascular infections and/or systemic inflammatory states may affect vascular endothelial cells in a way that favors thrombosis. However, infection and inflammatory mediators do not directly promote activated protein C resistance in the aPTT coagulation test.

(Choice E) A paraneoplastic syndrome of hypercoagulability may be seen in some patients with cancer, especially patients with adenocarcinomas of the pancreas, colon, or lung. The mechanism of cancer-induced hypercoagulability is thought to involve release of procoagulant tumor products. Vascular stasis due to obstruction of blood flow by the tumor, patient immobility, hepatic involvement and dysfunction, sepsis, and advanced age may also contribute to the tendency toward thrombosis in cancer patients. None of these mechanisms/factors directly promotes activated protein C resistance in the aPTT coagulation test.

The patient's plasma is resistant to the normally antithrombotic effects of activated protein C. Thus, the most likely diagnosis is a mutation in the factor V gene, which renders factor Va resistant to inactivation by activated protein C. Approximately 2–15% of Caucasians carry a specific factor V mutation, the Leiden mutation. The factor V Leiden mutation and mutations in the prothrombin gene are the most common inherited causes of hypercoagulability. Activated protein C resistance (factor V Leiden mutation) is detected in approximately 20% (range 12–40%) of patients with abnormal venous thromboses.

(Choice A) Antiphospholipid antibody syndrome is a common immune cause of hypercoagulability. This condition is defined by the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies) plus one or more of the following: venous thromboembolism, arterial thromboembolism, or frequent fetal loss. Unlike the patient in the vignette, patients with antiphospholipid antibody syndrome typically have a prolonged baseline aPTT. Lupus anticoagulants are the most common cause of aPTT prolongation.

(Choice B) Folic acid deficiency can cause hyperhomocysteinemia, which is a prothrombotic state. However, activated protein C resistance is not seen with this condition.

(Choice D) Endovascular infections and/or systemic inflammatory states may affect vascular endothelial cells in a way that favors thrombosis. However, infection and inflammatory mediators do not directly promote activated protein C resistance in the aPTT coagulation test.

(Choice E) A paraneoplastic syndrome of hypercoagulability may be seen in some patients with cancer, especially patients with adenocarcinomas of the pancreas, colon, or lung. The mechanism of cancer-induced hypercoagulability is thought to involve release of procoagulant tumor products. Vascular stasis due to obstruction of blood flow by the tumor, patient immobility, hepatic involvement and dysfunction, sepsis, and advanced age may also contribute to the tendency toward thrombosis in cancer patients. None of these mechanisms/factors directly promotes activated protein C resistance in the aPTT coagulation test.

Educational Objective:
Inherited causes of hypercoagulability should be considered in patients younger than age 50 who present with thrombosis and no obvious explanation for an acquired prothrombotic state. The factor V Leiden mutation, which causes factor Va resistance to inactivation by activated protein C, may account for approximately 20% of cases of atypical venous thrombosis.

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Item 26 of 34
Question Id: 1086

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A 42-year-old previously healthy woman comes to the office due to fever and sore throat. She has no cough. Physical examination shows tonsillar exudate and a nontender cervical lymph node that measures 3.5 cm in diameter. Oral antibiotic therapy is started and on a follow-up visit a week later, the patient reports that her symptoms have resolved. The previously enlarged cervical lymph node has decreased slightly in size. On several follow-up visits over the following year, the patient remains asymptomatic and the size of the lymph node fluctuates but does not disappear completely. Referral to a surgeon is made and excisional biopsy of the lymph node is performed. Which of the following most likely will be seen on biopsy?

- A. Acute lymphoid leukemia
- B. Burkitt lymphoma
- C. Diffuse large B-cell lymphoma
- D. Follicular lymphoma
- E. Hairy cell leukemia
- F. Mycosis fungoides

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Item 26 of 34
Question Id: 1086

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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A. Acute lymphoid leukemia [1%]
B. Burkitt lymphoma [17%]
C. Diffuse large B-cell lymphoma [17%]
✔ D. Follicular lymphoma [52%]
E. Hairy cell leukemia [2%]
F. Mycosis fungoides [8%]

Omitted
Correct answer
D

52%
Answered correctly

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Time Spent

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Explanation

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Explanation

This patient with persistent fluctuating lymphadenopathy, who may have had an unrelated pharyngitis (treated with antibiotics) on initial presentation, most likely has **follicular lymphoma**. Follicular lymphoma is the most common **indolent** non-Hodgkin lymphoma (NHL) in adults and the second most common NHL overall. It derives from follicular B cells and typically has a long, **waxing and waning** clinical course. This condition most often presents in middle-aged patients with **painless lymph node enlargement** or abdominal discomfort from an abdominal mass. **Histology** is notable for a mixture of **cleaved and noncleaved** follicle center cells in a nodular pattern. The majority of tumors exhibit a **t(14;18) translocation**, resulting in overexpression of the *bcl-2* oncogene that blocks programmed cell death.

(Choice A) Acute lymphoblastic leukemia is the most common leukemia in children. It presents with lymphadenopathy, hepatosplenomegaly, fever, bleeding, and bone pain. Neoplastic cells are pre-B or pre-T lymphoblasts.

(Choice B) Burkitt lymphoma is a highly aggressive (but generally chemotherapy-responsive) B-cell NHL associated with chronic Epstein-Barr virus infection and/or deregulation of the c-*myc* proto-oncogene. Patients typically develop rapidly growing tumor masses in the facial bone, jaw, or abdomen. Tumor doubling time is very rapid and spontaneous tumor lysis can occur.

(Choice C) Diffuse large B-cell lymphoma (most common NHL) typically presents with a rapidly enlarging nodal (neck, abdomen, mediastinum) or extranodal symptomatic mass. The Waldeyer's ring (oropharyngeal lymphoid tissue) and gastrointestinal tract are commonly involved, and systemic "B" symptoms (fever, weight loss, drenching night sweats) can also be seen.

(Choice E) Hairy cell leukemia presents with splenomegaly and pancytopenia in older men. Lymph node enlargement is not characteristic. Leukemic cells have hairlike cytoplasmic projections and are positive for tartrate-resistant acid phosphatase (TRAP).

(Choice F) Mycosis fungoides is a cutaneous T-cell lymphoma. Proliferating $CD4^+$ lymphocytes infiltrate the dermis and epidermis, where they form Pautrier microabscesses. This condition manifests with **plaques** (often on trunk or buttocks) that may be confused with eczema or psoriasis. Generalized erythema and scaling and thickening of the skin (erythroderma) may result.

Educational objective:
Follicular lymphoma is the most common indolent non-Hodgkin lymphoma in adults. It is of B-cell origin and presents with painless waxing and

(Choice A) Acute lymphoblastic leukemia is the most common leukemia in children. It presents with lymphadenopathy, hepatosplenomegaly, fever, bleeding, and bone pain. Neoplastic cells are pre-B or pre-T lymphoblasts.

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Educational objective:
Follicular lymphoma is the most common indolent non-Hodgkin lymphoma in adults. It is of B-cell origin and presents with painless waxing and waning lymphadenopathy. The cytogenetic change t(14;18) is characteristic and results in overexpression of the *bcl-2* oncogene.

References

- Follicular lymphoma: 2014 update on diagnosis and management.

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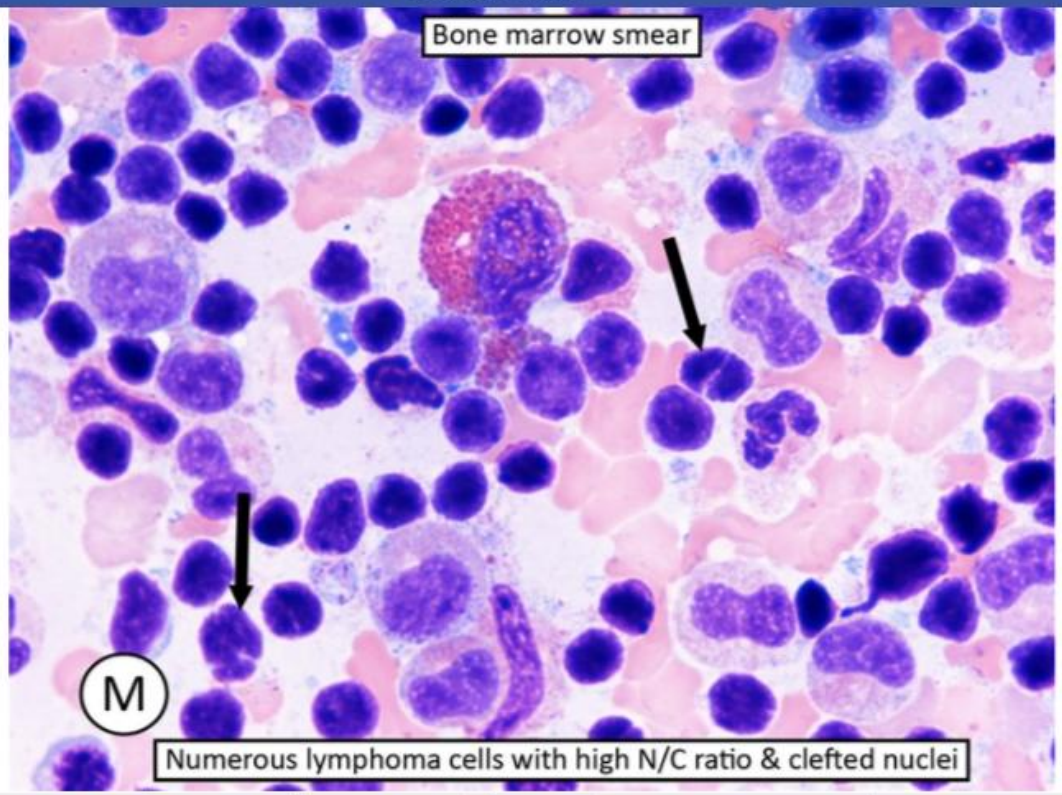

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(Choice E) Hairy cell leukemia presents with splenomegaly and pancytopenia in older men. Lymph node enlargement is not characteristic

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Item 27 of 34
Question Id: 1403

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A 32-year-old man comes to the office due to progressive fatigue, easy bruising, and recurring episodes of gum bleeding. Physical examination shows several ecchymoses in his lower extremities. Laboratory studies are as follows:

Complete blood count	
Hemoglobin	7.8 g/dL
Platelets	65,000/mm^3
Leukocytes	3,000/mm^3
Coagulation studies	
Prothrombin time	22 sec
Activated partial thromboplastin time	53 sec
Plasma fibrinogen	134 mg/dL (normal: 200-400 mg/dL)
D-dimer	4.1 µg/dL (normal: <0.5 µg/dL)

Bone marrow biopsy is performed and fluorescence in situ hybridization studies reveal a balanced translocation between the long arms of chromosomes 15 and 17. Which of the following proteins is most likely to be abnormal in the hematopoietic cells of this patient?

A. Epidermal growth factor receptor
B. GTP-binding protein
C. Platelet-derived growth factor receptor

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Platelets	65,000/mm³
Leukocytes	3,000/mm³

Coagulation studies

Prothrombin time	22 sec
Activated partial thromboplastin time	53 sec
Plasma fibrinogen	134 mg/dL (normal: 200-400 mg/dL)
D-dimer	4.1 µg/dL (normal: <0.5 µg/dL)

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- A. Epidermal growth factor receptor
- B. GTP-binding protein
- C. Platelet-derived growth factor receptor
- D. Retinoblastoma gene product
- E. Retinoic acid receptor

Submit

Platelets	65,000/mm³
Leukocytes	3,000/mm³

Coagulation studies

Prothrombin time	22 sec
Activated partial thromboplastin time	53 sec
Plasma fibrinogen	134 mg/dL (normal: 200-400 mg/dL)
D-dimer	4.1 µg/dL (normal: <0.5 µg/dL)

Bone marrow biopsy is performed and fluorescence in situ hybridization studies reveal a balanced translocation between the long arms of chromosomes 15 and 17. Which of the following proteins is most likely to be abnormal in the hematopoietic cells of this patient?

- A. Epidermal growth factor receptor [4%]
- B. GTP-binding protein [5%]
- C. Platelet-derived growth factor receptor [14%]
- D. Retinoblastoma gene product [3%]
- ✔ E. Retinoic acid receptor [71%]

Omitted
Correct answer

71%
Answered correctly

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02/06/2019
Last Updated

Explanation

Acute myelogenous leukemia (AML), characterized by failure of immature myeloid precursors (myeloblasts) to differentiate into mature granulocytes, is divided into 8 types (M0 through M7). **Acute promyelocytic leukemia** (APML), the M3 variant of AML, is associated with the **t(15;17)** cytogenetic translocation involving the promyelocytic leukemia (*PML*) gene on chromosome 15 and the retinoic acid receptor alpha (*RARA*) gene on chromosome 17. Fusion of these 2 genes produces ***PML/RARA***, a chimeric gene (illustrated in this **fluorescence in situ hybridization image**) that codes for an abnormal **retinoic acid receptor**, which then inhibits myeloblast differentiation. Abnormal promyelocytes and Auer rods are seen on the smear.

The clinical manifestations of AML, including anemia (fatigue, pallor), thrombocytopenia (petechiae, hemorrhages), and neutropenia (fever, opportunistic infections), result from marrow replacement by leukemic cells. As seen in this patient, APML is associated with **disseminated intravascular coagulation (DIC)**, which is characterized by activation of the coagulation cascade. Laboratory findings seen in DIC include thrombocytopenia, elevated D-dimer due to fibrinolysis, and prolonged coagulation profile times (eg, prothrombin time, activated partial thromboplastin time) and low fibrinogen due to consumption.

All-trans retinoic acid is used for treatment of APML.

(Choice A) Mutations in the genes that code for the epidermal growth factor receptors are associated with certain lung (*ERBB1*), breast (*ERBB2*, also known as *HER2/neu*), ovarian, and gastric tumors.

(Choice B) GTP-binding proteins are involved in cellular signal transduction.

(Choice C) A defective platelet-derived growth factor receptor plays a role in the pathogenesis of several cancers, including ovarian cancers.

(Choice D) An abnormal *RB* gene predisposes to development of retinoblastoma and osteosarcoma.

Educational objective:
The cytogenetic defect t(15;17) is associated with acute promyelocytic leukemia (APML). A translocation involving the retinoic acid receptor alpha (*RARA*) gene from chromosome 17 and the promyelocytic leukemia (*PML*) gene on chromosome 15 leads to the formation of *PML/RARA*, a fusion

granulocytes, is divided into 8 types (M0 through M7). **Acute promyelocytic leukemia** (APML), the M3 variant of AML, is associated with the **t(15;17)** cytogenetic translocation involving the promyelocytic leukemia (*PML*) gene on chromosome 15 and the retinoic acid receptor alpha (*RARA*) gene on chromosome 17. Fusion of these 2 genes produces ***PML/RARA***, a chimeric gene (illustrated in this **fluorescence in situ hybridization image**) that codes for an abnormal **retinoic acid receptor**, which then inhibits myeloblast differentiation. Abnormal promyelocytes and Auer rods are seen on the smear.

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The cytogenetic defect t(15;17) is associated with acute promyelocytic leukemia (APML). A translocation involving the retinoic acid receptor alpha (*RARA*) gene from chromosome 17 and the promyelocytic leukemia (*PML*) gene on chromosome 15 leads to the formation of *PML/RARA*, a fusion gene whose product inhibits differentiation of myeloblasts and triggers the development of APML.

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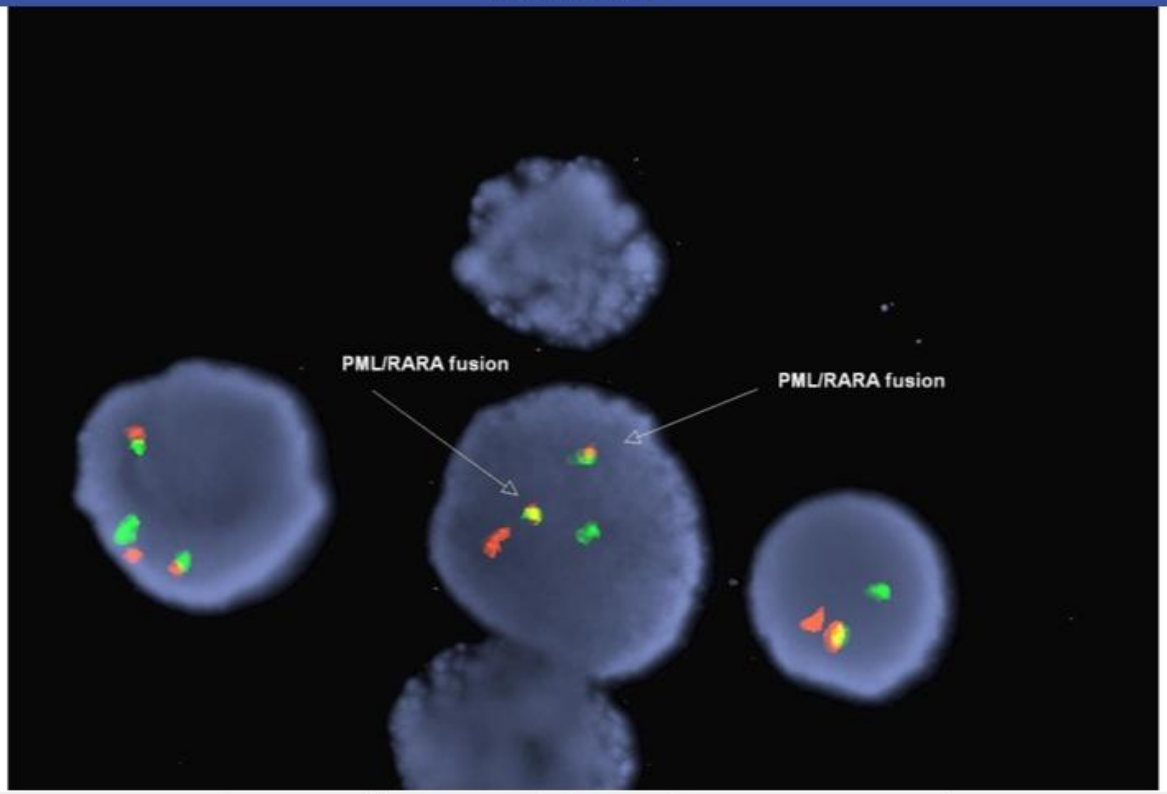

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A 45-year-old man comes to the office due to a week of purulent nasal discharge, headache, sore throat, and nonproductive cough. He has no significant past medical history except for an episode of infectious mononucleosis at age 22. The patient smokes a pack of cigarettes daily. His temperature is 38 C (100.4 F). He has maxillary sinus tenderness, pharyngeal erythema, and tender anterior cervical lymphadenopathy. Laboratory results are as follows:

Leukocytes	58,000/mm^3
Neutrophils	42%
Myelocytes	30%
Metamyelocytes	8%
Band forms	1%
Blast cells	1%
Eosinophils	6%
Basophils	4%

The leukocyte alkaline phosphatase score is low. Which of the following is the most likely diagnosis?

A. Acute lymphoblastic leukemia
B. Acute myelogenous leukemia
C. Burkitt lymphoma
D. Chronic lymphocytic leukemia

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Blast cells	1%
Eosinophils	6%
Basophils	4%

The leukocyte alkaline phosphatase score is low. Which of the following is the most likely diagnosis?

A. Acute lymphoblastic leukemia
B. Acute myelogenous leukemia
C. Burkitt lymphoma
D. Chronic lymphocytic leukemia
E. Chronic myelogenous leukemia
F. Diffuse large B-cell lymphoma
G. Follicular lymphoma
H. Fungal superinfection
I. Leukemoid reaction
J. Parasitic superinfection

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Blast cells	1%
Eosinophils	6%
Basophils	4%

The leukocyte alkaline phosphatase score is low. Which of the following is the most likely diagnosis?

- A. Acute lymphoblastic leukemia [1%]
- B. Acute myelogenous leukemia [14%]
- C. Burkitt lymphoma [13%]
- D. Chronic lymphocytic leukemia [3%]
- ✔ E. Chronic myelogenous leukemia [44%]
- F. Diffuse large B-cell lymphoma [4%]
- G. Follicular lymphoma [1%]
- H. Fungal superinfection [1%]
- I. Leukemoid reaction [12%]
- J. Parasitic superinfection [2%]

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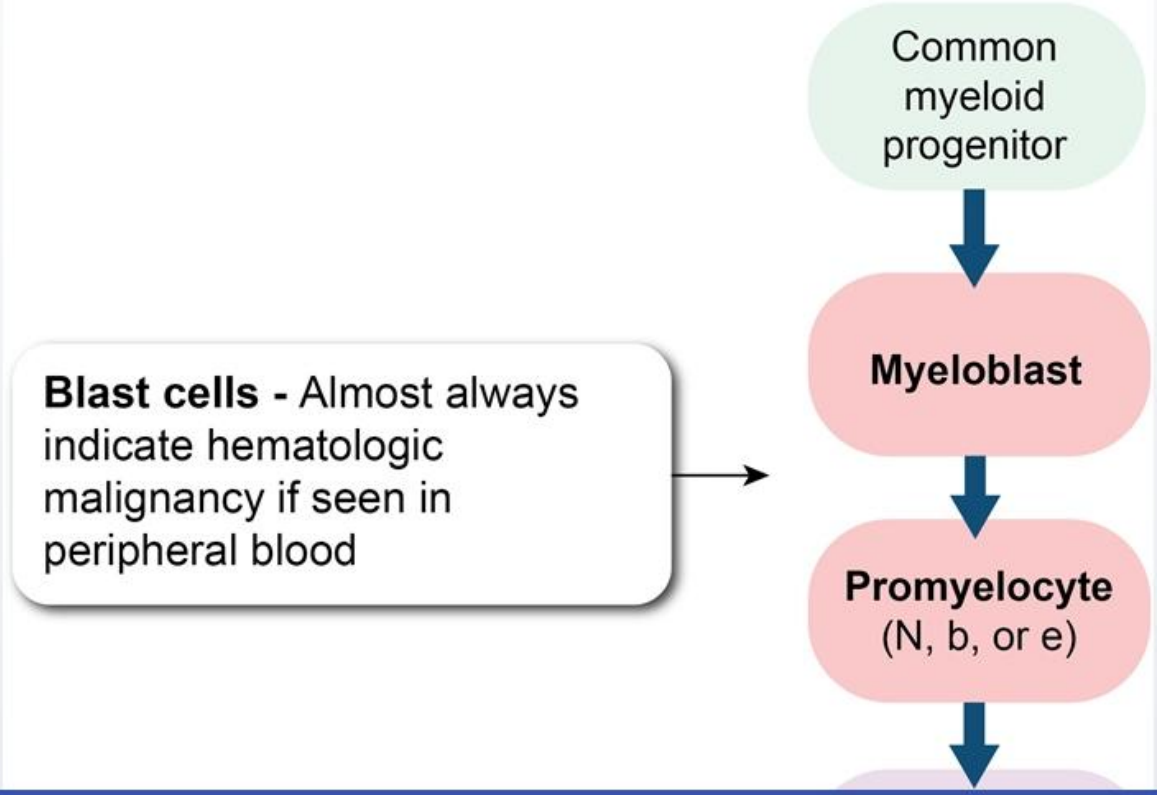
Hematopoiesis: Myeloid lineage



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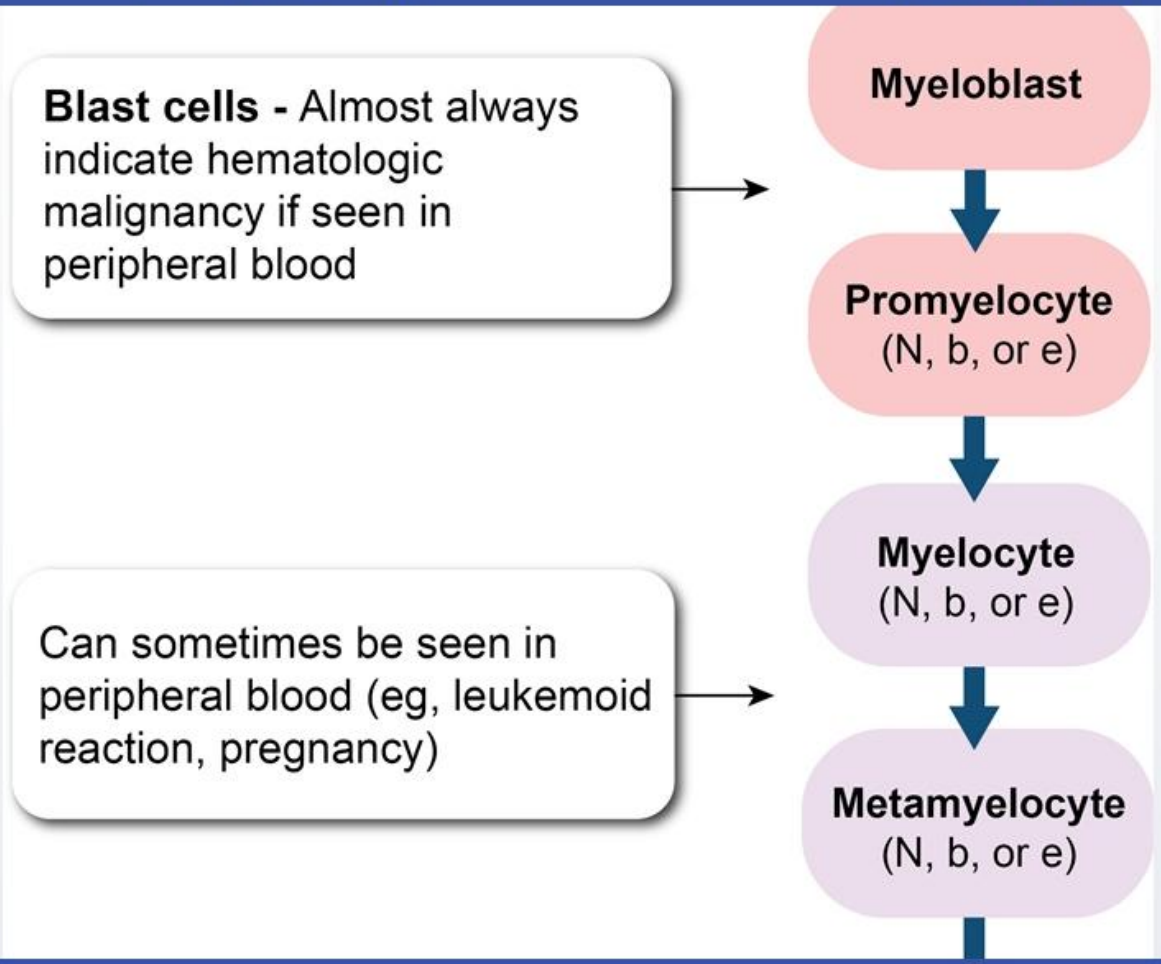

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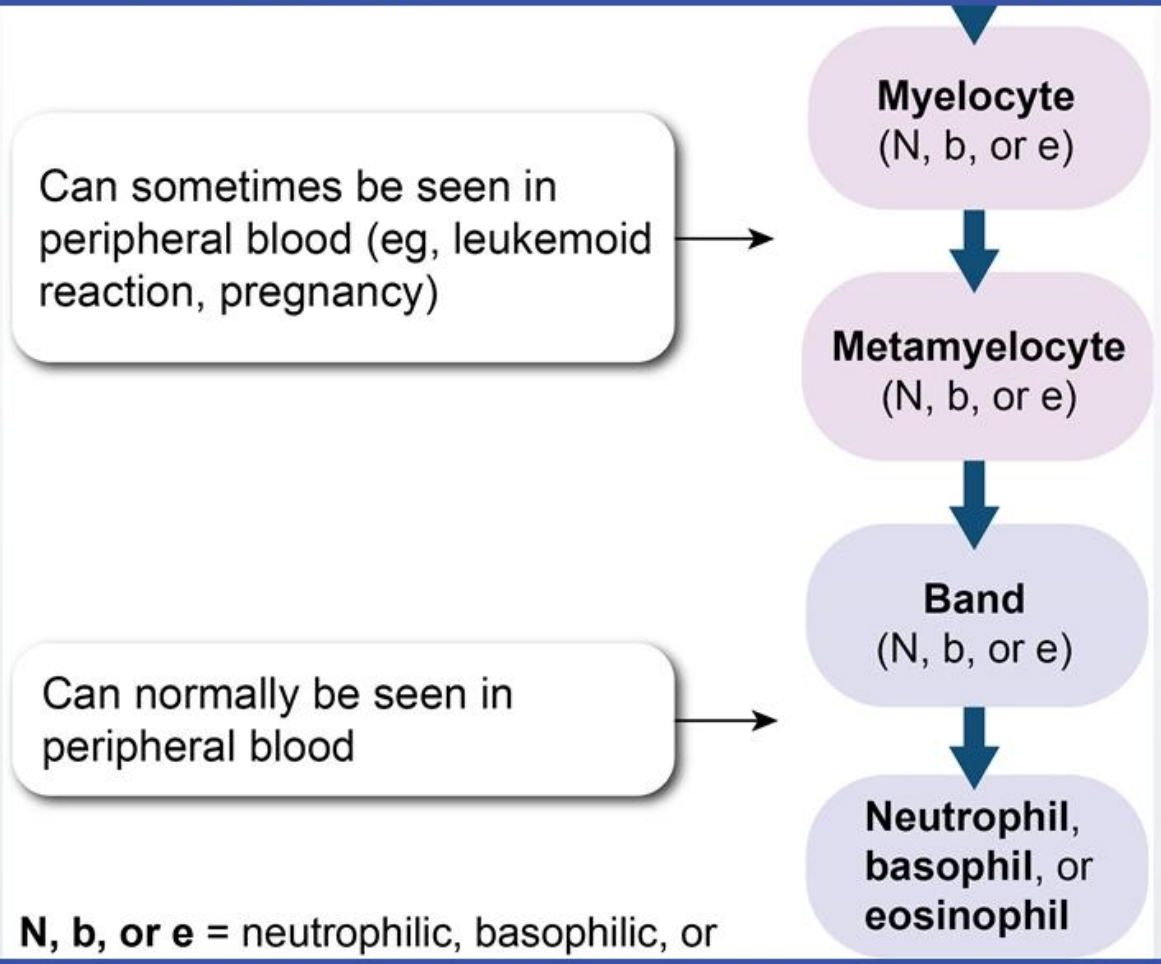
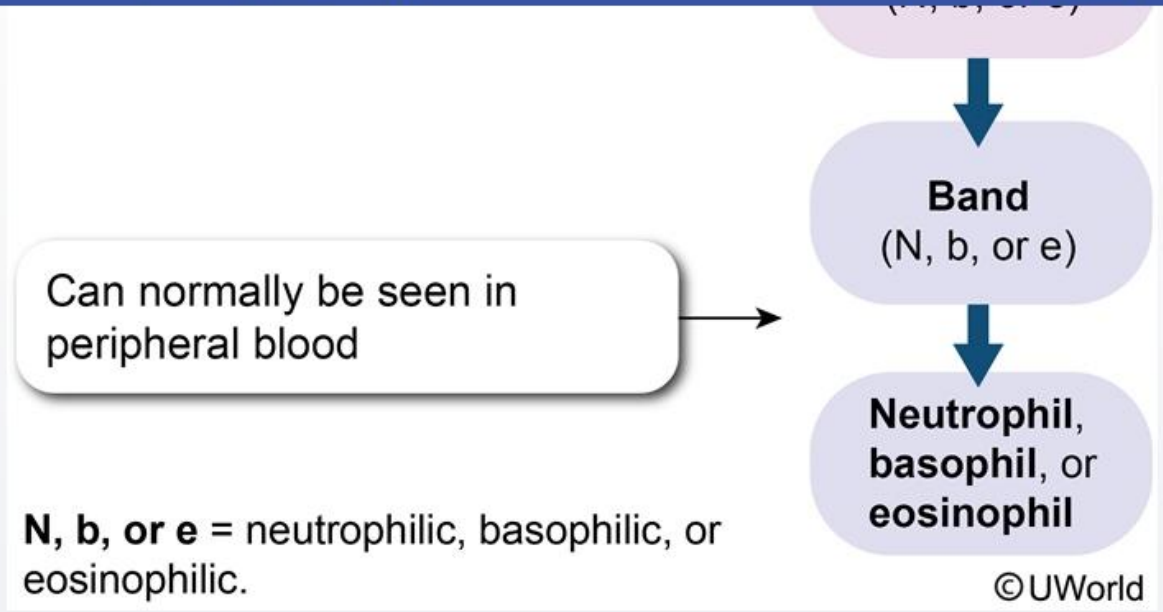

Myelocyte
(N, b, or e)
Metamyelocyte
(N, b, or e)
Band
(N, b, or e)
Neutrophil, basophil, or eosinophil
Can sometimes be seen in peripheral blood (eg, leukemoid reaction, pregnancy)
Can normally be seen in peripheral blood
N, b, or e = neutrophilic, basophilic, or



This patient with sinusitis is found to have a markedly elevated white blood cell (WBC) count with an increase in myeloid precursor forms on peripheral blood smear. The differential diagnosis is **chronic myelogenous leukemia** (CML) (uncontrolled mature granulocyte production, mostly neutrophils but also basophils and eosinophils) or leukemoid reaction (over-exuberant WBC response associated with bacterial infection or malignancy, among others). Both cause an **elevated WBC** count (≥50,000/mm^3) with **an increase in precursor forms** (eg, bands, metamyelocytes, myelocytes). However, the enzyme **leukocyte (neutrophil) alkaline phosphatase** is **decreased** in CML (as seen in this patient) because the WBCs are cytochemically abnormal; by contrast, it is normal or elevated in a leukemoid reaction **(Choice I)**.

Other clues to the diagnosis of CML are the predominance of myelocytes compared to more mature forms such as metamyelocytes (**"myelocytic bulge"**) and the absolute **basophilia and eosinophilia**. CML is confirmed by demonstration of the Philadelphia chromosome (translocation

eosinophilic.

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(Choice A) This patient has an abnormality of myeloid (not lymphoid) cells and his smear shows only 1% blasts. In general, >25% bone marrow lymphoblasts are seen in acute lymphoblastic leukemia, which is much more common in young children.

(Choice B) Acute myelogenous leukemia is the most common acute leukemia in adults. However, the mean age at diagnosis is around 65, and most patients will have a WBC count of about 15,000-20,000/mm^3 with a significant increase in blast cells (eg, ≥20%) rather than the 1% seen in this patient.

(Choices C, F, and G) Follicular lymphoma, Burkitt lymphoma, and diffuse large B-cell lymphoma cause lymph node and/or soft-tissue (not peripheral blood) abnormalities. In addition, these cancers are all lymphoid, not myeloid, in nature.

(Choice D) Patients with chronic lymphocytic leukemia have increased circulating mature lymphoid cells, not increased myeloid cells.

(Choices H and J) Parasitic superinfection (which can lead to eosinophilia) and fungal infection would not explain the predominance of myeloid neutrophil precursor forms in this patient.

Educational objective:

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(Choices H and J) Parasitic superinfection (which can lead to eosinophilia) and fungal infection would not explain the predominance of myeloid neutrophil precursor forms in this patient.

Educational objective:
Chronic myelogenous leukemia (CML) and leukemoid reaction can have presentations similar to leukocytosis; however, leukocyte (neutrophil) alkaline phosphatase level is normal or elevated in a leukemoid reaction but decreased in CML. The definitive diagnosis of CML requires demonstration of the Philadelphia chromosome t(9;22) or *BCR-ABL* fusion gene or mRNA.

References

- How I treat newly diagnosed chronic myeloid leukemia in 2015.

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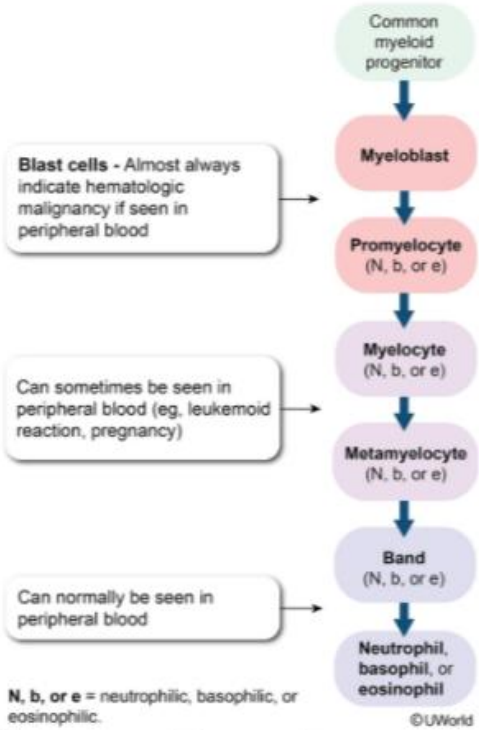
Hematopoiesis: Myeloid lineage



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Question Id: 1865

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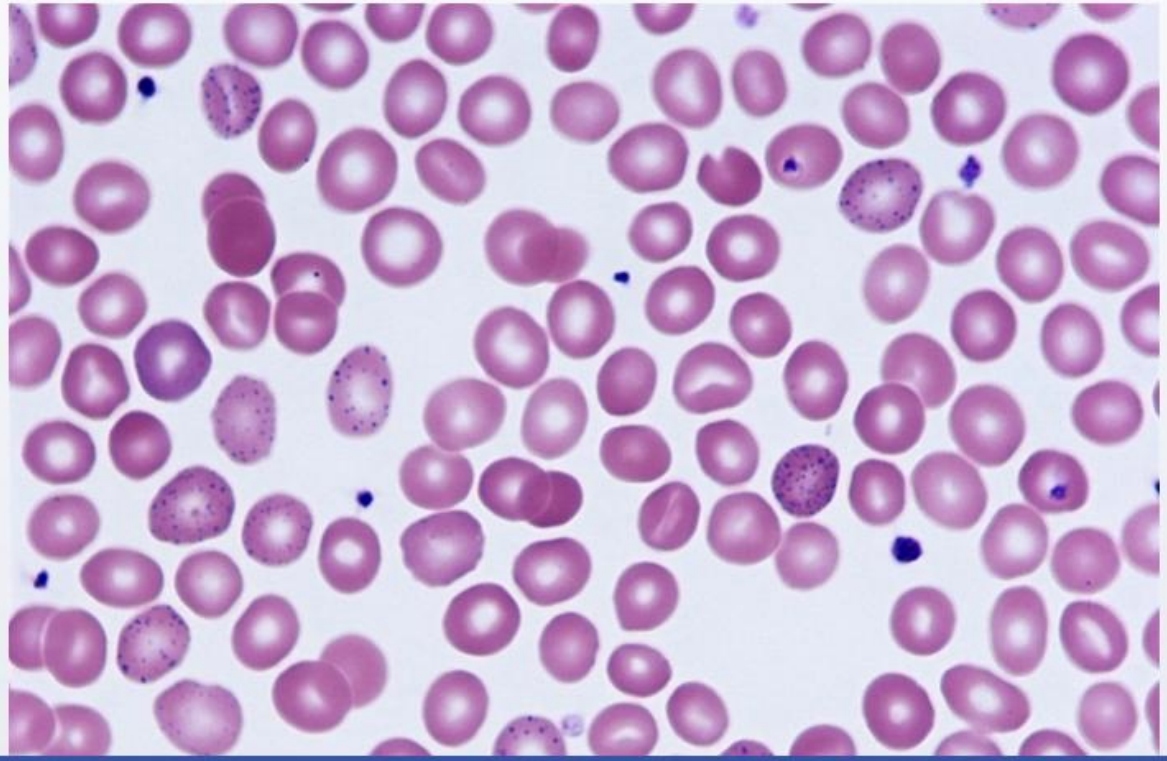
A 23-year-old man comes to the emergency department due to 4 days of cramping abdominal pain. He has been feeling weak for the past 2 weeks. He tried over-the-counter antacids without relief. He is an industrial laborer with no significant medical history or known allergies. The patient's parents have hypertension, and his siblings are healthy. Temperature is 37.1 C (98.8 F). Physical examination is unremarkable. The patient's peripheral blood smear is shown on the image below.



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Question Id: 1865

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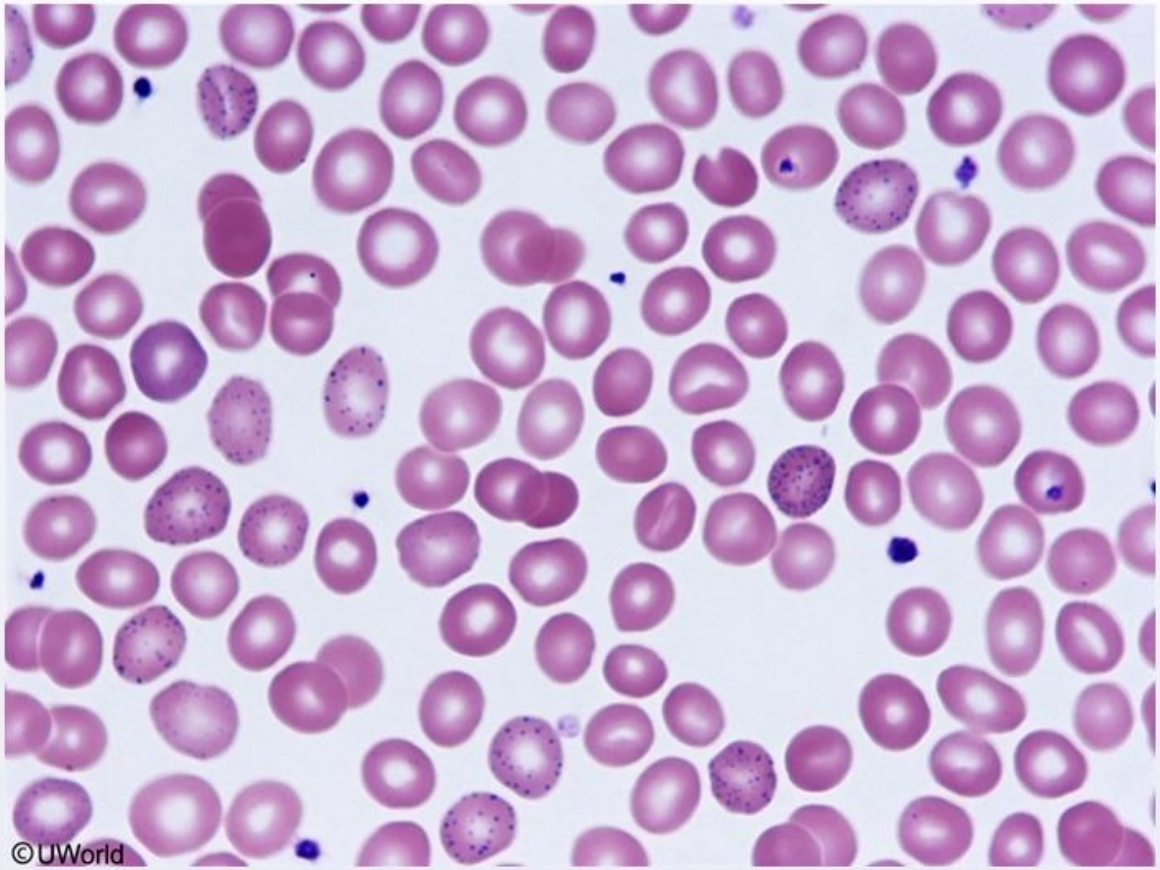
patient's peripheral blood smear is shown on the image below:



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

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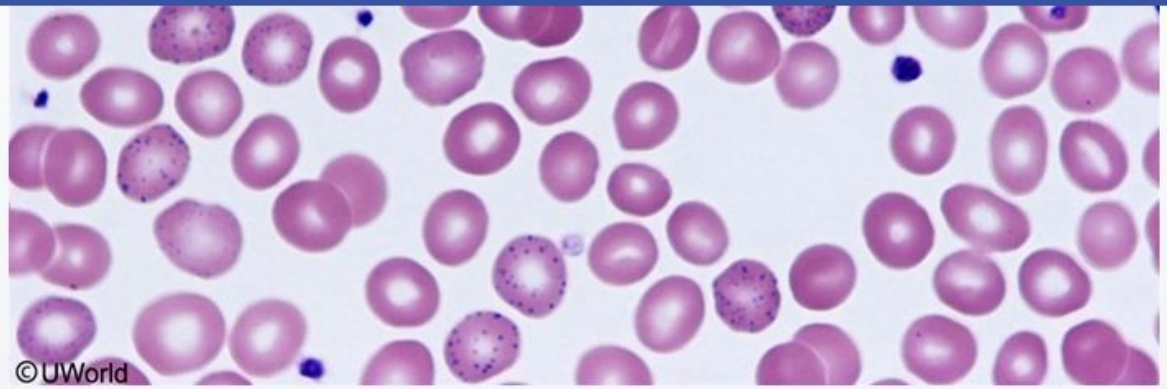

Which of the following is the most likely cause of this patient's symptoms?

- A. Acute intermittent porphyria
- B. Acute leukemia
- C. Atrophic gastritis
- D. Metal poisoning
- E. Non-Hodgkin lymphoma
- F. Poor nutrition

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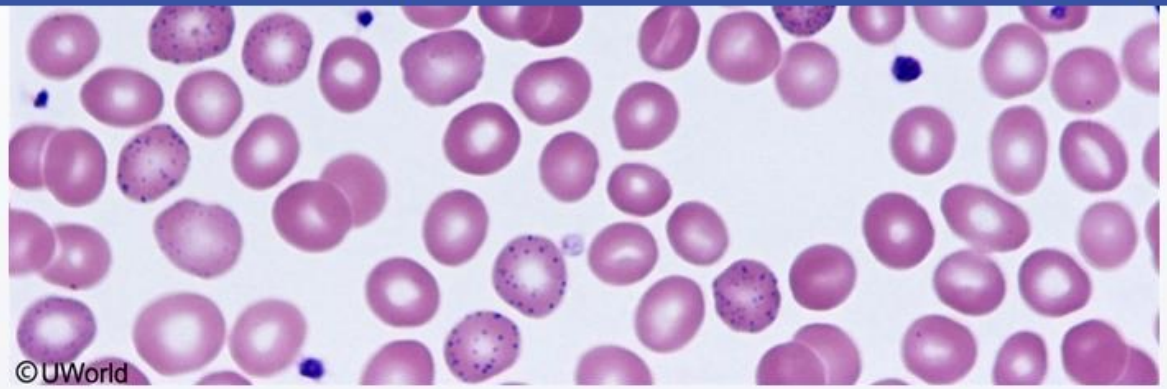

Which of the following is the most likely cause of this patient's symptoms?

- A. Acute intermittent porphyria [5%]
- B. Acute leukemia [0%]
- C. Atrophic gastritis [1%]
- ✔ D. Metal poisoning [90%]
- E. Non-Hodgkin lymphoma [0%]
- F. Poor nutrition [0%]

Omitted
Correct answer

90%
Answered correctly

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Time Spent

11/13/2018
Last Updated

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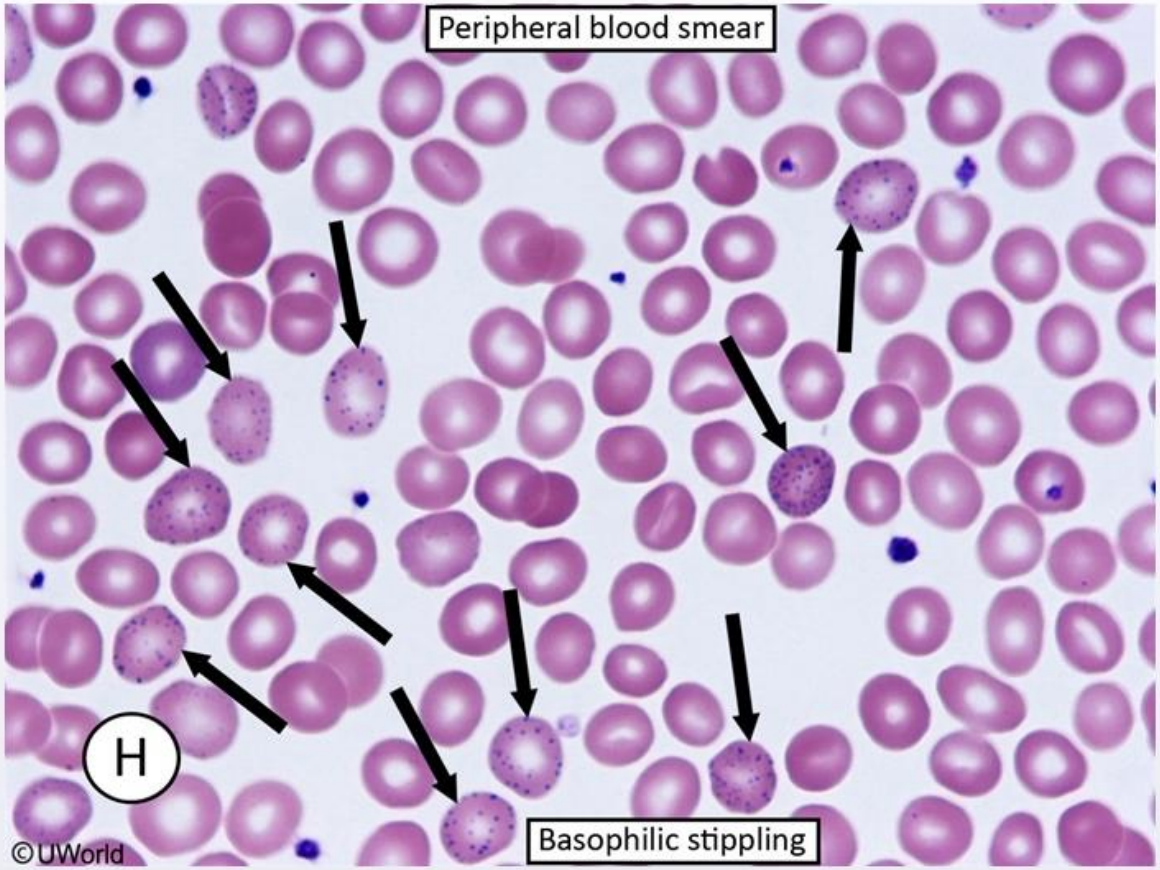

This patient likely has **lead poisoning**. In the United States, lead poisoning (plumbism) is typically a pediatric condition that results from children ingesting lead-containing **paint** chips. However, lead poisoning can also occur in adults. Affected individuals are usually **miners** or industrial

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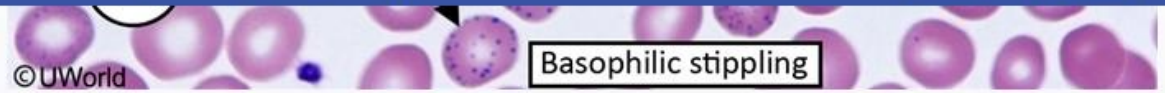

This patient likely has **lead poisoning**. In the United States, lead poisoning (plumbism) is typically a pediatric condition that results from children ingesting lead-containing **paint** chips. However, lead poisoning can also occur in adults. Affected individuals are usually **miners** or industrial workers (especially those in battery manufacturing) who inhale particulate lead while working. Adults with lead poisoning present with weakness, **abdominal pain**, and constipation. In severe cases, there may be **neurologic** manifestations (eg, headache, cognitive symptoms, peripheral neuropathy). On physical examination, patients may have **blue "lead lines"** at the junction of the teeth and gingivae.

The classic diagnostic finding on peripheral blood smear is coarse **basophilic stippling** on a background of hypochromic microcytic anemia. Basophilic stippling results from the abnormal degradation of ribosomal RNA (due to lead-induced inhibition of a nucleotidase). The hypochromic microcytic anemia results from inhibition of δ-aminolevulinate dehydratase (δ-ALA dehydratase) and the resultant reduced incorporation of iron into heme. The net effect of these defects is decreased hemoglobin synthesis.

(Choice A) Acute intermittent porphyria can cause attacks of abdominal pain (without abdominal tenderness) due to autonomic neuropathy. Erythropoiesis is not affected, and the peripheral blood smear is normal.

(Choice B) Myeloblasts containing cytoplasmic **Auer rods** on peripheral blood smear are a characteristic finding of acute myelogenous leukemia.

(Choice C) The autoimmune destruction of gastric parietal cells and/or intrinsic factor cause atrophic (autoimmune) gastritis, which can lead to pernicious anemia due to vitamin B_{12} malabsorption.

(Choice E) Non-Hodgkin lymphoma can invade the bone marrow, causing myelophthisic anemia. A peripheral blood smear would show leukoerythroblastosis (immature granulocytes and nucleated teardrop-shaped erythrocytes).

(Choice F) Malnutrition may lead to folate deficiency or, more rarely, vitamin B_{12} deficiency. Deficiencies of either vitamin cause **megaloblastic anemia**, with hypersegmented neutrophils and large erythrocytes on peripheral blood smear.

Educational objective:

Coarse erythrocyte basophilic stippling and microcytic hypochromic anemia are common peripheral blood smear findings in lead poisoning. High

ingesting lead-containing **paint** chips. However, lead poisoning can also occur in adults. Affected individuals are usually **miners** or industrial workers (especially those in battery manufacturing) who inhale particulate lead while working. Adults with lead poisoning present with weakness, **abdominal pain**, and constipation. In severe cases, there may be **neurologic** manifestations (eg, headache, cognitive symptoms, peripheral neuropathy). On physical examination, patients may have **blue "lead lines"** at the junction of the teeth and gingivae.

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(Choice F) Malnutrition may lead to folate deficiency or, more rarely, vitamin B_{12} deficiency. Deficiencies of either vitamin cause **megaloblastic anemia**, with hypersegmented neutrophils and large erythrocytes on peripheral blood smear.

Educational objective:
Coarse erythrocyte basophilic stippling and microcytic hypochromic anemia are common peripheral blood smear findings in lead poisoning. High-risk groups include young children ingesting paint chips and industrial workers inhaling particulate lead.

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A 64-year-old man comes to the office due to 3 months of constant, dull, low back pain that is worse with movement. The patient has also had intermittent episodes of difficulty urinating over the last year. He has no other medical conditions and takes no medications. The patient smoked a pack of cigarettes daily for 15 years but quit 10 years ago. Vital signs are within normal limits. On physical examination, the lungs are clear and heart sounds are normal. The abdomen is soft and nontender with no hepatosplenomegaly. Digital rectal examination shows a diffusely enlarged prostate with no nodules. Laboratory testing reveals a serum creatinine level of 1.9 mg/dL. Urine dipstick testing is negative, but 24-hour urinary protein excretion is elevated. Urine microscopy shows waxy, laminated casts. Imaging of the spine demonstrates diffuse osteopenia and multiple irregular, radiolucent lesions in the thoracic and lumbar vertebrae. Biopsy from one of the bone lesions is most likely to reveal which of the following histopathological findings?

A. Branching papillae lined by cuboidal cells with overlapping nuclei
B. Infiltrating glandular cells with substantial adjacent osteoblasts
C. Large, malignant cells containing keratin and intercellular bridges
D. Clusters of mature plasma cells and plasmablasts
E. Sheets of round or polygonal cells with abundant clear cytoplasm

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Item 30 of 34
Question Id: 15467

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- A. Branching papillae lined by cuboidal cells with overlapping nuclei [3%]
- B. Infiltrating glandular cells with substantial adjacent osteoblasts [21%]
- C. Large, malignant cells containing keratin and intercellular bridges [7%]
- ✔ D. Clusters of mature plasma cells and plasmablasts [55%]
- E. Sheets of round or polygonal cells with abundant clear cytoplasm [12%]

Omitted
Correct answer
D

55%
Answered correctly

3 Seconds
Time Spent

12/06/2018
Last Updated

Explanation

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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 older patient with back pain has several irregularly-shaped vertebral lesions, raising strong suspicion for metastatic disease. Differentiation of the **underlying tumor** is often assisted by whether the lesion is sclerotic (osteoblastic) or radiolucent (osteolytic). **Multiple myeloma**, a clonal plasma cell malignancy, is one of the most common causes of **radiolucent bone lesions** in adults; the tumor multiplies in the bone marrow and generates osteolytic cytokines, causing bone pain, bone destruction, pathologic fractures, and hypercalcemia.

Myeloma cells also produce excessive **monoclonal immunoglobulin** (paraprotein) that can clog the renal tubules and subsequently cause **light-chain cast nephropathy**. This is typically characterized by **mild renal insufficiency**, normal urine dipstick for protein (this test detects albumin only), elevated 24-hour urine protein (this test detects light-chain proteins), and waxy, laminated casts. Excessive light chains can also form fibrils and deposit in tissues, leading to amyloid light-chain amyloidosis. Monoclonal immunoglobulins are identified by urine or serum protein electrophoresis (M-spike).

The diagnosis of myeloma is confirmed by bone marrow aspirate or biopsy, which will demonstrate >10% **plasma cells**. Plasma cells are

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

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The diagnosis of myeloma is confirmed by bone marrow aspirate or biopsy, which will demonstrate >10% **plasma cells**. Plasma cells are identified based upon "clock-face" chromatin, abundant basophilic cytoplasm, and prominent perinuclear clear areas (Golgi apparatus).

(Choice A) Papillary thyroid cancer is characterized by **branching papillae** lined by cuboidal cells with overlying nuclei (often with calcified psammoma bodies). Most cases progress slowly and present with a thyroid mass that may invade adjacent structures; bone lesions are relatively uncommon.

(Choice B) Prostate adenocarcinoma is a **glandular tumor** that often spreads to the bones; however, it generates sclerotic (osteoblastic) bone lesions, not radiolucent bone lesions. Prostate cancer does not generally impinge on the urethra (no urinary symptoms) and is usually associated with a nodule on prostate examination. This patient's intermittent difficulty urinating and diffusely enlarged prostate with no nodules likely indicate benign prostatic hyperplasia.

(Choices C and E) Squamous cell lung cancer is associated with large, malignant cells containing keratin with **intercellular bridges**. Renal cell carcinoma is associated with sheets of **round or polygonal cells** with abundant clear cytoplasm. Although both tumors commonly form osteolytic lesions in the spine, neither regularly cause renal insufficiency, elevated urine protein, and waxy urinary casts.

and deposit in tissues, leading to amyloid light-chain amyloidosis. Monoclonal immunoglobulins are identified by urine or serum protein electrophoresis (M-spike).

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Educational objective:
Multiple myeloma is a plasma cell malignancy that replicates in the bone marrow and causes osteolytic bone lesions, bone destruction, hypercalcemia, and pathologic fractures. Histopathology will show replacement of the normal bone marrow with plasma cells and blasts.

References

- Bone disease in multiple myeloma: pathophysiology and management.

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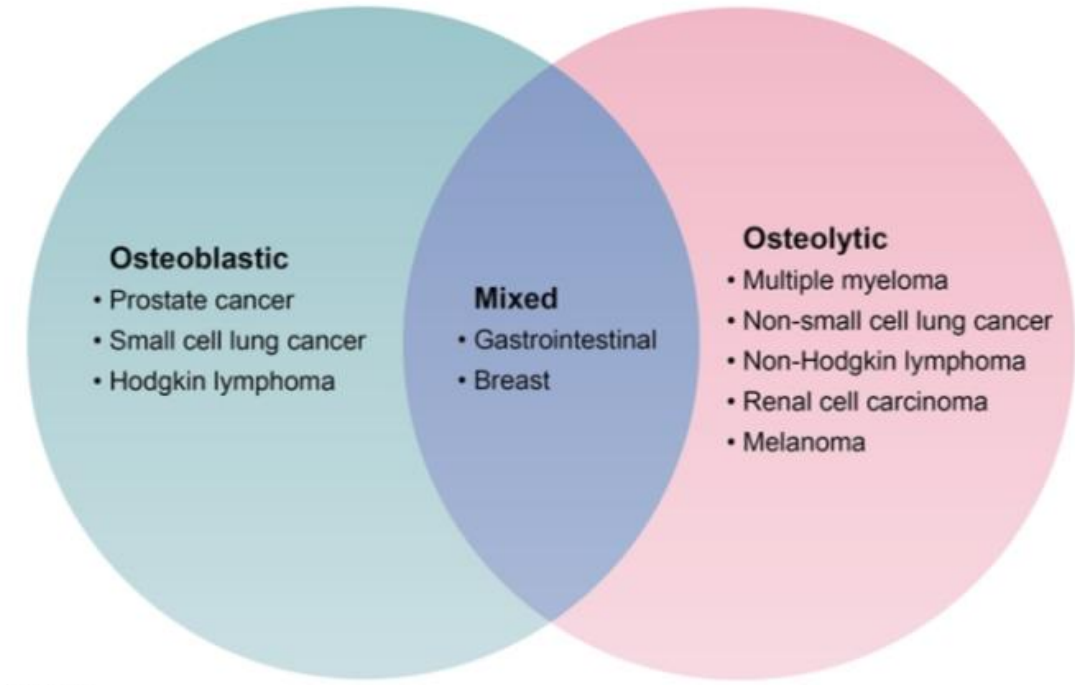
- Normocytic anemia

Exhibit Display

Bone metastases



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- Normocytic anemia

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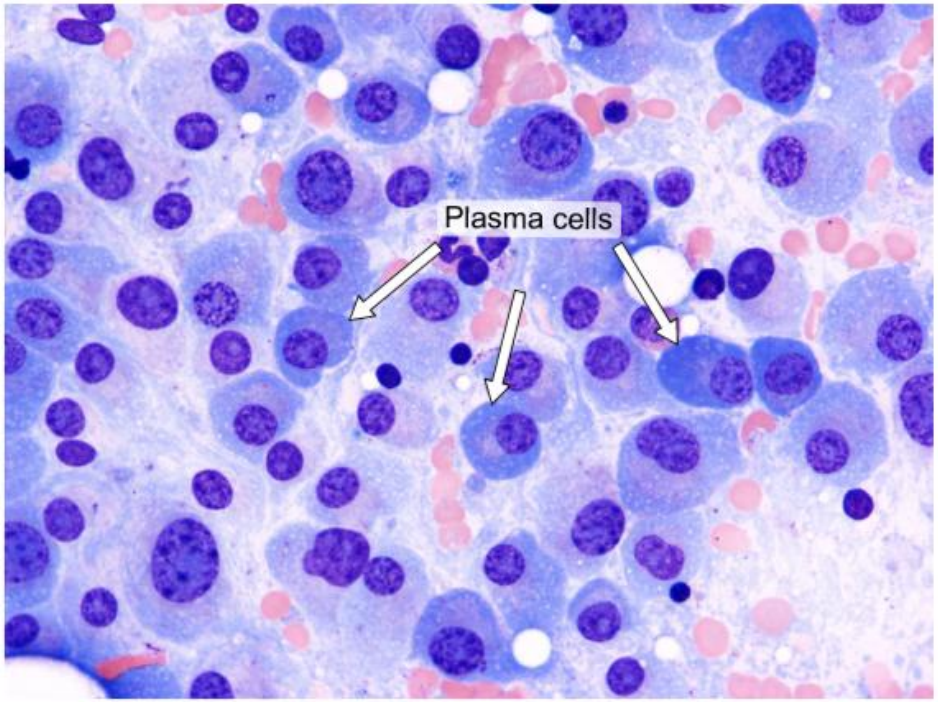

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Question Id: 1724

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A 52-year-old man comes to the office due to a progressively enlarging neck mass, fatigue, and weight loss over the past 2 months. Physical examination shows enlarged, firm, and nontender cervical lymph nodes. The patient also has enlarged tonsils, bilateral axillary lymphadenopathy, and splenomegaly. Excisional lymph node biopsy reveals diffuse sheets of atypical, large B cells with high nuclear-cytoplasmic ratio that has replaced normal tissue architecture. In situ hybridization of the tissue section is positive for Epstein-Barr virus. Which of the following is most strongly correlated with this patient's condition?

A. Advanced HIV infection
B. Aspirin and nonsteroidal anti-inflammatory drug use
C. Cigarette smoking
D. Radiation exposure
E. Socioeconomic status

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Question Id: 1724

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- A. Advanced HIV infection [70%]
- B. Aspirin and nonsteroidal anti-inflammatory drug use [0%]
- C. Cigarette smoking [6%]
- D. Radiation exposure [10%]
- E. Socioeconomic status [10%]

Omitted
Correct answer
A

70%
Answered correctly

3 Seconds
Time Spent

12/16/2018
Last Updated

Explanation

This patient likely has **non-Hodgkin lymphoma** (NHL). Depending on the subtype, NHL often presents with a rapidly progressive mass, lymphadenopathy, splenomegaly, and B symptoms (eg, night sweats, weight loss). Diagnosis is typically made with excisional lymph node biopsy, which usually shows a loss of normal tissue architecture and large, atypical B cells with a high nuclear-cytoplasmic ratio.

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Explanation

This patient likely has **non-Hodgkin lymphoma** (NHL). Depending on the subtype, NHL often presents with a rapidly progressive mass, lymphadenopathy, splenomegaly, and B symptoms (eg, night sweats, weight loss). Diagnosis is typically made with excisional lymph node biopsy, which usually shows a loss of normal tissue architecture and **large, atypical B cells** with a high nuclear-cytoplasmic ratio.

Lymphoma can be associated **Epstein-Barr virus** (EBV), a ubiquitous herpesvirus that primarily infects B lymphocytes and causes persistent latent infections. Although viral reactivation is uncommon, the latent EBV genome still transcribes viral gene products that can result in **malignant transformation** of infected cells. EBV is particularly associated with nasopharyngeal carcinoma, Hodgkin lymphoma, and some forms of NHL (eg, Burkitt lymphoma).

Patients with **HIV** are at greatest risk for EBV-associated lymphomas (risk is up to 60-fold greater). This is likely due to deficits in cell-mediated immunity (decreases immune recognition of EBV-infected cells) and chronic antigen-dependent B-cell stimulation (promotes B-cell proliferation). NHL is considered an AIDS-defining condition and can sometimes be the presenting manifestation of HIV infection.

(Choice B) Aspirin and nonsteroidal anti-inflammatory drugs may decrease the risk of colorectal cancer. Their use is not linked to an increased risk of NHL.

(Choice C) Cigarette smoking is a strong risk factor for the development of many types of cancer (eg, lung, bladder, pancreas) but is not closely linked with the development of NHL.

(Choice D) The link between radiation exposure and the development of NHL is controversial. However, most studies indicate that this is not a strong risk factor.

(Choice E) Although lower socioeconomic status may be associated with worse outcomes in patients with NHL, this marker has not been closely linked with the development of NHL.

Educational objective:

transformation of infected cells. EBV is particularly associated with nasopharyngeal carcinoma, Hodgkin lymphoma, and some forms of NHL (eg, Burkitt lymphoma).

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Educational objective:
Patients with HIV have much higher rates of lymphoma than the general population. Many cases are due to underlying Epstein-Barr virus infection.

References

- EBV and HIV-related lymphoma.

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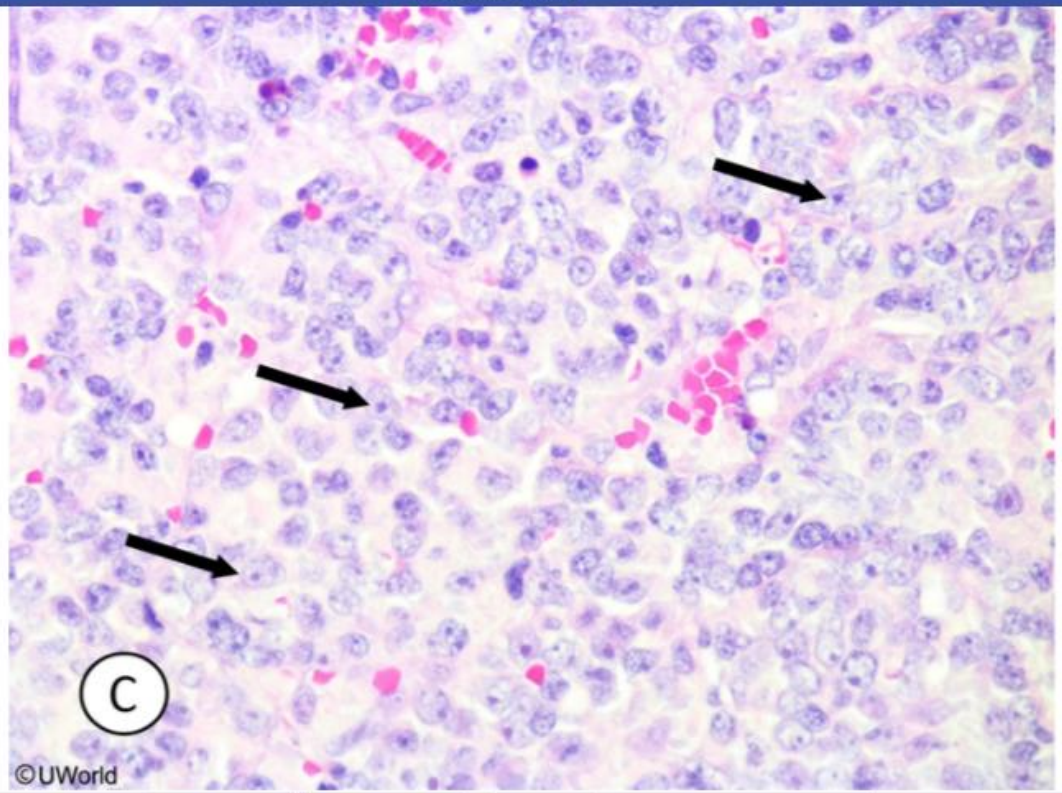

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Educational objective:

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Question Id: 1842

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A 12-year-old African American male is brought to the emergency room with high fever, chest pains, and dyspnea. His past medical history is significant for two prior hospitalizations for abdominal pain, which resolved with analgesics and hydration. Evaluation today reveals a hematocrit of 23% and reticulocyte count of 9%. Several hours after being admitted, the patient dies in the hospital. At autopsy, the patient's spleen is firm and brown; this finding is most likely related to:

- A. Work hypertrophy
- B. Follicular hyperplasia
- C. Vascular occlusion
- D. Pressure atrophy
- E. Dysplasia
- F. Lipid accumulation

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- A. Work hypertrophy [17%]
- B. Follicular hyperplasia [2%]
- ✔ C. Vascular occlusion [73%]
- D. Pressure atrophy [4%]
- E. Dysplasia [0%]
- F. Lipid accumulation [1%]

Omitted
Correct answer
C

73%
Answered correctly

3 Seconds
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02/06/2019
Last Updated

Explanation

In an African American patient with the hematologic findings described above and recurrent episodes of abdominal pain that resolve with

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Explanation

In an African American patient with the hematologic findings described above and recurrent episodes of abdominal pain that resolve with hydration, sickle cell anemia is the most likely diagnosis. Today this patient has presented with symptoms of "acute chest syndrome" (ACS), which is vaso-occlusive crisis localized to the pulmonary vasculature that can occur in patients with sickle cell anemia. ACS is commonly precipitated by pulmonary infection.

In patients with homozygous hemoglobin S disease, vaso-occlusive crises can also cause splenic infarctions. Repeated infarctions over time produce a spleen that is shrunken, discolored, and fibrotic. By the time they reach adulthood, most patients with sickle cell anemia have undergone "autosplenectomy" as a result of these infarcts and are left with only a small, scarred splenic remnant. The spleen may demonstrate brownish discoloration (hemosiderosis) due to extensive ingestion of sickled RBCs by splenic macrophages (extravascular hemolysis).

(Choices A and B) There may be hyperplasia and hypertrophy of normal splenic elements (especially macrophages and lymphoid cells) in systemic infections and various other disease states.

(Choice D) Pressure atrophy of the splenic parenchyma can be seen when there is a tumor infiltrating the spleen.

(Choice E) Dysplasia is disordered growth and/or abnormal hyperplasia of epithelia. This term is rarely applied to histologic components of the spleen.

(Choice F) Intrasplenic lipid accumulation might be seen in lysosomal lipid storage disorders like Gaucher's disease.

Educational Objective:
The major chronic pathologic changes in the spleens of patients with sickle cell anemia result from repetitive splenic infarctions caused by splenic microvessel occlusion. Fibrosis, brownish discoloration, and eventual autosplenectomy ultimately result.

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A 45-year-old man comes to the office for progressive weakness and fatigue over the last year. The patient was adopted and does not know his family history. After a comprehensive physical examination and laboratory evaluation, the patient undergoes genetic testing. A loss of expression mutation is identified in a gene coding for a protein found on the basolateral surface of hepatocytes and enterocytes. The protein is known to interact with the transferrin receptor. Which of the following conditions is this patient at greatest risk of developing?

- A. Basal ganglia atrophy
- B. Fat malabsorption and osteoporosis
- C. Iron deficiency anemia
- D. Liver cirrhosis and hepatocellular carcinoma
- E. Pulmonary emphysema

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A 45-year-old man comes to the office for progressive weakness and fatigue over the last year. The patient was adopted and does not know his family history. After a comprehensive physical examination and laboratory evaluation, the patient undergoes genetic testing. A loss of expression mutation is identified in a gene coding for a protein found on the basolateral surface of hepatocytes and enterocytes. The protein is known to interact with the transferrin receptor. Which of the following conditions is this patient at greatest risk of developing?

- A. Basal ganglia atrophy [4%]
- B. Fat malabsorption and osteoporosis [1%]
- C. Iron deficiency anemia [39%]
- ✔ D. Liver cirrhosis and hepatocellular carcinoma [52%]
- E. Pulmonary emphysema [1%]

Omitted
Correct answer
D

52%
Answered correctly

3 Seconds
Time Spent

01/19/2019
Last Updated

Explanation

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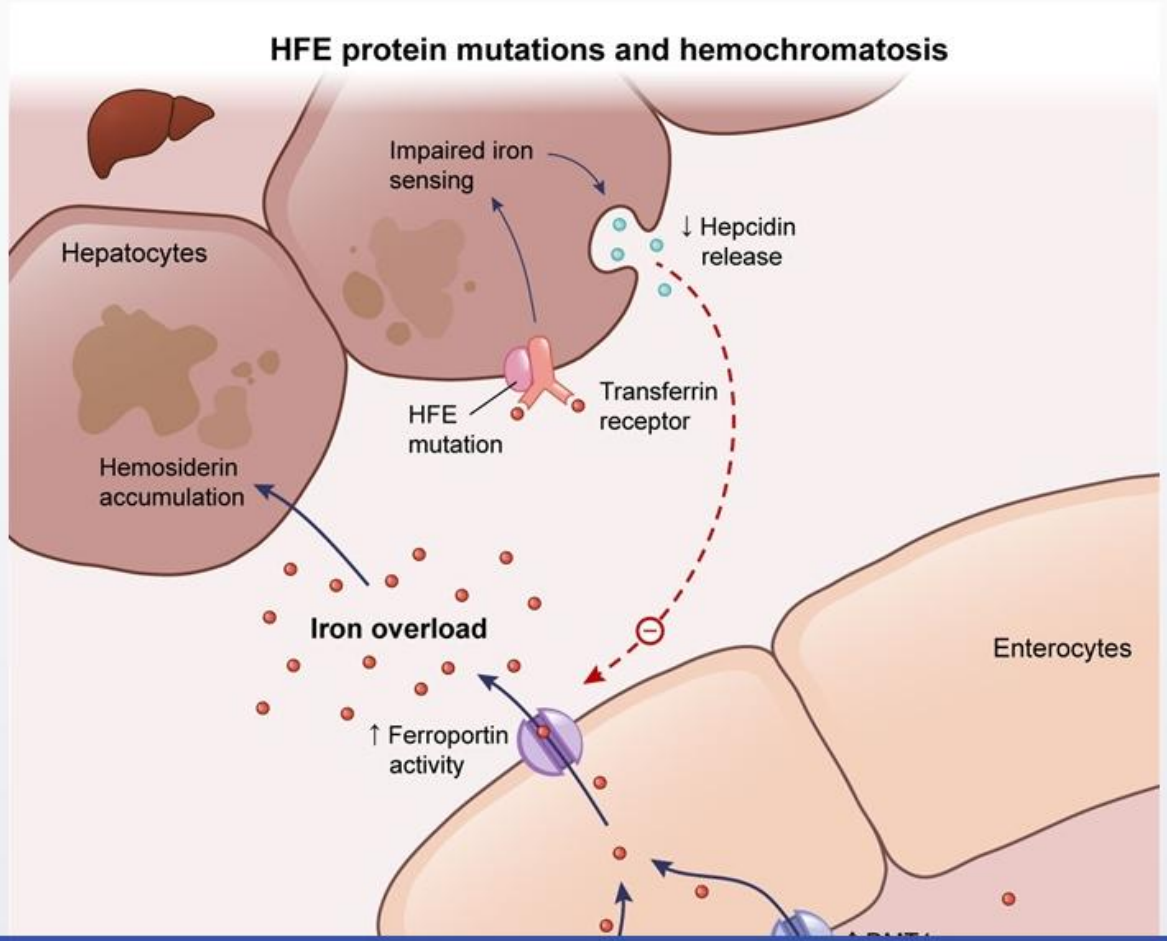

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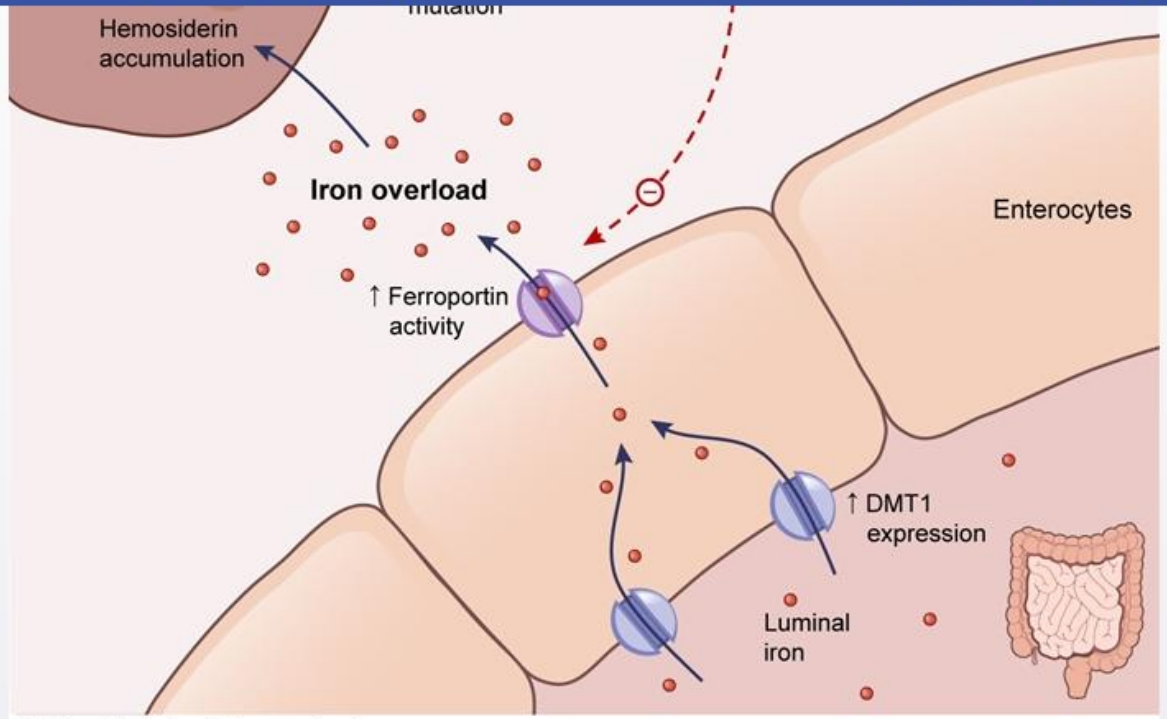

DMT1 = divalent metal transporter 1.

Primary hemochromatosis (ie, hereditary hemochromatosis) is most commonly caused by mutations affecting the **HFE protein**. This protein normally interacts with the transferrin receptor to form a complex that functions as a sensor of iron stores. Mutations that inactivate the HFE protein cause enterocytes and hepatocytes to **detect falsely low iron levels**. This increases iron accumulation in the body through the following 2 mechanisms:

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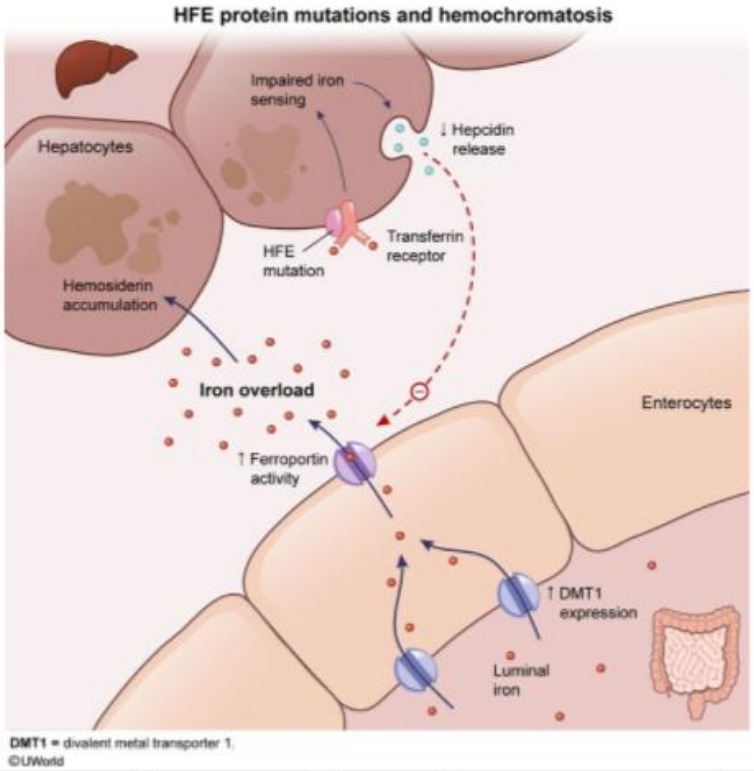

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DMT1 = divalent metal transporter 1.

Primary hemochromatosis (ie, hereditary hemochromatosis) is most commonly caused by mutations affecting the **HFE protein**. This protein normally interacts with the transferrin receptor to form a complex that functions as a sensor of iron stores. Mutations that inactivate the HFE protein cause enterocytes and hepatocytes to **detect falsely low iron levels**. This increases iron accumulation in the body through the following 2 mechanisms:

1. **Enterocytes** respond by increasing apical expression of divalent metal transporter 1 (DMT1), increasing iron absorption from the intestinal lumen
2. **Hepatocytes** respond by decreasing hepcidin synthesis; low hepcidin levels result in increased ferroportin expression on the basolateral surface of enterocytes. This allows increased iron secretion into the circulation, leading to iron overload

When body iron levels exceed 20 g, patients typically develop the classic triad of **micronodular cirrhosis**, diabetes mellitus, and skin pigmentation (ie, "bronze diabetes"). These patients are at an increased risk for **hepatocellular carcinoma**, congestive heart failure, and testicular atrophy/hypogonadism.

(Choice A) Basal ganglia atrophy is a potential complication commonly seen in Wilson disease (ie, hepatolenticular degeneration).

(Choice B) Exocrine pancreatic function is usually preserved in patients with hemochromatosis. Therefore, fat malabsorption and osteoporosis (due to decreased vitamin D) would not typically be seen.

(Choice C) Iron deficiency anemia is a potential complication of blood loss, lack of dietary iron, or an inability to absorb iron (eg, celiac disease). Hemochromatosis results in iron overload, not iron deficiency.

(Choice E) Pulmonary emphysema is a potential complication of alpha-1 antitrypsin deficiency.

Educational objective:
HFE protein mutations are the most common cause of primary hemochromatosis. Inactivation of the HFE protein results in decreased hepcidin synthesis by hepatocytes and increased DMT1 expression by enterocytes, leading to iron overload. Patients with hemochromatosis are at an

lumen

2. **Hepatocytes** respond by decreasing **hepcidin** synthesis; low hepcidin levels result in increased ferroportin expression on the basolateral surface of enterocytes. This allows increased iron secretion into the circulation, leading to iron overload

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(Choice E) Pulmonary emphysema is a potential complication of alpha-1 antitrypsin deficiency.

Educational objective:
HFE protein mutations are the most common cause of primary hemochromatosis. Inactivation of the HFE protein results in decreased hepcidin synthesis by hepatocytes and increased DMT1 expression by enterocytes, leading to iron overload. Patients with hemochromatosis are at an increased risk for liver cirrhosis and hepatocellular carcinoma.

References

- Hepcidin regulation of iron transport.

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↑ DMT1

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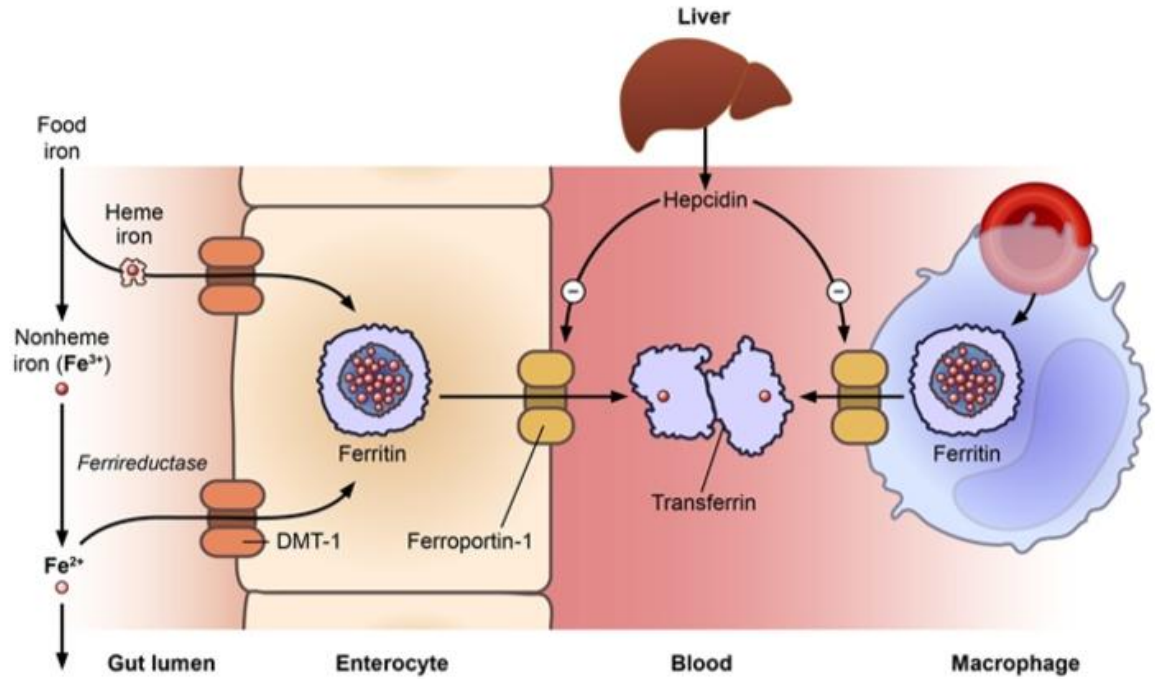
Hepcidin and body iron regulation



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Item 34 of 34
Question Id: 341

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A 76-year-old man comes to the office with a 2-month history of progressive lower back pain. The pain is relatively constant and nagging and is unrelieved by rest or position changes. It is especially bad at night and interferes with sleep. The patient has taken acetaminophen and ibuprofen without relief. Past medical history is significant for hypertension and osteoarthritis affecting the knees and hands. He used intravenous drugs occasionally when he was younger but he has not used them for over 30 years. Which of the following processes is most likely responsible for this patient's back pain?

- A. Degenerative
- B. Infectious
- C. Inflammatory
- D. Neoplastic
- E. Psychogenic

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Item 34 of 34
Question Id: 341

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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- A. Degenerative [35%]
- B. Infectious [3%]
- C. Inflammatory [5%]
- ✔ D. Neoplastic [54%]
- E. Psychogenic [0%]

Omitted
Correct answer
D

54%
Answered correctly

3 Seconds
Time Spent

08/24/2018
Last Updated

Explanation

Differential diagnosis of back pain

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Differential diagnosis of back pain	
Condition	**Clinical clues**
Degenerative (osteoarthritis)	• Positional • **Relieved with rest**
Radiculopathy (eg, disc herniation)	• **Radiates** to leg • Sensory & motor findings • Positive **straight leg raise test**
Spinal stenosis	• Pain with standing (spinal extension) • Relieved by spinal flexion
Spondyloarthropathy	• Young men • HLA-B27 • **Relieved with exercise** • Prolonged morning stiffness
Spinal metastasis	• Constant pain • Worse at night • Not responsive to position changes
Vertebral osteomyelitis	• Focal tenderness • Fevers & night sweats • Recent **infection**, **intravenous** drug abuse,

Radiculopathy (eg, disc herniation)	• **Radiates** to leg • Sensory & motor findings • Positive **straight leg raise test**
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Spinal metastasis	• Constant pain • Worse at night • Not responsive to position changes
Vertebral osteomyelitis	• Focal tenderness • Fevers & night sweats • Recent **infection**, **intravenous** drug abuse, or immune compromise

This patient has a number of features worrisome for **spinal metastases**, including advanced age, pain that is **worse at night**, and persistent and progressive pain that is not relieved with position changes or analgesics. Patients with malignant back pain may also experience **systemic symptoms** such as fever, weight loss, and night sweats. Known **history of malignancy** is also a strong predictor of metastatic back pain.

Prostate cancer is the most common malignancy in older men, and it frequently metastasizes to the axial skeleton and proximal femurs. Other malignancies with a propensity for bony metastasis include breast, kidney, thyroid, and lung (PB/KTL: mnemonic "**lead kettle**").

(Choice A) Degenerative arthritis (osteoarthritis) commonly affects the cervical and lumbosacral spine. It causes pain during activity that is

osteomyelitis	• Recent infection, intravenous drug abuse, or immune compromise

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(Choice A) Degenerative arthritis (osteoarthritis) commonly affects the cervical and lumbosacral spine. It causes pain during activity that is relieved by rest and most common analgesics. Persistent, nocturnal pain is not typical for osteoarthritis.

(Choice B) Infectious causes of pain, such as vertebral osteomyelitis (rest pain, focal tenderness) or epidural abscess (nerve root compression, radicular symptoms), are typically associated with fever, night sweats, or other systemic symptoms. They arise from contiguous or hematogenous spread from a known infection or from recent intravenous drug use.

(Choice C) Inflammatory back pain (eg, spondyloarthropathy) presents with prolonged (>1 hour) morning stiffness of the lumbosacral spine. The most common form is ankylosing spondylitis, a condition that causes progressive loss of spinal mobility.

(Choice E) Back pain may be psychogenic (factitious or malingering). Evidence of secondary gain (eg, litigation/compensation) and an unusual pattern of signs and symptoms can help identify these patients.

Educational objective:
Clinical features that suggest a malignant cause of back pain include occurrence at night, not relieved with rest or analgesics, advanced age, and systemic symptoms. Common malignancies with a propensity for bony metastasis include prostate, breast, kidney, thyroid, and lung.

References